Iranian Journal of Child Neurology

The Iranian Journal of Child Neurology

The Iranian Journal of Child Neurology, a quarterly journal published by the Iranian Child Neurology Society and Shahid Beheshti University of Medical Sciences

Publisher: *The Iranian Child Neurology Society & Pediatric Neurology Research Center*
Director-in-Chief: *Mohammad Ghofrani MD*
Editor-in-Chief: *Parvaneh Karimzadeh MD*
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Language Editor: *Mohammad Bagher Rokni MD*
Statistical Editor: *Eznollah Azargashb PhD*
Graphist: *Royan Pazhouh*
Page Setup: *Roya soury*
Printing: *Royan Pazhouh, Enghelab Square, Tehran, Iran.*
Price: *500,000 RLs (Hard Copy for Iranian people)*
Online version: *Free access*

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Mofid Children Hospital, Shariati Ave, Tehran, 1546815514, Iran.
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IRANIAN JOURNAL OF CHILD NEUROLOGY

◙ Approved as "Academic Research Journal" by the 74th Medical Journals Commission of Ministry of Health and Medical Education of Iran.

◙ Published by Iranian Child Neurology Society and Pediatric Neurology Department & Research Center of Shahid Beheshti University of Medical Sciences.

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REVIEW ARTICLE

Benign Enlargement of Subarachnoid Space in Infancy: "A Review with Emphasis on Diagnostic Work-Up"

How to Cite This Article: Khosroshahi N, Nikkhah A. Benign Enlargement of Subarachnoid Space in Infancy: "A Review with Emphasis on Diagnostic Work-Up". Iran J Child Neurol. Autumn 2018; 12(4):7-15

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Received: 06- May -2018
Last Revised: 27- May -2018
Accepted: 19-Jul-2018

Abstract

Macrocephaly is one of the most frequent reasons for referral to a pediatric neurologist. Benign enlargement of subarachnoid space (BESS) in infancy is the most common cause of macrocephaly and characterized clinically with large head circumference, normal or mildly motor and language delay and increased cerebrospinal fluid (CSF) in the subarachnoid space with normal ventricles or mild ventriculomegaly. In this review, we describe the etiology, epidemiology, clinical presentation, pathogenesis, neuroimaging, differential diagnosis, treatment and outcome of this entity from current literature with emphasis on diagnostic work-up.

Keywords: Benign enlargement of subarachnoid space; External hydrocephalus; Macrocephaly; Infant

Introduction

Large head (Macrocephaly) means head circumference more than two standard deviations above the mean for age, sex, and body size, established using measurements and a standard growth chart (1). About 2% of normal population has macrocephaly (1, 2). The causes of a large head include hydrocephalus (an excess volume of CSF intracranially), megalencephaly (enlargement of the brain), thickening of the skull and hemorrhage or non-bloody fluid into the subdural or epidural spaces (1, 2). Macrocrania in infancy can be due to both benign and pathologic causes. Pathologic cases are rare, alternatively, benign macrocrania of infancy is more common (3). External hydrocephalus is the most common cause of macrocephaly in infants (2-4). It is a condition in infants and children with enlarged subarachnoid space accompanied by increasing head circumference with normal or mildly dilated ventricles (4, 5).

Benign enlargement of subarachnoid space (BESS) encompasses a variety of names in literatures, such as benign external hydrocephalus (BEH), extraventricular hydrocephalus, benign subdural effusion, benign

extracellular fluid collection, extraventricular obstructive hydrocephalus, subdural hygroma, pseudo-hydrocephalus, benign extra-axial collections, subarachnomegaly, and subdural effusions of infancy which demonstrating the confusion surrounding the entity (5-7).

BESS is the most common cause of macrocephaly in infancy (4, 8, 9). It is more common in males (4, 10, 11). A genetic cause is likely in some cases, with the infants' father often having a large head (3, 12). Enlarging extra-axial fluid space is leading to an expansion of head circumference around 3 to 12 months of age, with head circumference measurement crossing percentile lines and often reaching above the 90th-98th percentile (Figure 1) (2, 3, 13). Mean age at presentation was 7.3 months (14). Head circumference at birth is normal (2, 13, 15) or slightly higher than normal (14, 15).

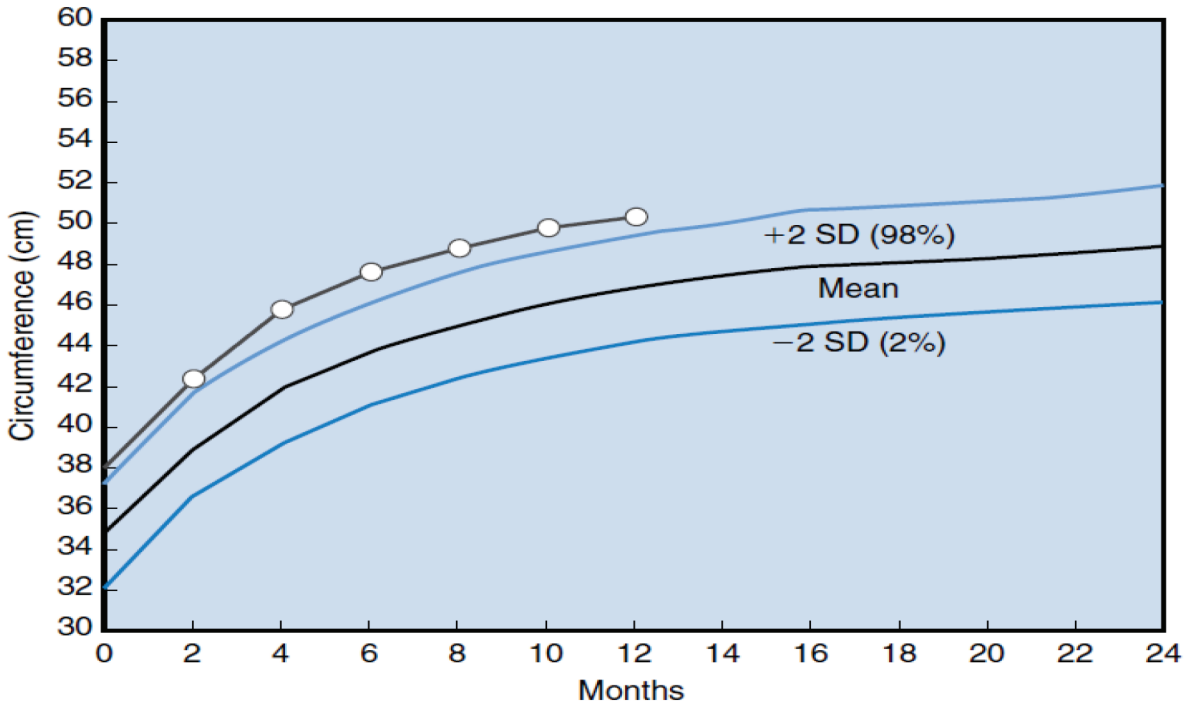

Figure 1. *BESS. Head circumference is large at birth and grows above 98th percentile (Fenichel Clinical Pediatric Neurology, 2013)*

Etiology

Some causes for external hydrocephalus are mentioned but there is no definite cause for external hydrocephalus, therefor it is classified as idiopathic condition (2, 4). Hydrocephalus due to IVH, prematurity, meningitis, metabolic disorder, neurosurgery and trauma is not considered here (4, 5). About 40% of children with external hydrocephalus had at least one male person in their family close relative with macrocephaly (5, 8, 10, 11). This coherence was 80%-90% (2, 3).

Autosomal dominant (3, 4, 15) and multifactorial model of inheritance have been assumed (4, 8, 16).

Epidemiology

An incidence of 0.4 per 1000 live births was reported only in one study (8). It is approximately 50% of hydrocephalic condition in retrospective and population based study in Norway (14). A review of incidental findings in a tertiary pediatric neurology center showed that 0.6% of the children had external hydrocephalus (15).

Historical notes

Initially intracranial fluid collections in infants were described in 1850s (17). The term benign external hydrocephalus (BEH) was first introduced in 1917 (7, 17, 18). Recently, the most usual name is BESS.

Clinical manifestations

The main feature of BESS is macrocephaly in a normal infant (2, 13-15). An otherwise normal infant is referred to medical attention because enlarging head size. Most studies report no signs and symptoms of increased intracranial pressure such as irritability, lethargy, vomiting, tense and bulging anterior fontanel (2, 3, 5). Rare studies reported a tense anterior fontanel (19, 20), dilated scalp veins (21), and frontal bossing (22). Sunset sign is not reported in any article (4). Neurologic findings are normal, but mild motor delay is often seen and final developmental status is often normal (2-4, 15, 16, 23).

Pathophysiology

The most accepted theory about pathophysiology of external hydrocephalus is delayed maturation of the arachnoid villi not able to absorb the CSF produced continuously (3, 24). Expansion of subarachnoid space due to excessive amount of circulatory CSF is not leading to intracranial hypertension (24, 25). Maturation of arachnoid villi occurs in 18 months of age and the process was ended. There is the discrepancy between the skull and brain parenchymal growing which leading to a transient subarachnoid space enlargement (8, 26). On the other hand, external hydrocephalus may be associated with some conditions such as; hypomagnesemia, mucopolysaccharidosis, achondroplasia, agenesis of corpus callosum, sotos syndrome and glutamic aciduria (4, 7, 27, 28).

Differential Diagnosis

1. Brain Atrophy: Is the first and important differential diagnosis because of presence of subdural fluid collection in both conditions (3, 6, 7). In brain atrophy, CSF collection remains equal anteriorly and posteriorly but in BESS larger anterior convexity collections were seen (3, 5, 6). There is global widening of cerebral sulci in brain atrophy not associated with an increasing head circumference (28).

2. Benign Familial megalencephaly: This familial condition is benign and head circumference may be normal at birth but increases during infancy and ultimately should be above 98th percentile. Development and neurologic examination are normal (28, 29).

3. Subdural fluid collection (SDE): In this disorder there is CSF collection without hemorrhage in subdural space. SDE usually occurs in infants and young children after intracranial infections and less commonly after minor head injuries or neurosurgical operations (30, 31).

4. Other causes of communicating hydrocephaly

such as; achondroplasia, choroid plexus papilloma, post meningitis hydrocephalus, basilar impression, Sotos syndrome and Glutaric aciduria type 1 (32).

Neuroimaging & Diagnostic work up

Neuroimaging findings are one of the criteria for the diagnosis of external hydrocephalus (7). The first step in confronting with an infant with macrocephaly is doing brain sonography via anterior fontanel (1, 33). This modality is fast, safe and non expensive tool used worldwide. Technical improvement in brain sonography have allowed more accurate visualization of the intracranial structures and may accurately evaluate ventricular size, extracerebral fluid collection and a significant number of a structural abnormality (33). Increased subarachnoid space was used as a diagnostic criterion. Three measurement tools for evaluation are sinocortical width (SCW), craniocortical width (CCW) and interhemispheric distance (IHD) (7, 5, 17). Ventricles are normal size or mildly enlarged without periventricular lucency. Normal ranges for CCW, SCW and IHD are from 4 mm to 10 mm, 2 mm to 10 mm and 6 mm to 8.5 mm, respectively (7, 9, 26, 34).

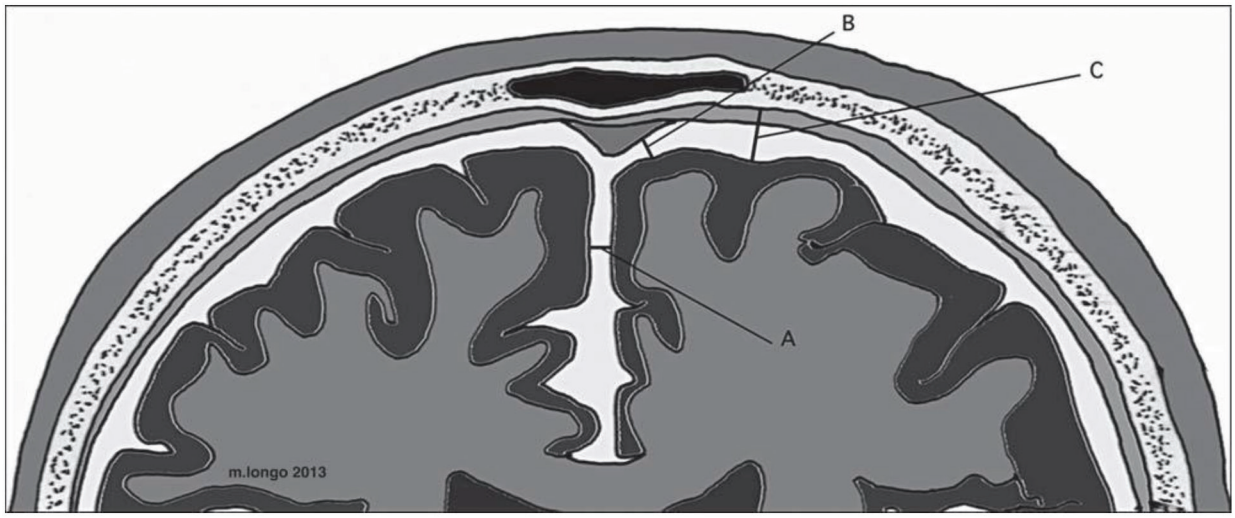

Figure 2: *Main neuroradiological criteria for BESS evaluation: A) inter-hemispheric fissure; B) sino-cortical width; C) cranio-cortical width (Schematic view).*

The second step in evaluation of infant with abnormal brain sonography is brain CT scan or brain MRI (1, 7, 15, 17). Recently use of CT scan is limited because of its radiation and probable risk of malignancies especially in infants and young children (35, 36). MRI appears essential in the differential diagnosis between benign enlargement of subarachnoid space and subdural collection in infants and preferred to CT (37-39). CT and MRI without contrast are also important for evaluating the most common complications associated with external hydrocephalus (7, 38, 39) (Figure 3).

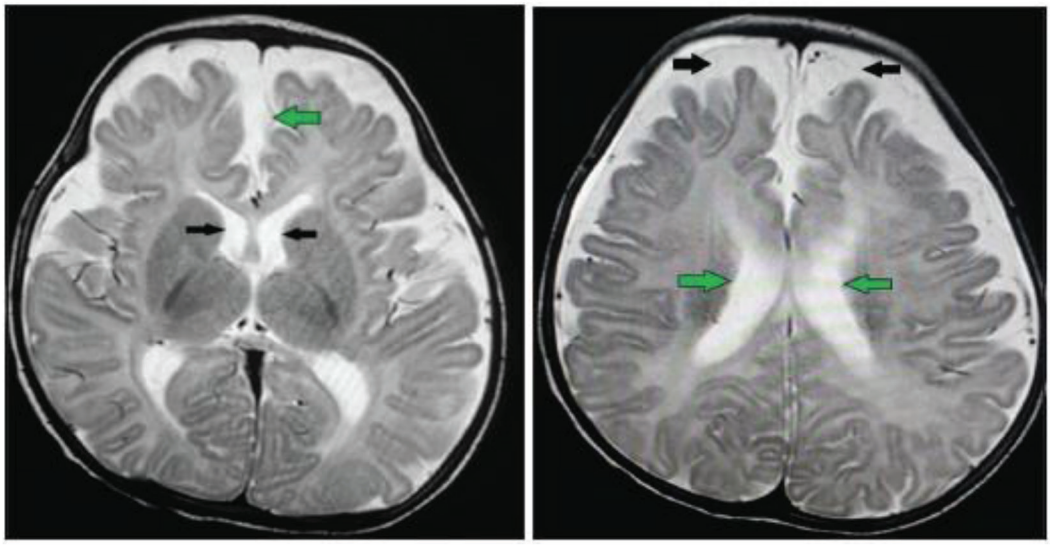

Figure 3. *BESS: (Left): Axial T2W MR image of the brain reveals mild prominence of both the lateral ventricles (black arrows) with increased anterior inter-hemispheric distance (green arrow).(Right): Axial T2W MR image of the same infant shows enlarged subarachnoid space along the anterior aspect of the brain (black arrows) with prominent of bilateral lateral ventricles (green arrows). Moreover, the anterior cranio-cortical distance (black arrows) is obviously increased.*

There is a very important note in diagnostic work up of BESS. Repeated imaging is unnecessary unless head growth deviates from the normal curve, neurological examination is abnormal, or social and language development are slow (2, 3, 13, 15, 17, 20, 33).

Final diagnostic note: Patients with typical findings in brain ultrasonography suggestive of external hydrocephalus with normal neurodevelopment without any complications and focal neurologic findings do not require subsequent brain CT / MRI (40-42).

Complications

The most common complication of BESS in infants and young children is increased risk of subdural hematoma after minimal or even without head trauma (3, 4, 12).

Outcome

The head circumference usually stabilizes before the age of 18 months (2, 9). Measurements afterwards typically lie above but parallel to the upper (95th-98th) percentiles (2, 19). Overall, 11%-87% of these infants ending up with macrocephaly (10, 11). Mild gross motor delay with minimal language delay that decreased and disappeared within 1-4 years (15, 23). Most studies report in general normal physical and neurological findings on last follow-up (10, 20, 24, 44). Some studies report failure to reach developmental milestones especially in gross motor function (10, 11, 44). Mental retardation seems relatively rare (22, 23). The symptoms related to increased intracranial pressure which often can be seen initially, all appear to be absent at long-term follow-up (4). Generally the developmental delays are transient

and children catch up milestones by the age of 2 yr (44, 45).

Treatment

BESS is a self-limiting condition (3-5, 44, 45). A few old articles suggested use of a carbonic anhydrase inhibitor (Acetazolamide) for few weeks. Acetazolamide therapy for 4-8 wk in 125 mg/bd was recommended (22, 23, 45). This drug decreases CSF production (6, 23, 24, 45). There is no clear evidence of effectiveness of this agent in final outcome because of excellent nature of disease (25). Most patients do not need neurosurgical intervention (3, 4) and ventricular shunts (2, 18, 25, 45).

In conclusion, BESS is a benign self-limited condition, mostly were seen in infants. It is characterized by macrocephaly and enlargement of subarachnoid space with normal or mildly dilated ventricles. Neuroimaging study is necessary for establishing of diagnosis. First step for evaluation of infant with macrocephaly is brain sonography. If sonographic findings are matching with clinical findings, it is enough for diagnosis and further neuroimaging modalities are unnecessary. Second step for evaluation especially if any complication or suspicious underlying structural abnormality occurs is brain MRI.

Acknowledgment

None

Authors' Contribution

Nahid Khosroshahi participated in design and coordination and she drafted this manuscript.

Ali Nikkhah critically revised the manuscript for important intellectual content.

All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

The authors declare that there is no conflict of interest.

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REVIEW ARTICLE

The effects of Constraint Induced Movement Therapy on functions of Children With Cerebral Palsy

How to Cite This Article: Jamali AR, Amini M. The Effects of Constraint-Induced Movement Therapy on Functions of Cerebral Palsy Children. Iran J Child Neurol. Autumn 2018; 12(4):16-27

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Received: 07- Feb -2017
Last Revised: 10- June -2017
Accepted: 04- July -2017

Abstract

Objectives

Constraint-Induced Movement Therapy (CIMT) is an intervention method that can enhance cerebral palsy (CP) children's hand function. CP is a pervasive and common disorder which affects many aspects of a child life. Hemiplegic CP affects one side of a child's hand and has great effect on child's independence. We investigated the CIMT's studies conducted in Iran, and indicated the effectiveness of CIMT on duration and children age?

Materials & Methods

This systematic review was conducted using the electronic databases such as Medline PubMed, CINAHL, etc. performed from 1990 to 2016. Iranian and foreigner famous journals in the fields of pediatrics such as Iranian Journal of Pediatrics (IJP), Iranian Rehabilitation Journal (IRJ) and Google scholar with some specific keywords such as CP, CIMT, and occupational therapy were searched.

Results

Overall, 43 articles were found, from which, 28 articles were removed because of lack of relevancy. Ten article were omitted because of duplication and exclusion criteria, so finally 15 articles were included.

Conclusion

CIMT is effective compared to no intervention but there are some inconsistencies regarding some parts of CIMT effectiveness such as its effectiveness on muscle tone and protective extension.

Keywords: Constraint-induced movement therapy; Cerebral palsy; Hemiplegia; Rehabilitation; Systematic review

Introduction

Cerebral palsy (CP) is one of the primary causes of childhood disability, and it has a deep effect on physical and social functions (1). Although in recent years a lot of progress in prenatal care, genetic screening, birth control

methods, NICU, and advanced centers for children care has emerged, nevertheless the prevalence of CP has remained stable between 1/5 and 2/5 per thousand live births. According to American Statistics Center, CP's prevalence is between 2.6 to 2.9 per thousand live births (2). Low birth weight or premature children are susceptible to the CP. This children's brain suffers from periventricular leukomalacia and intraventricular hemorrhage (3, 4).

Since the major skill-based activities and physical-based activities accomplished outside, need physical abilities so children with CP have fewer abilities to participate in such activities because of their psychical problems (5). These problems even affect children daily routine occupational performance, quality of life and, societal participation (6). We have different kinds of interventions for CP children such as upper limb splinting, virtual reality, kinesio taping, constraint-induced movement therapy (CIMT) and traditional techniques like Bobath technics (7-10).

In this study, articles in the field of CIMT for hemiplegic CP children were systematically reviewed. Although the prevalence of this disability is different in parts of the world, spastic hemiplegia is the most common subtypes of CP (11). Cortical and additionally subcortical lesions caused by asymmetrical periventricular leukomalacia, middle cerebral artery stroke, or intraventricular hemorrhages, happened within motor areas of the contralateral hemisphere to the affected limb are the main causes of this type of CP (12). Children with hemiplegic CP are experiencing such problems related to their upper extremity more than other parts of the body. Problems such as difficulty performing intricate movements, weak grasping ability, hypertonia, changed proprioception and decreased selective motor control (13). These children not only feel limitation in their capacity but also tend to limit the affected limb usage in daily routines activities. The desire for less use of affected limb in developing children is called developmental disregard (14). Developmental disregard can be seen as inability to use hand or affected limb potentials in daily routines activities. It generally has been compared with learned nonuse, which is a phenomenon can occur after stroke (15, 16).

CIMT is a deviation from traditional treatments, used to treat hemiplegia. Its aim is to stimulate the functional use of the affected limb and reverse the process developmental is disregard (17). In this method, the unaffected or less affected limb is restrained, so the person has to use the affected limb. This method has risen up out of the intersection of behavioral brain research/learning hypothesis and disclosures in neuroscience with respect to neuroplasticity. CIMT is a kind of paradigm shift in rehabilitation of central nervous system injuries. It changes the paradigm from emphasis on compensatory skills to a desire for partial restoration (18). CIMT is the most convincing clinical treatment to improve sensory and mobility functions in hemiplegic CP children (13, 19). Two possible mechanisms may lead to more use of the affected limb (Overcoming developmental disregard). These two are a) Overcoming the learned non-use of the more affected arm (for example increased use of the more affected arm) and b) use-dependent cortical reorganization. By using Trans cranial Magnetic Stimulation (TMS), motor cortex mapping before and after CIMT were studied and the increase of motor output area size

and MEP amplitudes were noticed (20). It shows enhanced neuronal excitability in the damaged hemisphere and the target muscles. With the use of FMRI8 activation of the motor cortex changes after CIMT (20).

CIMT drove from fundamental researches on monkeys (21). Traditionally in CIMT, the less affected or non-affected hand is restrained for 90% of the day. During this period the affected limb has to perform everyday activities (22). Difficulties of CIMT traditional protocol leads to establishment of new protocols with different training programs. One of these protocols is modified CIMT (mCIMT) (23). In CIMT treatment sessions lasts for 30 min and for ten weeks conducted three times per week. mCIMT includes three basic components of CIMT. These components are constrained, repeated practice and using behavioral techniques such as shaping (24).

Three therapeutic protocols are most widely implemented in interventions. The first is derived from the work that determined this protocol for an eight-week intervention period. During these eight weeks, the child has to participate once a week in therapeutic sessions and practice 2 h a day in a structured fashion. A five-week intervention and the child's hand must be restrained 8 h a day. In addition, the child must practice 2 h a day with his parents (25). Therapeutic interventions are given once or twice a week. Appropriate intervention time is two weeks and during each week the children practice 5 d and six hours a day in a group (25). However, we still do not know the optimal constrain duration for the best outcome, the best type of restriction and the best period of clinical training. For example, more studies need to be done to understand at what age the CIMT has the greatest influence on child's performance (20). CP children treated by CIMT have different abilities on the level of performances and restrictions. It has to be determined how effective the intervention is on each of these children.

Because of the recent popularity of this therapy for upper limb movement restrictions of CP children (18, 26, 27), more research is needed to justify more intensive treatments such as CIMT (28). This study was done with the aim of a systematic review of the CIMT procedure between CP children groups in Iran.

Materials & Methods

This study was a systematic evidence-based study. Searches was performed from 1990 to 2016. Following sources were used for data gathering.

1. **Electronic databases:** Medline PubMed, CINAHL, OVID Medline, Google Scholar, CINAHL Plus with Full Text, Cochrane databases of systematic reviews, ProQuest, Up to Date, Web of Science, OT search, OT direct, Pedro, SID, Magiran, IRAN MEDEX, MEDLIB and Iran doc.
2. **Iranian and foreigner famous journal in the fields of pediatrics:** Iranian Journal of Pediatrics (IJP), Iranian Rehabilitation Journal (IRJ), Iranian Journal of Child Neurology (IJCN), Archive Physical Medicine and Rehabilitation, Developmental Medicine, Child Neurology, physical and occupational therapy in pediatrics, American journal of occupational therapy, etc.

With the help of MESH, we used following keywords for searching in mentioned databases.

The main goal of this study was to determine the articles with CIMT intervention. Main keywords for search were CP, CIMT, Iranian CP children, constraint-induced movement therapy, OT, physical therapy, rehabilitation, Intensive intervention and mCIMT.

The inclusion criteria were applied as follows: 1) Articles that are about Iranian CP children 2) All articles since 1990 till 2016 3) Published in full text 4) Published in English or Persian 4) Contains CIMT intervention. The review included interventional studies.

Results

Overall, 43 articles were found, because of lack of relevancy and other issues the 18 articles were removed. Ten articles were omitted based on duplication and exclusion criteria, so finally 15 articles were included (Table 1).

Table 1. The summary of the results and methodology of the studies used in this study

	Authors	Year	Title	Method and protocol	Procedure	Outcome measures	Results	Conclusion
1	Rostami et al.(29)	2012	Effect of treatment environment on modified constraint-induced movement therapy results in children with spastic hemiplegic cerebral palsy: a randomized controlled trial	Randomized controlled trial (RCT) mCIMT	15 h of modified CIMT, three times/ week for 10 sessions every other day Restriction: splint	**A**: upper limb coordination and upper limb speed and dexterity **B**: amount of use and quality of movement	All variables changes were significant. Include: upper limb coordination, upper limb speed, and dexterity, amount of use, quality of movement	Modified CIMT is effective in improving upper limb function in spastic hemiplegic children.
2	*Hosseini* et al. (30)	2012	Effectiveness of ICF-based modified constraint-induced movement therapy on hand functions in children with hemiplegic cerebral palsy	Single subject (SS design) mCIMT	2 groups First group: conventional OT interventions Second group: 6H of mCIMT during 10 d Restriction: splint	**A**: bimanual coordination, upper extremity coordination, dexterity and, visual motor control **B**: dexterity ***C***: muscle tone ***D:*** ROM ***E:*** Caregiver perception	All variables changes were significant. Include: 2 point discrimination, PROM of wrist, bimanual coordination, dexterity, Caregiver perception, muscle tone	Implementing adapted CIMT through a child-friendly approach was proved to improve hand functions and activities of daily living.
3	Sabour et al. (31)	2013	The effect of combination of constraint-induced movement therapy with bimanual intensive therapy on upper limb function of children with hemiplegic cerebral palsy	RCT CIMT	2 groups Control group: OT interventions Intervention group: CIMT and BIM for 10 d for 45 min Restriction: sling	***A:*** for UE function, ***B:*** for muscle tone	UE function changes were significant but muscle tone didn't change significantly.	The findings suggest that combination of CIMT and bimanual intensive therapy improved upper limb Function in the hemiplegic CP children.

4	Hosseini et al. (32)	2011	Effect of mCIMT on weight bearing and protective extension in hemiplegic CP children	Clinical trial mCIMT	2 groups Control group: OT interventions Interventions group: OT interventions plus 45m mCIMT for 6 wk 3 sessions per week Restriction: splint	***A***: weight bearing and protective extension	Weight-bearing changes were significant but a protective extension change was not.	mCIMT had effect on weighing bearing but it had no effect on protective extension.
5	Rostami et al.(33)	2010	Study of treatment environment effect on CIMT intervention outcome in hemiplegic CP children	RCT CIMT	Two groups CIMT for 10d of 3 wk for 1/5H Restriction: splint	***A:*** UE coordination, speed and skill ***B:*** quantity and quality of the motion	All variables changes were significant. Include: UE coordination, speed and skill, quantity and quality of the motion	Hand function improved in children with hemiplegic CP and better improvements at home shows enhancement of learning process and practice at familiar condition and environment.
6	Rostami et al. (34)	2011	Comparison of virtual reality technique and CIMT on upper extremity of hemiplegic CP children	RCT CIMT	3 groups 1/5H of every other day and for 4 wk. Interventions were virtual reality technique and CIMT Restriction: splint	***A:*** for speed and skill ***B:*** for quantity and quality of the motion	All variables changes were significant. Include: speed and skill, quantity and quality of the motion	Base on this study results, virtual reality technique, and CIMT are alternative to each other for improvement of upper extremity function in hemiplegic CP children
7	Garib M et al. (35)	2010	Effect of mCIMT on quality of affected upper extremity in hemiplegic CP children	SS design mCIMT	2 groups Control group: OT interventions Intervention group: OT interventions plus 3H of mCIMT for 6 wk Restriction: splint	***A***: grasp, WB, protective extension, separated motions	All variables changes were significant. Include: grasp, WB, protective extension, separated motion	This study showed that mCIMT is more effective on quality of upper extremity grasp capability.
8	*Rostami*, et al. (36)	2012	Efficacy of combined virtual reality with constraint-induced movement therapy on upper limb function of children with hemiparetic cerebral palsy	SS design CIMT	4 groups of CIMT, VR, CIMT+VR, and controls. Subjects in experimental groups participated in 1/5 H therapeutic sessions every other day during a four-week period Restriction: splint	***A:*** for quantity and quality of the motion, ***B:*** Test for speed and skill	All variables changes were significant. Include: quantity and quality of the motion speed and skill	Incorporating VR and CIMT may improve upper limb functioning of children with hemiparetic cerebral palsy.

9	*Kavoosipor*, et al. (37)	2010	Effects of constraint-induced movement therapy on improving in-hand manipulation skills of hemiplegic hand: A single-subject experimental study	SS design CIMT	21d of intervention with CIMT protocol plus30 min group program Restriction: splint	***A:*** for quality of finger to palm, palm to finger, simple shift, simple rotation, complex shift and complex rotation transfer. Frequency of finger to palm and palm to finger transfer. Rate of simple shift, complex rotation, and complex shift. Duration of simple rotation.	These were significant immediately after intervention: quality of Palm to finger and Complex shift transfer and Duration of simple rotation	A client-centered intervention will facilitate the use and quality of finger and hand motion. Moreover, group activities can encourage clients to participate more and better in therapy.
10	*Akbar Fahimi* et al.(38)	2011	Emotional Problems After Using Constraint Induced Movement Therapy in Children with Hemiplegic Cerebral Palsy	RCT CIMT	CIMT 6 h/day for 8 wk consecutive d Restriction: splint	***A:*** behavioral assessment	Statistical analysis showed no significant difference in total score and subscales scores of SDQ between two groups.	Using CIMT in children with hemiplegic CP could result in more usage of affected limb without any Behavior problems, especially emotional problems.
11	Hosseini et al.(39)	2010	Effect of Child-friendly Constraint-Induced Movement Therapy on unimanual and bimanual function in hemiplegia	SS design CIMT	Two groups of CIMT and conventional therapy. Intervention at CIMT was done six h every day, for 10 d, whereas another group received conventional occupational therapy. Restriction: splint	***A:***bilateral coordination, upper limb coordination, and upper limb dexterity and unimanual function ***B:*** Caregivers' perception ***C:*** test for hand function	Changes of Unimanual function, Jebson-Taylor test, Dexterity, Bimanual function, Bilateral coordination, Caregivers' perception (How Much), Caregivers' perception (How Well) were significant but Bimanual coordination changes were not.	Child-friendly CIMT has fairly good effects on unimanual function and some variables of bimanual function of children with hemiplegia.
12	Kavousipor [illegible]	2012	Can constraint induced movement therapy improve In-Hand Manipulation skills: a single subject design	SS design mCIMT	21 d of intervention 30 min every Day at clinic 6 H at home Restriction: splint	***A:*** quality of finger to palm, palm to finger, simple shift, simple rotation, complex shift and complex rotation transfer. Frequency of finger to palm and palm to finger transfer. Rate of simple shift, complex rotation and complex shift. Duration of simple rotation.	These variable changes were significant: Quality of palm to finger transfer. Frequency of palm to finger transfer. Quality of simple shift. Rate of simple shift. Quality of complex shift. Rate of complex shift. Duration of simple rotation. quality of complex	A client center intervention will facilitate the use and quality of fingers and hand motion. Also, a group activity can motivate participants to participate more and better.

13	Sabour et al.(41)	2013	Comparison of combination of CIMT and BIM training with CIMT alone on fine Motor Skills of children with Hemiplegic Cerebral Palsy	RCT CIMT	2 groups CIMT and BIM training and CIMT alone First group: 3H of CIMT and 3H BIM Second group: 6H of CIMT BOTH for 10 d Restriction: Sling	***A:*** test of hand function to evaluate the unilateral performance of the affected limb, ***B:*** bilateral coordination, upper limb coordination, and upper limb dexterity and speed, ***C:***scale for muscle tone	These variables changes were significant: Fine motor skills , bilateral function domain of Bruininks –Oseretsky and Jobson-Taylor and Bruininks-Oseretsky test items. But muscle tone didn't significantly change	Results showed that these two treatment approaches improved fine motor skills in the hemiplegic children with cerebral palsy. Therefore, it is suggested to use a combination of CIMT and BIM training instead of CIMT alone in order to make the tasks more attractive and easier for the children
14	Abootalebiet al. (42)	2010	The effects of "Constraint-Induced Movement Therapy" on fine motor skills in children with hemiplegic cerebral palsy	RCT mCIMT	2 groups intensive occupational therapy program for both five hours per day for 21 d intervention group: 5H of CIMT for 21 d restriction: sling	***A:*** fine motor skills, ***B:*** muscle tone ***C:*** was for neurofeedback	Peabody developmental motor scales changes were significant. But changes of modified Ashworth scale, H reflex and H/M ratio was not.	Results suggest that the use of CIMT needs to more studies and should be considered experimental in children with hemiplegic CP
15	Garib M et al. (43)	2011	Effect of mCIMT on grasp quality in hemiplegic CP children	RCT mCIMT	2 groups occupational therapy program for both for 6W intervention group: 3H CIMT for 6W Restriction: splint	***A:*** for grasp quality	grasp quality significantly improved	The results of this study showed that mCIMT has effect on grasp quality in hemiplegic CP children

Discussion

The aim of this study was to investigate the CIMT interventions carried out in Iran. CIMT is an effective intervention method for CP children. Eight studies had used traditional CIMT and 7 studies had used mCIMT protocol.

CIMT for CP children has little to do with age. The age range for CIMT in the studies is between two years to 14 years and in all of them, CIMT had acceptable results. The therapeutic effect of CIMT was not age-related (44). They also confirmed the results of sung and DeLuca's study (2, 3). There were no differences between boys and girls for this therapy and CIMT was equally effective for both genders. Gender was reported as an ineffective factor in CIMT too (21, 45).

Articles reviewed in the study had used only two kinds of restrictions. Most of them had used a splint for restriction (12 of them) and three of them had used sling for restriction. For this reason, maybe the use of splints and slings are easier for children. Other kinds of restriction were reported too. Restrictions such as Short arm casts and Long arm casts, holding child's hand, using a glove or mitt and Slings (20). CIMT effect on the left or right side is the same because no study mentioned to affected side.

For concerning the effect of CIMT on muscle tone the result of four articles about the impact of CIMT on muscle tone was inconsistent. CIMT had an influence on muscle tone (30). CIMT was considered as an ineffective method on muscle tone

(31, 41, 42). CIMT was considered as an ineffective way of reducing muscle tone (46). However, this study did not find definite conclusion about the impact of CIMT on muscle tone. This issue requires further studies in the future.

CIMT has a good effect on protective extension. It was not effective on protective extension (32); however, it was effective on protective extension (35). CIMT was effective on protective extension (20), however, in another study; CIMT was not effective on protective extension (47). In this case, literature are not unified and more studies are needed.

There were no significant adverse effects for CIMT in the studies. Nevertheless, early implementation of CIMT for children who are in the stages of development of bilateral hand can cause a negative effect on the growth of bilateral hand development. Therefore, CIMT should be used with caution for children under twelve months (48). In addition, restriction of the non-affected hand for a long time (e.g. plastering) had negative effects on the development of motor skills (46).

CIMT was examined efficacy on children's participation in activity of daily living, and no studies had measured CIMT effect on occupational performance (30). Improvement of sub-skills do not always accompany improvement of daily living activities occupational performance, so future studies would also consider this issue. Because the ability of an intervention to improve the level of independence is undeniably important.

In conclusion, in recent years CIMT has attracted much attention in Iran and different studies with different methods have been conducted. Researchers have used various restriction time and different outcome measures. There are some inconsistencies in some aspects of CIMT effectiveness such as muscle tone and protective extension. These areas need future research. In addition, more studies are needed to investigate negative effects of CIMT from physical and social aspects.

Follow-ups are an important aspect of rehabilitation intervention. Less than half of the studies had included follow-up in their method. In the end, if we consider hands as brain's tool for independence in everyday activities more attention has to be paid on follow-ups and other occupational aspects.

Acknowledgement

No funding was secured for this study

Author`s Contribution

Malek Amini: conceptualized the study, helped in literature review, and approved the final manuscript as submitted.

Ali Reza Jamali: carried out the literature review, collected the data, wrote the manuscript.

The authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of interest

The authors declare that there is no conflict of interests.

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ORIGINAL ARTICLE

Clinical Trial of Efficacy Evaluation of Omega-3 with Risperidone on Seizures Frequency in Children with Refractory Epilepsy and Attention-Deficit/Hyperactivity Disorder

How to Cite This Article: Fallah R, Eiliaei S, Ferdosian F. Clinical Trial of Efficacy Evaluation of Omega-3 with Risperidone on Seizures Frequency in Children with Refractory Epilepsy and Attention-Deficit/Hyperactivity Disorder. Iran J Child Neurol. Autumn 2018; 12(4):28-36

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Received: 11-Aug-2016
Last Revised: 23- Apr-2017
Accepted: 14- June -2017

Abstract

Objectives

We aimed to answer the question whether or not previous antiepileptic drugs with combination of omega-3 and risperidone are more efficient than previous antiepileptic drugs with risperidone alone in decreasing of seizures monthly frequency of children with refractory epilepsy and attention-deficit/hyperactivity disorder (ADHD).

Material & Methods

In a randomized clinical trial (IRCT201604212639N18), participants referred to Pediatric Neurology Clinic of Shahid Sadoughi Hospital, Yazd, Iran from Jun 2015 were distributed randomly into two groups. In group I, one capsule of omega-3 daily and 0.5 mg of risperidone was divided into two doses with previous antiepileptic drugs and in group II, 0.5 mg of risperidone was divided into two doses with previous antiepileptic drugs were given. The drugs use was continued for three months and the children were followed up monthly for three consecutive months. Primary outcomes included seizure monthly frequency and good response (more than 50% of reduction in seizures monthly frequency). Secondary outcome was clinical side effects.

Results

Overall, 23 girls and 33 boys with mean age of 9.24±0.15 yr (29 children in omega-3 group and 27 children in control group) were evaluated. Omega-3 therapy was effective in decreasing of seizures monthly frequency (10.41±3.92 times vs. 17.01±4.98, P=0.03). Good response was seen in three children (11.1%) in control (95% confidence interval: 8%-22.8%) and in 9 children (31%) in omega-3 (95% CI: 47.83%-14.17%) group, which showed that omega-3 was more effective in seizure control. (P=0.001). Frequency of side effects was not different in the two groups (14.8 % in control vs. 20.7% in omega-3 groups, P=0.5).

Conclusion

Omega-3 might be used as an effective and safe drug in seizures control of children with refractory epilepsy and ADHD.

Keywords: Epilepsy; Refractory epilepsy; Omega-3; ADHD

Introduction

Epilepsy defined as at least two unprovoked seizures occurring at least 24 h apart, has a cumulative lifetime incidence of 3% and annual prevalence of 0.5%-1% (1). Intractable or refractory epilepsy defined as recurrence of at least one seizure in a week in spite of taking two or three appropriate antiepileptic drugs with sufficient dosage and includes approximately a third of newly treated epileptic (2-4).

On the other hand, attention-deficit/hyperactivity disorder (ADHD) characterized by inattention, including increased distractibility and difficulty sustaining attention, poor impulse control and decreased self-inhibitory capacity, and motor overactivity and restlessness, is the most common neurobehavioral disorder of childhood (5) continued to adult and an adult ADHD types include inattentive and emotional dysregulation (6). Worldwide-pooled prevalence of ADHD in a meta-analysis study was 3.4% (7). Epileptic children have more ADHD-related symptoms and association between epilepsy and ADHD (8-11).

The three most important polyunsaturated fatty acid of omega-3 including alpha-linolenic, eicosapentaenoic and docosahexaenoic acids are necessary for the correct function of the organism and take part in many brain physiological processes. The body cannot synthesize these omega-3 fatty acids in enough amounts, and therefore they must be added to the diet and omega-3 polyunsaturated fatty acids may inhibit neuronal excitability and may have anticonvulsant effects and a potential treatment use of medically resistant epilepsy (12).

Eicosapentaenoic acid alone (13), eicosapentaenoic acid plus docosahexaenoic acid (14) and omega-3 polyunsaturated fatty acids (15) were effective in reduction of severity or frequency of epileptic seizures. On the other hand, ratios of both blood omega-6 to omega-3 and arachidonic acid to eicosapentaenoic acid have been elevated in ADHD children (16). A clinical trial study showed that dietary supplementation with omega-3 fatty acids reduced ADHD symptoms (17).

Effect of omega-3 fatty acids on seizures control and omega-3 efficacy in reduction of ADHD symptoms have been assessed in other studies, but, we did not find any research which evaluated effectiveness of these fatty acids in children with combination of refractory epilepsy and ADHD. Therefore this clinical trial was conducted to answer the question whether or not previous antiepileptic drugs with combination of omega-3 and risperidone is more efficient than previous antiepileptic drugs with risperidone alone in decrease of seizures monthly frequency of children with refractory epilepsy and ADHD.

Materials & Methods

In a randomized single-blinded parallel group, clinical trial, all consecutive 7-11 yr old children with combination of refractory epilepsy and ADHD referred to Pediatric Neurology Clinic of Shahid Sadoughi Hospital, Yazd, Iran from Jun 2015, were enrolled. Sample size was determined by help of statistical consultant based on Z formula and a confidence interval of 95% with 80% power type one error of 5%, and an effect size (difference in frequency of good response between the two groups) of 30% based on result of our pilot study, was assessed in 30 children in each group.

Inclusion criteria for eligible participants we as follows: Children aged 7-11 yr, had refractory

epilepsy based on definition of the International League against Epilepsy (1), had ADHD based on DSM-IV criteria, had at least score of 20 in ADHD diagnostic rating scale via parent interview (5) and were able to walk. Exclusion criteria consisted of receiving all kinds of supplement within the past two months, other psychiatric disorders, status epilepticus during research period, allergy to omega-3 capsule or risperidone, change in antiepileptic drugs regimen, use of phenobarbital or topiramate, irregular drugs usage and discontinuation of omega-3 capsule or risperidone usage for more than one week.

The trial used computer-generated equal simple randomization by random numbers and allocation ratio was 1:1 for the two groups. Randomization and blinding were done by an investigator with no clinical involvement in the trial. Data collectors, outcome assessors, and data analysts were all kept blinded to the allocation. Concealment was done by placing the group number for each serially participating child in a numbered and sealed opaque envelope opened by the pediatric neurologist of research immediately before study enrollment. The drug was delivered by the mothers of the patients and primary and secondary outcomes were assessed by the intern of research not informed of the drug group assignment. The children were randomly distributed into two groups. In group, I, one capsule of omega-3 daily and 0.5 mg of risperidone divided into two doses with previous antiepileptic drugs and in group II, 0.5 mg of risperidone divided into two doses with previous antiepileptic drugs, were given. The drugs use was continued for three months and the children were followed up monthly for three consecutive months.

The capsule of omega-3 that used in this research was fish oil (Omega-3) from 21st Century Co, the USA that each capsule contains 1000 mg of omega 3 fish oil, 180 mg of eicosapentaenoic acid and 120 mg docosahexaenoic acids. Moreover, risperidone tablet of 1 mg was from Abidi Co, Iran.

Primary outcomes included seizure monthly frequency and good response (more than 50% of reduction in seizures monthly frequency) compared before and after three months of treatment. Secondary outcome was clinical side effects.

The data were analyzed using SPSS version 17 (Chicago, Illinois, USA) statistical software. Recorded data were assessed for normal distribution using the Kolmogorov-Smirnov test and Chi-square test was used for data analysis of categorical variables and continuous and mean variables were compared using independent *t*-test between the two groups. Differences were considered significant at *P*-values of less than 0.05.

Informed consent was taken from the parents of the children before enrolling and this study has been approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran. This research is registered in Iranian Clinical Trials (www.irct.ir) under registration number: IRCT201604212639N18.

Results

Sixty-four children were enrolled, but three children did not return and five children stopped taking medications after 3-4 wk. Therefore, they were excluded and finally, 56 children including 23 girls and 33 boys with mean age of 9.24±0.15 (29 children in group of omega-3 and 27 children in control group) were evaluated in the two groups (Figure 1). By Kolmogorov-Smirnov test, the data had normal distribution.

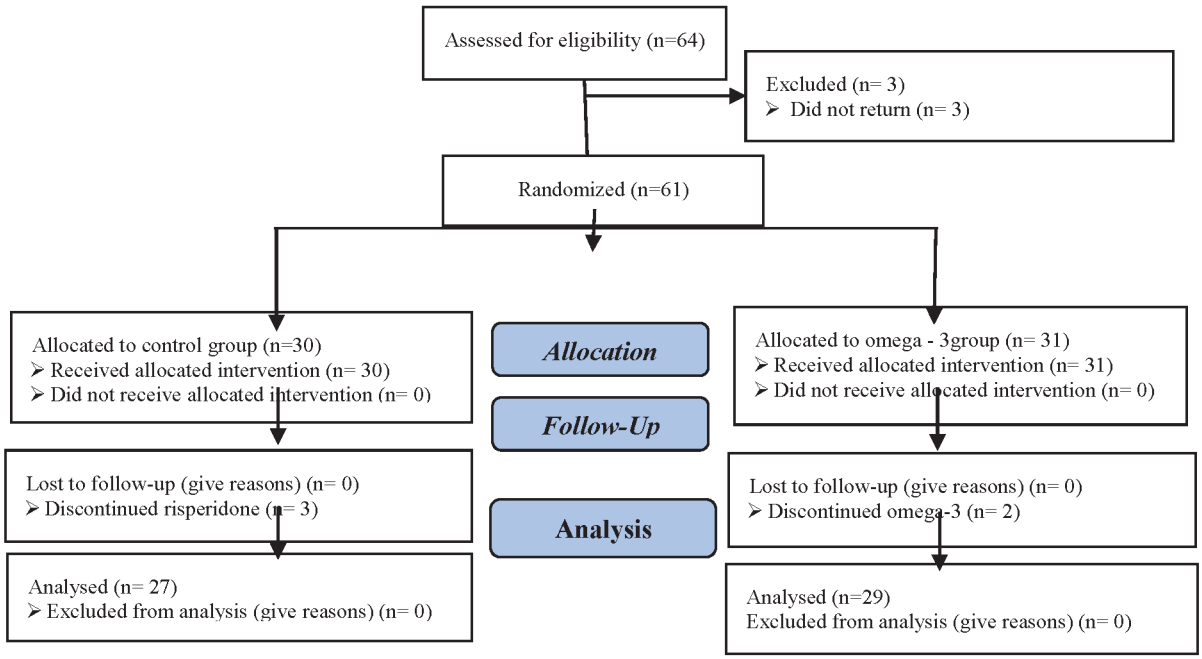

Fig 1. CONSORT flow diagram

Comparison of some characteristics of the children in the two groups is shown in Table 1 which indicates that no statistically significant differences were seen from viewpoints of sex distribution, seizure type, epilepsy classification and developmental status.

Table 1. Comparison of some characteristics of children in the two groups

Groups / Data		Control	Omega- 3	P-value
Sex	Girl	10	13	0.9
	Boy	17	16	
Seizure type	Generalized	13	12	0.7
	Partial	4	6	
	Mixed	10	11	
Epilepsy classification	Symptomatic	14	17	0.8
	Cryptogenic	8	9	
	Idiopathic	5	3	
Developmental status	Delay	19	19	0.9
	Normal	8	10	

Table 2 shows comparisons of the mean of age, weight, and seizure monthly frequency in the two groups and indicates that no statistically significant differences were seen from these viewpoints.

Table 2. Comparison of mean of age, weight and seizure monthly frequency in the two groups

Groups / Data	Control	Omega- 3	P-value
Age in years (mean ± SD)	10.57 ± 2.44	10.11 ± 2.13	0.4
Weight in kilogram (mean ± SD)	8.59 ± 1.56	8.34 ± 2.45	0.6
Monthly seizure frequency (mean ±SD)	16.7 ± 6.68	15.8 ± 8.49	0.09

Comparison of frequency of good response and monthly seizure frequency at the end of research period in both groups is shown in Table 3 which shows that omega-3 therapy was effective in decreasing of monthly frequency of seizures. More than 50% of reduction in monthly seizure frequency (good response) occurred in 3 children (11.1%) in control (95% confidence interval: 8%-22.8%) and in 9 children (31%) in omega-3 (95% CI: 47.83%-14.17%) group, respectively, combination of omega-3 and risperidone with previous antiepileptic drugs was more effective in controlling of seizures. (*P*-value=0.001)

Side effects included sleepiness in two children, anorexia in one child and constipation in one child were seen in 14.8% of control group and sleepiness in two children, diarrhea in two children and nausea and vomiting in two children (20.7%) were seen in omega-3 group and frequency of adverse events was not different in the two groups (*P*=0.5).

Table 3. Comparison of frequency of good response and monthly seizure frequency in both groups

Groups / Data		Control	Omega- 3	P-value
Good response	Yes	3	9	0.001
(> 50% of reduction in monthly seizure frequency)	No	24	20	
Monthly seizure frequency at the end of research (mean±SD)		17.01±4.98	10.41±3.92	0.03

Discussion

Based on our results, daily usage of 1000 mg of omega-3 fish oil, 180 mg of eicosapentaenoic acid and 120 mg docosahexaenoic acids for 12 wk with combination of previous antiepileptic drugs and risperidone was more efficient than previous antiepileptic drugs and risperidone alone in reducing of seizures monthly frequency of children with refractory epilepsy plus ADHD.

We did not find any research that evaluated the efficacy of omega-3 in children with refractory epilepsy and ADHD.

In a case-control study in Alexandria, Egypt, the efficacy of omega-3 supplements as fish oil in decrease of frequency and severity of epileptic seizures of 70 children with refractory epilepsy were evaluated. Omega-3 caused significant reduction in seizure frequency and fish oil could elevate the seizure threshold in medically resistant epileptic children, but there was not any statistically significant difference in seizures severity improvement between cases and control (18).

In California, USA, the efficacy of high dose and low dose of fish oil versus placebo (corn oil, linoleic acid) in 24 patients with refractory epilepsy was compared and low-dose fish oil (3 capsules/d, 1080 mg eicosapentaenoic acid plus docosahexaenoic acid) was more effective than placebo in reduction of seizures. High-dose fish oil did no cause difference than placebo in reducing seizures (19). In London, UK, daily usage of 1000 mg of eicosapentaenoic acid for 3 months caused 12%-56% reduction in seizure frequency in six from ten patients and in one other person had markedly reduced seizure severity (13).

Efficacy of 12 wk treatment of daily one gram of eicosapentaenoic acid and 0.7 gr docosahexaenoic acid on 57 epileptic patients were evaluated by randomized, placebo-controlled clinical trial. “Seizure frequency was reduced over the first 6 wk of treatment in the supplement group, but this effect was not sustained” (14).

Significant reduction in both frequency and severity of seizures occurred in all five epileptic patients with central nervous system diseases treated with 5 gr of omega-3 polyunsaturated fatty acids at every breakfast for 6 months (15).

A 7-year-old boy with Lennox-Gastaut syndrome and refractory epilepsy was reported successfully treated with a polyunsaturated fatty acid -enriched modified Atkins diet without any life-threatening side effects (20).

However, in USA, eicosapentaenoic acid plus docosahexaenoic acid, 2.2 mg/day in a 3:2 ratio for 12 wk was not superior to placebo in twelve adults with refractory focal or generalized epilepsy (21). A possible explanation for this discrepancy may be related to differences in the age of the patients, dosage of omega-3, ratio of eicosapentaenoic acid to docosahexaenoic acid ratios and treatment duration.

Approximately 60% of the dry weight of brain includes lipids and about 30% of brain lipid consists of polyunsaturated fatty acids (omega-3, omega-6...) and omega-3 can regulate neuronal function via stabilizing neuronal membranes by inhibiting the voltage-dependent sodium and calcium currents, modulating of membrane biophysical properties, regulation of neurotransmitter release, signaling of neurotransmitter and synthesis of biologically active oxygenated derivatives and possible

antiseizure effects of omega-3 may be due to increasing in seizure thresholds and lowering of inflammatory cytokines in epileptic patients (22) and by these mechanisms, omega-3 fatty acids can decrease seizure-associated cardiac arrhythmias and sudden cardiac deaths in epileptic patients (23).

In this study, omega-3 was safe and no life-threatening clinical side effect was seen in children. Safety of omega-3 even at high doses has also been reported in other studies (18, 19-21).

In conclusion, our results are promising and omega-3 can be considered as an effective and without life-threatening side effects drug in control of seizures in children with refractory epilepsy and ADHD. It is worth to do other clinical trials with larger sample sizes, different omega-3 fatty acid preparations, different doses and longer treatment duration.

Acknowledgement

This study was funded by a grant from the Deputy for Research of Shahid Sadoughi University of Medical Sciences, Yazd, Iran. It is a part of thesis presented for obtaining the Medical Doctor (MD) degree by Shiva Eiliaei.

Author`s Contribution

Razieh Fallah: participated in design of the study, the acquisition, analysis, and interpretation of the data.

Shiva Eiliaei: participated in selection the subjects and taking informed consent, also statistical analysis of data.

Farzad Ferdosian: drafted and revised the manuscript and also supervised the final approval of the version to be published .

All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest

The researchers received no financial support from the drug company. The authors declare that there is no conflict of interests.

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ORIGINAL ARTICLE

Autistic Children Are More Responsive to Tactile Sensory Stimulus

How to Cite This Article: Asmika A, Oktafiani LDA, Kusworini K, Sujuti H, Andarini S. Autistic Children Are More Responsive to Tactile Sensory Stimulus. Iran J Child Neurol. Autumn 2018; 12(4):37-44

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Received: 22- Mar -2017
Last Revised: 21-Nov-2017
Accepted: 22- Jan -2018

Abstract

Objective

This research was an experimental study that was aimed to detect differences response of tactile sensory stimulus between normal children and children with sensory brain development disorders such as Autism Spectrum Disorder (ASD).

Materials & Methods

A total of 134 children, in two groups including 67 healthy children (control) and 67 children with autism were studied. Tactile sensory stimulus responses in children were tested directly using a Reflex Hammer. In addition, tactile sensory sensitivity was also assessed via questionnaire Short Sensory Profile (SSP) filled out by the child's parents. All response data were analyzed using Fisher's Exact Test; questionnaire data was analyzed with the Mann-Whitney U Test.

Results

Autistic children were more sensitive to palpation and pain than children who were not autistic. Furthermore, the value of SSP was also significantly higher ($P<0.05$) in autistic children, which means that they always responded to all categories in the SSP questionnaire than children who are not autistic.

Conclusion

Autistic children are more sensitive to tactile sensory stimulus and all categories of SSP than children who are not autistic.

Keywords: Autistic Children; Tactile Sensory; Short Sensory Profile

Introduction

Sensory organs are peripheral components of the somatosensory system whose function is to record physical and chemical changes in the external and internal environment of the body and turn them into electrical impulses that are processed by the nervous system (1). One of the largest sensory

systems is located on the skin, which delivers information on stimuli such as touch, vibration, pressure, pain, and temperature. This sensory aspect reception pattern has occurred since the age of children to adult (2).

In children, this neurological system helps the process of categorizing and developing responses to information obtained from the environment. Each child has a different ability to process and to respond to information or stimuli from the environment (3). Normally, children who receive stimulation on the skin or body surface process it in the brain and then generate appropriate responses to the sensation or stimulus received (4). However, some children with sensory processing disorder find it difficult to interpret and to respond appropriately to the stimulus received (5).

Generally, children with autism syndrome have problems associated with neural development in the brain such that the processes of sensory integration in the brain are distracted (6). The Tactile Sensory system is a sensory system set up by tactile response and pain receptors in the skin (7); the Short Sensory Profile (SSP) is a method of measuring sensory system response using a questionnaire, usually used to determine the contribution of the sensory aspects of children in everyday life and can be used to explain differences in tactile sensitivity (8, 9).

We aimed to show differences in sensory integration in children with sensory brain development disorder (Autism Spectrum Disorder), especially in tactile sensory sensitivity and SSP values.

Materials & Methods

Research Subjects

This study used random sampling to get the respondents. Respondents were normal children who were in elementary school and autistic children at the Center for Autism Services, Extraordinary Schools and Inclusion Elementary School in Malang, Indonesia aged 6–13 year. This study was conducted in July-August 2016. Respondents totaled 134 children: 67 were normal children and 67 autistic children. Gender and demographic characteristics was not necessary for respondent selection as long as all respondents lived with their parents.

This study received approval from the Research Ethics Committee of the Faculty of Medicine, Brawijaya University, Indonesia No.502/EC/KEPK/09/2015.

Tactile Sensory Measurement

Tactile sensory sensitivity was measured using a Reflex Hammer due to it was the most popular tool in Indonesia and could provide reliable data. The testing procedure was applied along with SSP questionnaires (Supp.data1). The Touch Assessment Test (Reflex Hammer) touches and scratches the skin of the arm of the blindfolded respondents for 1.5 seconds at a random location. Then the respondents were asked to tell where on their arm they felt the stimulus touches. Reflex Hammers were used to view the tactile sensitivity to touch and pain response.

SSP questionnaires were given and filled by caregivers, consisted of 38 questions designed to uncover the sensory experiences in the children's daily lives, using a tactile scale score. (Tomchek and Dunn, 2007).

Statistical Analysis

The data obtained were tabulated and analyzed.

The data's sample characteristics, in general, were analyzed with descriptive statistics. The differences in tactile sensory response (tactile and pain response) between both groups were analyzed using Fisher's Exact Test, and in the SSP using the Mann-Whitney U Test. The entire analysis was using the statistical program SPSS for Windows version 17.0 (Chicago, IL, UA).

Results

General Characteristics of Respondents

76.1% of the respondents were male while 29.9% of the normal children's parents did not graduate from elementary school. It was contrasted with the autistic children's parents who had graduated from junior high school, senior high school and vocational school to master degree. Almost all respondent's fathers have job (Table 1).

The difference of the Tactile Sensory Response between Normal and Autistic Groups

The differences of the tactile sensory response of

Table 1. General Characteristic of Respondents

Category	Group			
	Normal (n=67)		Autistic (n=67)	
	n	%	n	%
Ages (yr)				
6-8	1	1.5	22	32.8
9-11	42	62.7	32	47.8
≥12	24	35.8	13	19.4
Gender				
Male	29	43.3	51	76.1
Female	38	56.7	16	23.9
Fathers Recent Education				
Uneducated	20	29.9	1	1.5
Elementary School Graduate	12	17.9	5	7.5
Junior High School Graduate	14	20.9	12	17.9
Senior High School Graduate	15	22.3	31	46.3
Degree Graduate	6	9.0	18	26.8
Mothers Recent Education				
Uneducated	20	29.9	1	1.5
Elementary School Graduate	14	20.9	8	11.9
Junior High School Graduate	9	13.4	14	20.9
Senior High School Graduate	23	34.3	23	34.3
Degree Graduate	1	1.5	21	21.4
Father's Occupation				
Have no job	17	25.4	2	3.0
Have job	50	74.6	65	97.0
Mothers Occupation				
Unemployed	51	76.2	41	61.2
Work	16	23.8	26	38.8

Note: n: real number of participant; %: percentage ratio in the group

touch and pain between both groups were analyzed using Fisher's Exact Test. Statistical test results showed significant differences in all categories of tactile sensory responses in both groups (P = 0.001). Children with autism were very sensitive to the touch and pain responses (Table 2).

Table 2. The difference of Tactile Sensory Response Touch and Pain Category

Tactile Sensory Response	Group				Fisher's Exact Test (p)
	Normal		Autistic		
	n	%	n	%	
Touch	None	66	98.5	8	11.9	0,001
	Sensitive	1	1.5	59	88.1	
Pain	None	61	91.0	3	4.5	0,001
	Sensitive	6	9.0	64	95.5	

* Within a row, values with different superscripts are significantly different, P < 0.05. n =134

Note: n: real number of participant; %: percentage ratio in the group

The Differences of Short Sensory Profile (SSP) Values between Normal and Autistic Groups

SSP values were analyzed using Mann-Whitney U Test. Statistical test results showed significant differences of SSP values in both groups (P = 0.001) (Table 3). Autistic children were always responding to all category of SSP questionnaire (Table 4).

Table 3. The Differences of Short Sensory Profile (SSP) Value

SSP Category	Group		Mann-Whitney Test (p)
	Normal (Mean Rank)	Autistic (Mean Rank)	
Tactile	47.15	87.85	0.001
Taste	52.48	82.52	0.001
Move	57.48	77.54	0.001
Sensastion of Seeking	39.11	95.89	0.001
Auditory	41.43	93.57	0.001
Weakness	51.76	83.24	0.001
Visual	48.96	86.04	0.001

Table 4. Differences in the Autism and Control group's Short Sensory Profile (SSP) based on parent reports.

Category	Autism (Mean-rank)	Control (Mean-rank)	*P*
Touch Sensitivity			
• Looks unhappy when asked to tidy up (eg wearing clothes and combing hair)	62,14	73,95	0,010
• Prefer long-sleeved clothes when hot; Short sleeves when cold	62,59	73,49	0,002
• Avoid barefoot roads, especially in grass or sand	58,66	77,48	0,0001
• React emotionally or aggressively to touch	54,74	81,46	0,0001
• Likes to avoid splashing water	67,52	68,49	0,662
• Have difficulty standing near other people	64,56	71,49	0,017
• Rub or scratch the other person touches	66,54	69,49	0,254
Sensitivity of Flavor			
• Avoiding certain flavors of food or the smell of food that is usually part of a child's diet	53,74	82,47	0,0001
• Just want to eat foods with a certain flavor	61,64	74,44	0,008
• Restrict eating textured foods (eg solid/flaccid, rough/soft foods or temperature (hot/cold))	60,17	75,95	0,001
• Picky eater especially related to the texture of the food	60,65	75,46	0,002
Motion Sensitivity			
• Become more anxious or depressed when the feet do not step on the ground	66,54	69,49	0,254
• Fear of falling when in height	62,65	73,43	0,028
• Do not like the head in upside down position	60,65	75,46	0,001
Sensation of seeking			
• Love foreign sounds or search for sound sources	51,31	84,94	0,0001
• Pay attention to all movements and disrupt routine activities	51,27	84,98	0,0001
• Too excited during mobile activities	50,88	85,37	0,0001
• Touching people and objects / likes to touch certain parts of an object and person	45,35	90,99	0,0001
• The face with no expression	56,68	79,49	0,0001
• Moving from one activity to another	49,81	86,46	0,0001
• Letting her clothes wrap around or tight on the body	62,11	73,98	0,003
Hearing Information			
• Interrupted or having difficulty functioning in noisy environments	66,57	69,46	0,431
• Does not seem to hear or empathy with what people say	48,80	87,49	0,0001
• Can not work in noise situations	56,74	79,43	0,0001
• Having difficulty completing tasks when radio is turned on	56,70	79,47	0,0001
• Does not respond when his/her name is called	58,16	77,99	0,0001
• Has difficulty changing attention	45,85	90,48	
Weakness in Power Movement			
• Seem to have weak muscles (not trained)	62,60	73,48	0,005
• Easily tired especially when standing / using the limbs	60,63	75,49	0,0001
• Has a weak hand grip	58,65	77,49	0,0001
• No ability to lift heavy objects	65,05	70,99	0,031
• Need a backrest to help him / her	63,58	72,49	0,010
• Weak resistance / easy to feel fatigue	65,56	70,48	0,123
Visual/Auditory Sensitivity			

• Respond negatively to loud sounds that are suddenly heard	51,76	84,48	0,0001
• Often closing the ears to protect the ear from noise	59,19	76,94	0,0001
• Easily glare or uncomfortable with sunlight or bright lights	67,54	68,46	0,773
• Observe the movements of everyone around the room	56,24	79,94	0,0001
• Often rub or squint to protect eyes from light	65,13	70,92	0,221

Discussion

Early detection for autism condition is necessary for further treatment. This study provided basic knowledge to understand autism condition. In individuals with good sensory integration, the brain has the ability to organize and process sensory input and use that input to respond appropriately to outside stimuli. However, some children with sensory processing disorder find it difficult to interpret and to respond appropriately to the stimulus received (5). Children with autism syndrome have problems associated with neural development in the brain so that the processes of sensory integration in the brain are distracted. This disturbance in the system impacts the recording and interpretation of sensory inputs, resulting in problems in learning, development, and/or behavior (10).

The results showed that the group of autistic children were more sensitive to touch and pain response than the group of normal children. Moreover, the results of the questionnaire SSP completed and reported by parents about their children in this study also showed that the group of autistic children always responded to all categories in the questionnaire SSP: tactile, taste, move, sensation of seeking, auditory, weakness, and visual aspect compared to the group of normal children. Younger children are more likely to exhibit sensory hyperresponsiveness than older children. Children with ASD were reported that they are over-responsiveness (11). The results of that study indicated that ASD children were significantly more sensitive/over-responsive compared to controls. There was also a correlation between over-responsiveness with the tactile stimuli from parent reports and a lack of socializing (12). Besides, children with autism could be clearly seen to have sensory processing disorders. They tend to be more responsive to stimuli received compared to normal children.

The development of the somatosensory system in early infancy is hypothesized to be foundational for social and communication skills later in life (13). However, neurodevelopmental abnormalities in the brain may have a targeted influence on symptoms associated with ASD occurred in autism (14). Certain neurological development disorders in the brain cause many problems in processing tactile sensory input, causing sensations from the environment that are normally recorded and interpreted in the brain or central nervous system to be distracted: unable to filter inputs, often failing to process important information and prone to stress and anxiety (5,10). The neurobiological mechanisms against the incidence of abnormality of tactile system and symptoms of ASD are still not known clearly and definitely. These abnormalities

may be exacerbated due to the dysfunction in the excitation/inhibition balance of the central nervous system of those with ASD (15).

In conclusion, autistic children are more sensitive to touch, pain, and all categories of SSP than children who are not autistic. Basic understanding of children with ASD will help the parent in handling in daily life. This study finding could be used to recover motoric of children with ASD. The parents have main role in handling ASD children. Further research is necessary to explore more sample and comprehensive study by considering the social background of family. The information of relation between social background and ASD children condition could resolve this issue.

Acknowledgement

The authors thank to University of Brawijaya for supporting this study through DIPA Program (No. 042.01.2.400919/2017)

Authors' Contribution

All three authors were involved in data collection, and writing the article.

Conflict of Interest

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

Comparison of the Quality of Sleep and Intensity of Headache between Migraine, Tension Headache, and Healthy Children

How to Cite This Article: Cheraghi F, Shamsaei F, Fayyazi A, Molaaei yeganeh F, Roshanaei G. Comparison of the Quality of Sleep and Intensity of Headache between Migraine, Tension Headache, and Healthy Children. Iran J Child Neurol. Autumn 2018; 12(4):45-54

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Received: 21- Mar -2017
Last Revised: 11- Jun -2017
Accepted: 09-Oct-2017

Abstract

Objectives

Headache and sleep problems are commonly reported in children, and both can adversely impact the child's life. We aimed to compare the sleep quality and intensity of headache between school-age children with migraine as well as tension headache and healthy children.

Materials & Methods

In this cross-sectional study, 198 children 6-12 yr old in three groups were enrolled from Aug 2015 to Mar 2016. Migraine and tension headache groups from the Outpatient Clinic of Imam Khomeini of Hamadan, western Iran and healthy group from elementary schools were randomly selected (66 children in each group). Data were collected using demographic questionnaire, Child Sleep Habits Questionnaire (CSHQ), Numeric Scale of Pain Intensity and Wong-Baker Faces Pain Rating Scale. The data were analyzed using SPSS by descriptive statistic and multivariate ANOVA, one way ANOVA, Chi-square, Kruskal-Wallis and linear regression tests.

Results

Approximately, 45.5% of children with migraine and 37.9% of them with tension headache had experienced severe headache. Only a significant relationship was seen between mean scores of headache intensity and sleep quality in migraine group ($P<0.05$). There was a significant difference in mean scores of sleep quality among three groups ($P<0.001$).

Conclusion

The children with migraine experienced more unsuitable sleep in duration of severe headache. Highlighting the co-morbidity between intensity of headache and sleep problem of children with migraine and tension headache is important to improve treatment strategies and to know the impact of headache on their normal life.

Keywords: Tension headache; Migraine; Sleep quality; Child

Introduction

"Headache is one of the most common neurological symptoms reported in childhood and adolescence" (1). Prevalence range of migraine in the pediatric population is 3.3%-21.4% and it increases from childhood to adolescence (2). "The prevalence of migraine headache was 12.3% (95% CI: 10.2–14.4) and tension-type headache was 4.2% (95% CI: 2.9-5.6) in Yazd City, Iran" (3).

Due to the impact on quality of life and reduced efficiency in children, migraine and tension headaches are considered as two fundamental problems in childhood (4). Tension headaches are usually not enough severe to cause serious disruption in social life of children (5). However, children with migraine headache have worse consequences, especially in terms of quality of life and school attendance, compared to those without migraine (6). Migraine headache in most cases is accompanied by other symptoms such as nausea and vomiting. Fatigue and physical activity can also exacerbate these symptoms (7). Regardless of the economic impact of pharmaceutical costs, repetition and persistence of headache in children has adverse effects on personal performance, social and educational situation (8). Besides, migraine and tension headaches have adverse effects on sleep quality and mental health. In fact, both sleep disturbances and headache disorders are widespread health problems during childhood (6).

The existence of a complex and multilateral relationship between sleep quality and headache intensity has been recognized for over a century, although the nature of this association is still enigmatic. It is known as sleep deprivation or a prolonged sleep can favor the onset of headache, in particular, migraine attack in many cases, and especially in children (6). On the other hand, headache may be one of the causes of sleep problems (9). Sleep difficulties in children with migraine and tension headaches when they suffer from severe headache included insufficient sleep, difficulties falling asleep, anxiety and stress related to sleep, restless sleep, night waking, nightmares, and fatigue during the day (10). Moreover, sleep quality and insomnia factors affect their quality of life as well as the intensity of headache (11). Many studies were done with different approaches and different age ranges, but found similar results. A significant relationship between insomnia and tension and migraine headaches is reported (12, 13), and patients with migraine had high midnight insomnia, sleepwalking and sleep disorders overnight and low pain threshold (14). Almost 50% of people with migraine headache had insomnia, 38% slept less than six hours per night and 50% of patients had sleep disturbances during migraine headache attacks. Moreover, children with tension headaches in the age range 8-15 yr were sleepy during the day and had little energy (15).

Total sleep time in children with migraine and tension headaches are lower than those have no headaches. Insomnia is a common complaint in children with tension and migraine headaches (16). Because of the differences in the duration, frequency, and intensity of pain in migraine and tension headaches, effect of it on sleep quality of children is different. Since, sleep plays an important role in physical, behavioral and emotional growth of children, it also affects the cognitive function, academic achievement, and concentration power.

When the headache diagnosis is established, management must be built on the frequency and

severity of a headache and the influence on the child's lifestyle. The pediatric nurses in outpatient clinics have a key role in management and providing counseling for the children and their families to prevent further headaches and any discomfort (17). The importance of childhood headaches and other reports about sleep quality and associated factors, so we decided to compare the quality of sleep and headaches between school-age children with migraine well as tension headaches and healthy children.

Material & Methods

In this cross-sectional study, the sample was 198 school-age children divided into three equal groups as follows: 66 patients with migraine headache, 66 participants with tension headache and 66 healthy children. The study was conducted from Aug 2015 to Mar 2016.

The sample size was calculated (18) and the following equations: By considering α=0.05, 80% of power and 10% loss, the required sample size in each group was calculated to be 66.

$$\delta = \mu_{\max} - \mu_{\min} = 12$$

$$s = 18$$

$$d = \frac{\delta}{s} = \frac{12}{18} = .3$$

$$f = \frac{d}{2}\sqrt{\frac{k+1}{3(k-1)}} = 0.3$$

Children with migraine and tension headaches based on inclusion criteria were selected using simple random sampling method from their medical records archive in the Outpatient Clinic of Imam Khomeini in Hamadan, western Iran. For healthy group, four elementary schools (2 females' and 2 males' schools) was selected using cluster random sampling method from the schools of two regions of Education Office in Hamadan City. Then based on the inclusion criteria and the list of student names, subjects were selected using simple random sampling from each class of selected schools.

Inclusion criteria were children aged 6 to 12 yr enrolled in one of the six grades of elementary school; non-admitted to the hospital at the time of the study; diagnosis of migraine and tension headaches by a neurologist (history and physical and neurological examination, diagnostic criteria for migraine and criteria for tension and chronic daily headaches; a history of migraine and tension headaches at least four months; experienced at least two attacks of migraine or tension-type headaches during last months; lack of other acute and chronic diseases; and having parents/caregivers with basic education to be able to read and write. Additional inclusion criteria for healthy group were absent a history of physician visit because of chronic or recurrent headaches; no school absence due to any headache experiences.

Data collection tools included demographic questionnaire, Numeric Scale of Pain Intensity, Wong-Baker Faces Pain Rating Scale and Child Sleep Habits Questionnaire (CSHQ). Demographic questionnaire contains 22 questions about age, sex, the length of disease, age at an onset headache, cause of headache, type of drug use, duration of drug use, history of migraine in the family, parent level of education, the job of parents, etc. The self-reporting Numeric Scale of Pain Intensity (Version 11) includes of numerical rating ruler in the range of 0- 10. Zero score indicates without pain and 10 indicate the highest level of pain. The scale is

applicable for children 9 yr and older who are able to count the numbers. The child was asked to select a score that better express the severity of their last experience of headaches (19). Wong-Baker Faces Pain Rating Scale is a self-reporting scale for children 3-8 yr old. It had six images from smiley face (indicating pain-free status and its score are equal to zero) to tearful face (the highest level of pain and its score is equal to 10) (20). The Child Sleep Habits Questionnaire (CSQH) is a parental report questionnaire about a child's average sleep in the close recent usual week (21).ـ It has 33 items with three Likert options (usual, sometimes and seldom) in eight subscales: (a) Bedtime Resistance (BTR), (b) Sleep Onset Delay (SOD), (c) Sleep Duration (SD), (d) Sleep Anxiety (SA), (e) Night Wakening (NW), (f) Parasomnia (PS), (g) Sleep-Disordered Breathing (SDB), and (h) Daytime Sleepiness (DTS). There are 2 items (Item 5 and 8) that are common to the BTR and SA subscales. A total score can be obtained by summing up the scores of the 33 items and the score range was 33-99. Subscale's scores can be obtained by summing up their respective items. Higher scores indicate more sleep problems (22).

Numerical Rating Scale of Pain Intensity and Wong-Baker Faces Pain Rating Scale has been used in several studies (19, 22-23). Spearman correlation coefficient of 0.90 represented a perfect reliability for Wong-Baker Faces Pain Rating Scale (22). In the present study for both scales, Cronbach's alpha was 0.87. Spearman correlation coefficient of 0.97 represented a perfect reliability of the Persian version of CSQH [23]. In our study, Cronbach's alpha was 0.84 for CSQH (23).

Demographic and CSQH questionnaires were completed by one of the parents. The tools for self-report evaluation of headache intensity were Wong-Baker Faces Pain Rating Scale in children 6-8 yr old and Numerical Scale in children aged 9-12 yr old. Data gathering was made under parents' supervision.

Data analysis

Statistical analyses were performed using SPSS version 16 (Chicago, IL, USA). Data were presented as means ± SDs, frequency distributions and in order to compare the characteristics of studied groups, one-way and multivariate ANOVA, chi-square, Kruskal-Wallis and linear regression tests were used. In order to assess the relationship between sleep quality and headache Spearman correlation coefficient was used. In all statistical tests, significance level was 0.95.

Ethics

The study was approved by the Ethics Committee of Hamadan University of Medical Sciences (IR.UMSHA.REC.1394.188). Written informed consents were obtained from the parents or legal surrogates of the study subjects.

Results

The majority of subjects with migraine (57.6%), tension headache (60.6%) and healthy groups (45.5%) were female and in the age range of 8-10 yr old (48.5%). In tension headache group, the majority of subjects did not consume any medication (84.8%). In both groups with migraine and tension headache, the incidence of headache attacks at day was more than at night. Moreover, in 66% of children with migraine headache, there was a positive history of headache in their family. The mean hours of sleep at night were 6.751.31± h in migraine group, 7.7± 1.27 h in the tension

headache group and 8.02±0.89 in healthy group.

One-way ANOVA analysis showed a significant difference in mean scores of sleep quality of children between three groups (F (2195) = 29.675, *P*<0.001). Based on Post Hoc test, the sleep quality in children with migraine was lower than in other two groups (Table 1). The highest mean score of sleep quality subscales belongs to daytime sleepiness subscale in migraine group (14.33 ± 3.59) and then in tension headache (12.52 ± 2.52). Kruskal-Wallis nonparametric test showed a significant difference in the mean score of all eight subscales of sleep quality between three groups (*P*< 0.05).

Table 1. Comparison of sleep quality between three groups

Groups	Sleep quality			*P*-value
	Minimum	Maximum	Mean ± SD	
Migraine headaches	22	78	57.14 ± 8.72	F= 29.67 df_1 = 2 df_2= 195 *P*<0.001
Tension headaches	43	63	52.55 ± 4.8	
Healthy	37	39	48 ± 6.22	

The findings in relation to the intensity of migraine headache showed that 45.5% of children with migraine and 37.9% of them with tension headache had experienced severe headache (Table 2). Chi-square test showed no significant difference between the intensity of children's headache in these two groups.

Table 2. Comparison of headache severity between Migraine and Tension type groups

Headache Severity	Migraine		Tension type		*P*-value
	N	%	N	%	
Low	4	6.1	15	22.7	
Moderate	29	43.9	22	33.3	
Severity	33	50	29	44	*P*= 0.048
Total	66	100	66	100	

According to the Spearman correlation, there was a significant relationship between mean scores of intensity and sleep quality in migraine group (P<0.05). In other words, in children with migraine headache, the sleep quality was decreased due to severe headaches (Table 3).

Table 3. Relationship between sleep quality and headache severity in Migraine and Tension type groups

Group	Sleep quality and headache severity	
	R	*P*-value
Migraine	0.0002	*P*= 0.935
Tension	0.203	*P*= 0.041

Sleep quality of children in migraine group was significant related with onset and duration of headache, type and dosage of medication, history of migraine headaches in the family, amount of sleep during day and night (P<0.001), and the age of first headache attack (P<0.05) (Table 4).

Table 4. Liner Regression result in migraine group

Variable	Beta In	S. E.	T	*P*-value
Constant	61.085	0.579	105.381	.000 v
Length of migraine disease (month)	0.008	0.008	0.991	0.322
Duration of headache (minute)	0.042	0.009	4.570	.000*
Duration of using medication (month)	2.424	0.244	9.910	.000*
Dosage of medication	0.025	0.001	17.21	.000*
The age of first headache attack (year)	-0.455	0.056	8.048	.000*
History of migraine in the family	0.203	0.222	0.915	0.36*
Amount of sleep during day (hour)	0.528	0.068	7.741	.000*
Amount of sleep during night (hour)	-1.702	0.065	31.07	.000*

Dependent Variable: sleep quality Significant in P< 0.001

Discussion

Children with migraine headache experienced more sleep disturbances than those with tension headache and healthy children. Sleep quality in children with migraine headache was lower particularly when they experienced severe headaches. Sleep is one of basic and essential needs for the survival and health of children. Moreover, sleep quality has a key role in health

maintenance as well as healing (8). Therefore, reducing sleep quality for any reason can endanger children's physical and mental health. Although, different surveys in large pediatric populations have confirmed the strong association between headache and different sleep disorders, such as parasomnias, insomnia, sleep-breathing disorders, and daytime sleepiness (24,25). The association between headache and sleep quality was examined in children and adolescents with migraines aged 5-15 yr old. Sleep quality in children with migraine was lower than that of healthy children (26). One of the largest clinical studies published to date reported sleep complaints among 1283 migraine patients presenting for headache treatment (27). In contrast, in another study, the type of sleep pattern was effective in headache occurrence and poor sleep was known as the main cause of headache (28).

Among adolescents and children with migraine and tension-type headache, insomnia is the most common sleep complaint, reported by one-half to two-thirds of patients with headache in outpatient clinic (29). However, in the present study, all type of sleep problems happened more frequent among school-age children with migraine compared with tension headache and healthy children. However, daytime sleepiness was the common sleep complaint among the children with migraine and tension headache. Similar to the present study, the sleep problems were more frequent among school-aged with migraine compared with non-migraine and no headache groups (30).

Our findings showed that there was a relationship between sleep quality and pain intensity in children with migraine and tension headaches, inconsistent with another study (31). The headache severity and time of onset of headache were two important factors of sleep disorders in children and adolescents with migraine aged from 10 to 18 yr old (32).

After controlling for child demographics, we found that the months of migraine disease and duration of headache, type and dosage of medication, history of migraine headaches in the family, amount of sleep during day and night and the age of first headache predicted the sleep quality of children in migraine group. The duration of headache attacks was one of predicting factors of school-age children with migraine's lifestyle (33). As medications can have adverse consequences on sleep of children with migraine, headache 6-13 yr old patients taking any medications were compared with headache patients taking no medications. Contradicted with our finding, they did not find any difference in the frequency of sleep disturbances between the headache patients who used medications with those who did not use any medications (30).

Although this study has reached its aims, but as a limitation, it was conducted only on a small size of population because of as shortage to time. Therefore, to generalize the results for larger groups, we suggest repeating the study involved more participants at different ages.

In conclusion, Migraine and tension headaches are the most common acute and recurrent headache pattern experienced by school-age children. The relationships between headache and sleep quality are showing poorer sleep quality and daytime sleepiness. Highlighting the comorbidity between headaches and sleep disorders is important to improve treatment strategies. Therefore, the clinical evaluation of childhood headache should include a

careful analysis of sleep habits and patterns and the evaluation of the presence of sleep disturbances, in order to develop better treatment methods for both sleep and headache.

Acknowledgement

The present study was conducted at the Mother and Child Cares Research Center, Hamadan University of Medical Sciences, Hamadan, Iran. This work was supported by Hamadan University of Medical Sciences, Hamadan, Iran (No. 9407143767).

Author`s Contribution

Fatemeh Cheraghi and Farshid Shamsaei: Study concept and design, Development of original idea and writing the manuscript.

Afshin Fayyazi and Fahimeh Molaaei Yeganeg: Help in study performance and data collection. Ghodratolah Roshanaei: Advisor of statistical analysis.

All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest

None of the authors have any conflicts of interest to declare.

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ORIGINAL ARTICLE

The Effect of Non-Nutritive Sucking and Maternal Milk Odor on the Independent Oral Feeding in Preterm Infants

How to Cite This Article: Khodagholi Z, Zarifian T, Soleimani F, Khoshnood Shariati M, Bakhshi E. The Effect of Non-Nutritive Sucking and Maternal Milk Odor on the Independent Oral Feeding in Preterm Infants. Iran J Child Neurol. Autumn 2018; 12(4):55-64

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Received: 06-Mar-2017
Last Revised: 19- Jul-2017
Accepted: 05-Sep-2017

Abstract

Objectives

Given the positive effects of stimulation with breast milk odor and non-nutritive sucking (NNS) on preterm feeding skills, we examined the effect of NNS and milk odor, on the time of achieving independent oral feeding in preterm infants.

Materials & Methods

This study was conducted at two Neonatal Intensive Care Units of Tehran, Iran in 2016. Overall, 32 neonates with gestational ages of 28-32 wk were enrolled in two groups; NNS with and without olfactory stimuli (breast milk odor). The stimulations were performed in both groups during the first five minutes of gavage, three times per day, and over ten consecutive days. Weight gain, time of achieving oral feeding and chronological age at discharge were as measures of the effectiveness of the interventions. The results of the interventions were analyzed and compared using SPSS.18.

Results

NNS with breast milk odor resulted to a lower post-menstrual age at the first oral feeding, independent oral feeding and discharge from the hospital, but had no effects on their daily weight gain and weight at the time of discharge.

Conclusion

These results show the effectiveness of combining milk odor and NNS as two important stimuli in achieving oral feeding and earlier discharge from the hospital.

Keywords: Breast milk; Milk odor; Preterm infant; Oral feeding; Non-nutritive sucking

Introduction

Although neonatal death, particularly premature neonates, is still a major concern in developing countries (1), with the advancement of medical technology, the number of surviving premature infants is on the rise (2). Premature infants are born into their new environment as immature

organisms and should learn to adapt themselves to the new conditions (3). While trying to establish a connection with this new environment and have a natural process of growth, the infant also faces nutritional problems (3). Sucking is a vital activity in the early development of infants (4). Premature infants frequently face oral feeding problems due to their underdeveloped oral skills and the lack of coordination between sucking, swallowing and breathing (5). Effective feeding is impossible in infants prior to 34 wk and premature infants are fed by gavage. Gavage feeding is associated with complications such as respiratory conditions in low-birth-weight infants (6), feeding problems and irritations around and inside the mouth (6, 7), hyperactivity, the gag reflex, bradycardia and the parents' lack of acceptance and their disappointment (3).

Moreover, premature infants undergo unpleasant oral-motor stimulations in the form of medical procedures (the insertion of breathing tubes, feeding tubes, and airway suction) during their hospitalization (7). The presence of such unpleasant stimuli and the lower maturity of these infants lead to a longer hospitalization and the imposition of emotional and financial burden on the family. The consequent health risks and environmental demands in these infants necessitate the provision of developmental supportive interventions (8). The immediate start of a widespread and relatively severe program of oral stimulation can facilitate the speed and success of transition from non-oral feeding to oral feeding (3). Non-Nutritive Sucking (NNS) has been proposed as a useful oral stimulus by speech-language pathologists (4). Numerous studies have demonstrated the advantages of NNS in weight gain, the faster achievement of independent oral feeding, earlier hospital discharge, improved breathing, improved heart rate and reduced pain (3, 8-12).

As a social activity, feeding involves smell and touch senses, both of which are essential to the early development of infants (4). The maternal odor is very helpful for hospitalized infants and leads to increased mouth movements in them and aids nipple acceptance; moreover, this odor has calming effects on stressed or crying infants and can relieve pain in premature infants (13, 14). Stimulation by maternal milk odor can affect both NNS and independent oral feeding in infants by increasing the number of sucking bursts and sucks (15) and reinforcing NNS (16). Moreover, some studies have revealed maternal milk odor to directly affect a faster achievement of independent oral feeding, an earlier hospital discharge (2, 17) and increased mouthing movements (13). Nonetheless, no studies have yet examined whether combined stimulation with maternal milk odor and NNS can be an effective treatment for the faster achievement of independent oral feeding and earlier discharge.

We aimed to determine the effect of milk odor and NNS at the time of achieving the oral feeding skill, discharge from the NICU, weight gain between the intervention and control groups.

Materials and Methods

Study Design and Participants

The present study was conducted at the NICU of Mahdieh and Shohada-e Tajrish Hospitals in Tehran, Iran in 2016, as a clinical trial (IRCT ID: IRCT2016082829574N1). Forty infants were enrolled based on the inclusion criteria; however, eight of the subjects were ultimately excluded from

the research due to discharge before the end of the intervention, the mother's inability to breastfeed, hydrocephalus, respiratory problems and transfer to other hospitals. Finally, 32 infants (Shohada-e-Tajrish hospital=4 infants, Mahdieh hospital=12 infants) remained in the study.

This research was approved by the Ethics Committee of the University of Social Welfare and Rehabilitation Sciences. Informed consent was taken from the parents before the study.

The inclusion criteria consisted of gestational age 28 to 32 wk at birth, having started gavage feeding and being able to tolerate it, a minimum birth weight of 1000 gr, a five-minute Apgar score above six and physiological stability (heart rate, blood pressure, age-appropriate respiratory rate and oxygen concentration) during the 24 h before beginning the stimulations. Infants with general congenital disorders, chromosomal disorder syndromes, chronic medical problems such as bronchopulmonary dysplasia, intraventricular hemorrhage (grade 3 or 4), necrotizing enterocolitis, asphyxia and neonatal seizures, requirements for mechanical ventilation, jaundice leading to exchange transfusion, sepsis and those needing to be transferred to other centers were excluded from the study.

After selecting eligible infants and obtaining consent forms from their parents, the subjects were divided into an intervention and a control group using simple random allocation.

Intervention

The infants were randomly divided into two groups; an intervention group that received NNS combined with olfactory stimuli (n=16) and a control group that received NNS only (n=16). All the simulations were provided by a trained speech-language pathologist after the start of gavage feeding and as per the instructions are given by a neonatologist blinded to the study. The NNS interventions were performed with the little finger covered by latex gloves and with quiet strokes to the infant's palate (9). The olfactory stimulations were performed with cotton pads (Golbahar brand) impregnated with breast milk from the infant's mother and hold it around 2-3 cm near the infant's nose. The breast milk supplies were prepared on a daily basis and kept in the refrigerator in milk storage bags (PUR brand, made in Thailand) and were then warmed up for use to reach the body temperature using a breast-milk heater (NUK brand, made in Germany) so as to preserve the natural smell of the mother's breast milk (2). In the intervention group, both simulations were given simultaneously in the first five minutes of gavage feeding, on three successive feeding occasions each day, over ten consecutive days.

In the control group, NNS was given similarly as in the intervention group with cotton pads not impregnated with any substances and with the same timing and frequency.

The infants' weight gain was recorded in the first and second weeks of the research and at the time of discharge with the help of a nurse blinded to the study and in the morning before performing the interventions. The duration of NICU stay was also recorded in days. PMA[1] at first oral feeding (i.e. the first oral feeding recorded in the infant's feeding chart), PMA at the time of achieving eight independent oral feedings per day and PMA at

1 Post-Menstrual Age: The sum of fetal and chronological age as we calculated in week + day

the time of discharge from the hospital were also recorded as measures of the effectiveness of the interventions.

Both groups received similar medical interventions and nursing care measures as per the routine NICU plan of the select hospitals.

Statistical Analysis

Data were described using the mean, standard deviation and percentage and then analyzed in SPSS ver.18 (Chicago, IL, USA). The Shapiro-Wilk test was used to assess the normality of the data, Levene's test to assess the equality of variances and the independent t-test to compare the two groups; a nonparametric test was used if the conditions were not equal.

Results

Both the intervention and control groups were studied based on basic characteristics including gestational age, birth weight and gender and their distribution were examined across the two hospitals; however, no statistically significant differences were observed between the two groups in terms of gestational age, birth weight and gender (Table 1).

Table 1. Demographic characteristics of the participants

Characteristic	NNS and Olfactory Stimuli	NNS	*P*-Value
Gestational age at Birth (week+day) ± (sd*)	(29w+5d)±(0w+6.6d)	(30w+.1d) ± (1w+4.8d)	0.5
Birth Weight (gr)	1320.9±148.0	1311.2±159.1	0.8
Gender Distribution Female / Male (number)	9/7	9/7	
Chronological Age at the Beginning of Stimulation (day)	5.13±1.821	5.25±1.880	0.8

*s Sd defined in week+day

No statistically significant differences were observed between the two groups in terms of the PMA at the time of achieving oral feeding, hospital discharge, the duration of hospital stay, daily weight gain and weight at discharge. However, the mean PMA at the time of achieving the first and eight oral feedings per day was (31w+6.8d)±(1w+0.3d)[2] and (33w+1.6d) ±(1w+0d) in the intervention group and (32w+2.7d)±(1w+4.5d) and (33w+2.9d)±(1w+4.3d) in the control groups, revealing a lower PMA in the intervention compared to the control group at the time of achieving the first oral feeding and eight oral feedings per day (2.9 and 1.3 d versus 3 and 1 d respectively). Hospital discharge according to PMA was two days less in the intervention group compared to the controls (Table 2).

The standard deviation values obtained for PMA at the time of the first and eight oral feedings, time of discharge, duration of hospital stay, and daily weight gain were all smaller in the intervention

2 (week+day)±(sd (week+day))

Table 2. Comparison characteristics of the two groups (NNS with and without Olfactory Stimuli)

Variable	NNS and Olfactory Stimuli	NNS	*P*-Value
PMA* at the time of the first oral feeding (week+ day)± (sd)**	(31w+6.8d)±(1w+0.3d)	(32w+2.7d)±(1w+4.5d)	0.4
PMA at the time of eighth oral feedings per day (full oral feeding) (week+day)±(sd)	(33w+1.6d)±(1w+0d)	(33w+2.9d)±(1w+4.3d)	0.7
PMA at the discharge (week+day)±(sd)	(33w+2d)±(1w+0.2d)	(33w+4.2d)±(1w+3.8d)	0.5
Duration of hospital stay (days)	25.5±6.0	24.5±6.1	0.6
Mean weekly weight gain in the first week of the intervention (gr)	1273.3±145.8	1286.6±152.7	0.8
Mean weekly weight gain in the second week of the intervention (gr)	1372.4±120.3	1428.0±161.9	0.2
Weight at the discharge (gr)	1565.6±93.6	1588.1±84.4	0.4

* Post-Menstrual Age: The sum of fetal and chronological age.

** Sd defined in week+day

group compared to the controls, indicating the closeness of the data to the mean value and their lower dispersion in the intervention group.

All of the infants achieved independent oral feeding and discharged at less than 34 wk of gestation in the intervention group, compared to the controls (81.3%) (P value=0.07) (Table 3)

Table 3. Independent oral feeding and hospital discharge comparison between two groups

Variable	PMA*	NNS+ olfactory stimuli	NNS	*P*-value
Independent oral feeding	Less than 34 wk and 6 d	16 (100%)	(81.3%) 13	0.07
Hospital discharge	Less than 34 wk and 6 d	16 (100,0%)	(81.3%) 13	0.07

* Post-Menstrual Age: The sum of fetal and chronological age.

Discussion

We examined the stimulatory effect of milk odor on preterm infants who received NNS so as to determine whether the treatment was effective on the achievement of independent oral feeding, weight gain, and earlier discharge. As an oral stimulation such as NNS leads to a faster transition from tube to oral feeding in preterm infants. Stimulation with maternal milk odor also improves

the infant's NNS skills and accelerates the transition from tube to oral feeding. Despite the lack of significant differences in the time of achieving the first and eight oral feedings per day between the intervention and controls groups, the mean PMA was 3, 1 day, respectively, less in the intervention group compared to the controls. Nonetheless, the infants' gestational age at birth was two days less in the intervention group compared to the controls. Although the infants in the intervention group were more preterm, they still achieved their first oral feeding and independent oral feeding earlier than the control group.

The natural odor of the mother forms part of the process of mother-infant bonding (18). The mother's milk odor can direct the infant's head to the breast and nipple from the very first minutes of birth; this smell affects the infant's motor activity and the state of consciousness pertaining to the successful location of the breast and sucking (19). The mother's natural odor was found to lead to increased mouth movements, a better breast acceptance and more calming effects on the infant (13). The mother's milk odor is also part of these odors that can lead to a better mother-infant bonding, increased mouth movements, better breast acceptance and reduced neonatal stress and is one of the reasons the intervention group achieved its first oral feeding earlier than the control group in this study.

Stimulating premature infants with their mothers' breast milk odor can lead to longer sucking bursts and a significantly larger number of sucking bursts (20). Long sucking bursts imply the infant's transition to a more mature feeding and sucking pattern (21). Stimulating preterm infants with their mothers' milk odor leads to more sucks on average and more sucking bursts and effectively improves NNS in them (15, 16). NNS is a sensory-motor stimulation that can accelerate the infant's transition from gavage feeding to bottle or breastfeeding. Maternal milk odor can increase NNS skills in infants. The simultaneous use of the two noted stimuli thus accelerated the transition to the first, and eight oral feedings in the infants examined in this study.

The results of this study are consistent with the results that stimulating premature infants with nothing but maternal milk odor led to a faster achievement of full oral feeding by chronological age (2, 17). In the present study, the infants in the intervention group also achieved full oral feeding at a lower PMA age.

In a study conducted on term infant's breastfed for two weeks, infants recognized the smell of their mother's milk and underarm and were attracted to it (19). This result confirms the findings of the present study regarding premature infants' greater tendency to breastfeeding once they are fed from her milk for the first times since they learn to recognize the smell of their mother's breast.

The improved sucking skills learnt by several sessions of providing olfactory stimuli persist after the olfactory stimuli are taken away (20), and the achievement of independent oral feeding after the end of the olfactory stimuli period by most of the subjects in this study thus confirms the ability of infants to continue oral feeding and achieve independent oral feeding at a lower PMA.

There were no statistically significant differences between the two groups in terms of daily weight gain in the two weeks of the intervention and at the time of hospital discharge, which is consistent with

the results that showed no differences between the daily weight gain of the infants in the case and control groups.

There were also no statistically significant differences between the two groups in terms of PMA at the time of hospital discharge. Nonetheless, the comparison of the means in the two groups shows that, given the greater prematurity of the intervention group in terms of gestational age in days, the infants in the intervention group were discharged two days earlier in terms of their PMA at discharge, which is consistent with the results obtained (20).

On the other hand, of the 1,347,845 infants born every year, 9.2% or 124002 are preterm (22). If all of these infants are discharged two days earlier (given the price of a NICU bed per night equal to 143.720 USD), near to 35,212,202.790USD are saved in the total treatment costs incurred due to preterm births. Thus, use of olfactory stimuli combined with NNS can be said to help the economy in the health sector and reduce treatment costs.

The lower standard deviation obtained for the time of achieving the first and eight oral feedings per day in the intervention group can be explained by noting that this group received maternal milk odor stimulation in addition to NNS for motor oral stimulation, proven to affect oral feeding in premature infants, and this supplementary stimulation must have helped compensate for a deficiency that the infant experiences outside the uterus (such as the lack of maternal odor) and achieve uniformity in the development of oral motor skills; however, no such effects were observed in the control group, which received NNS only.

A difference in standard deviation was also observed for the weight gain in the first and second weeks of the intervention and also the PMA at the time of discharge; providing olfactory stimuli together with NNS led to a uniform weight gain and growth in the infants of the intervention group.

Sucking and swallowing are abilities that develop in infants from the 28 wk of gestation onwards, but preterm infants learn to coordinate their sucking with their swallowing at weeks 32 to 34 of gestation (3, 23). A larger number of infants achieved independent oral feeding and were discharged from the hospital at less than 34 wk in the intervention group (Table 3). This finding suggests that combined stimulation with maternal milk odor and NNS can accelerate maturation in preterm infants and enable their earlier achievement of feeding skills and lead to discharge at a lower gestational age.

Gavage feeding is associated with complications such as respiratory problems in low-birth-weight infants (6), feeding problems and irritations on mouth (6, 7), hyperactivity, gag reflex abnormality, bradycardia and the parents' lack of acceptance and their disappointment (3). An earlier achieving of independent oral feeding can thus reduce the number of tube feedings, and also reduce substandard oral stimulations.

The limitations of this study were the medical problems detected in the infants, which led to their exclusion from the study, thus lead to small sample size and the lack of no-interventional control group. The researchers opted out of no- interventional control group because the effects of stimulation with NNS have been proven in other studies (3, 8-12) and because speech therapy services are

routinely provided at the NICUs of Shohada and Mahdieh Hospitals and depriving an entire group of infants of the benefits of these services would be immoral.

In conclusion, although this study showed the lack of statistically significant differences between the intervention and control groups, the use of olfactory stimuli to supplement NNS could lead to the maturation of feeding skills in premature infants at a lower PMA and subsequently accelerate their discharge. Combined stimulation with maternal milk odor and NNS is therefore recommended by neonatal therapist as a harmless intervention provided at NICUs to improve premature infants' feeding skills. Training parents on these simulations can also lead to their greater participation in neonatal care, relieve the mother's and infant's stress and increase the willingness to breastfeed and its continuation.

In order to better investigate the effectiveness of the combined use of these two stimuli, studies with larger sample sizes and a no-interventional control group are recommended.

Acknowledgement

We would like to thank physicians, nurses, and the parents of newborns in Mahdieh and Shohada hospitals. Afjeh A, Rayegani M and Elyaspour D, are also appreciated for their support and cooperation. This study was performed as a clinical trial (IRCT ID: IRCT2016082829574N1). This article was derived from a master thesis affiliated to University of Social Welfare and Rehabilitation Sciences.

Author`s Contribution

Zahra Khodagholi designed the research method, and wrote the draft of the manuscript; Talieh Zarifian and Maryam Khoshnood Shariati did the interpretation of the data; Farin Soleimani revised the manuscript critically; Enayatollah Bakhshi did the data analysis.

All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest

The authors declare that there is no conflict of interest.

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ORIGINAL ARTICLE

A Web-Based Caring Training for Caregivers of Children with Cerebral Palsy: Development and Evaluation

How to Cite This Article: Nobakht Z, Rassafiani M, Hosseini SA. A Web-Based Caring Training for Caregivers of Children with Cerebral Palsy: Development and Evaluation. Iran J Child Neurol. Autumn 2018; 12(4):65-84

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Received: : 27-Mar-2017
Last Revised: 15-Aug-2017
Accepted: 23-Sep-2017

Abstract

Objectives

Caregivers of children with cerebral palsy (CP) have to spend a long time to take care of their children. We aimed to develop a user-friendly web-based intervention for training parents of children with CP and evaluate the process of development using modified CeHRes roadmap.

Materials & Methods

The study was conducted from September 2016 to September 2017 in Tehran, Iran. We did it in four main steps including determining the needs of users, content development, design, operational development and evaluation.

Results

The website for caregiver training provided nine general topics and had the possibility that the caregivers could determine their educational priorities. Moreover, the users could share their experiences with other users and could ask questions from an expert. Ten caregivers completed a usability questionnaire after four weeks of use. The average score of 70.5 out of 100 was shown among caregivers. The average score of all statements was above three on a Likert scale between 1 and 5.

Conclusion

The website has the possibilities including registering caregivers of children with CP, the possibility to confirm registration with an SMS and the possibility to determine the caregiver educational priorities. It has the usability for training caregivers of children with CP.

Keywords: Web-based intervention; Cerebral palsy; caregiver

Introduction

Cerebral Palsy (CP) describes a group of permanent disorders of the development and posture, causing activity limitation, attributed to non-progressive disturbances that occurred in the developing fetal or infant brain (1). Children with CP are more dependent on their caregivers to perform

their Activities of Daily Living (ADL). As a result, parents of these children have to spend a long time to feed, bathe and clothe a child with the low capability of mobility (2). Therefore, taking care of these children with disability is time-consuming and is a source of stress for their caregivers. Dealing with stressful situations has a negative impact on caregivers' quality of life. Taking care of a child with CP affects physical and social welfare, freedom and independence, comfort and financial stability of the family (3, 4).

Majority of caregivers of children with CP had a low or moderate level of knowledge about appropriate caring for their children (5). Some caregivers do not receive any training in this area or the training they receive is not commensurate with their educational needs (6). To reduce or prevent their problems, these parents and caregivers are required to receive special training in caring for these children. There is evidence that shows the effectiveness of parental training in increasing parents' knowledge, reducing their stress and improving their quality of life (6-8). There are several methods for caregivers' training including face to face training, training through workshops, offering booklets, training through videos and using telehealth. The effectiveness of caring training through workshops, offering booklets and face to face training in Iran is documented(7, 9, 10). In the field of telehealth, there is growing evidence of providing web-based interventions for people with diabetes and another diagnosis in Iran (11-14). Internet penetration rate in Iran is more than 50% and increased dramatically in recent years. Internet penetration rate is an indicator that represents the percentage of the population of a country or region that uses the Internet (15).

Telehealth is a broad term that includes both telemedicine and telerehabilitation and refers to the use of electronic information and telecommunication technologies to provide health-related services (16). Telehealth as a model of service delivery can be used in various fields including evaluation (tele-evaluation), intervention (tele-intervention), consultation (teleconsultation), monitoring a client (telemonitoring) and supervision (tele-supervision) (17, 18). Interest in the use of web-based intervention is increasing along with development in information and telecommunication technologies. It is now widely used in various fields including education and counseling for different age groups and a variety of diagnoses. Therefore, this model can be used to provide caring training for caregivers of children with CP. The use of telerehabilitation in comparison with other interventions provides benefits such as better clinical outcomes, more participation, and completion of interventions, more time for consultations and more client satisfaction (19). Accessibility to professionals and avoiding unnecessary delays in receiving care are other positive points about this model (19). Rehabilitation is a long-term and continuous process which sometimes leads to the disruption of a caregiver's job, daily routines and the role of the family member. Satisfaction of clients with this model is high due to saving their time and low cost of services (19, 20).

Studies with the aim to development and evaluate a web-based intervention are summarized in Appendix 1. There are various methods for development of a web-based intervention and evaluation of the process of development. These include CeHRes roadmap, Intervention Mapping

protocol, lifecycle method, etc. the CeHRes Roadmap is one of the methodsused as guidance for the developmental process of web-based interventions (21-23). This roadmap is generally appropriate for telehealth studies in which all the requirements and details needed for development are considered (24).

This roadmap consists of five main steps as follows: The first step is to investigate the situation. The goal is to determine the problem with health care, what the contribution of technology would be to meet the problem and who will benefit from this technology. Research stakeholders with different backgrounds (financial stakeholders, patients, caregivers, etc.) are identified by the research team. The second step is to determine the value. This step refers to articulating the previous step. The third to fifth steps respectively are design, operationalization, and summative evaluation. Evaluation in this roadmap is done through two methods including 1) formative evaluation, done at each step with the aim of evaluating each step of the process; and 2) summative evaluation, which determines what can be achieved within the specified time. In this roadmap, formative evaluation is emphasized. At the end of each step experts' and users' comments are necessary for making necessary changes. Summative evaluations must consider both the uptake and impact of eHealth technologies. Uptake of eHealth technologies refers to the data received from the website, for instance, number of logins. Impact of eHealth technologies denotes the data gathered by outcome measurement (24). Intervention mapping protocol was used in two studies as a general framework (25, 26).

This is a six-step protocol. 1) Determining the needs of the study population, 2) Determining performance objectives, and change objectives, 3) Determining the methods based on the theory and practical applications, 4) Developing and pretesting program components,5) Adoption and implementation and 6) Evaluation (26). This protocol covers development and intervention but formative evaluation is less pronounced in this protocol in comparison with the CeHRes roadmap. It can be used to design any intervention. Due to the importancegiven to the intervention in IM protocol special emphasis has not been put on the design and providing a model in IM protocol. The life cycle method consists of five stages: 1) Determine the needs of the user, 2) System design, 3) System development, 4) System evaluation and 5) System Application (27). In this method, unlike the IM protocol emphasis is on system design. The content development and attention to technology needs in accordance with user needs are not considered between the first and the second stage. The process of formative evaluation in this method has not received sufficient attention. Therefore, we used CeHRes Roadmap in accordance with our research conditions.

It is essential to provide training for caregivers. Continuous attendance in rehabilitation centers, traveling distances and spending a lot of money make it difficult for a caregiver to care for a child with cerebral palsy. It should consider providing training and childcare facilities in a child's living environment, so they do not have to spend a long time and cost. This issue is important in large cities, small towns and remote areas. In big cities, difficulty intraveling over long distances and in small towns, limited numbers of experts reduce training accessibilities. Therefore, online education is essential. The internet-based health

service was theorized usage of family caregivers. They mapped three main factors influenced the use of the intervention: a) caregiver needs (personal capacity, available social support, and caregiving belief); b) information communication technology (ICT) factors (accessibility barriers and perceived efforts to use the technology); and c) style of using the technology (preference for using e-mail or the customized website). New caregivers employed interactive intervention such as using e-mail and more experienced caregivers used more reflective learning such as information on the website(28). Therefore, a web-based intervention for caregivers of children with CP is more appropriate for more experienced caregivers.

In general, the quality evaluation of the developmental process of a web-based intervention can be done through various procedures including system quality, content quality, and service quality. System quality means the technology is user-friendly, secure and easy to access. Content quality means the content is understandable, meaningful and convincing. Service quality refers to whether the service is provided sufficiently (24, 29).

This study was conducted with two aims. The first was to develop a user-friendly web-based intervention for training caregivers of children with CP. The second was to evaluate the process of development. To achieve these aims the method of development and evaluation was specified by the researcher and also the factors affecting the researcher's decision about the method was determined.

Appendix 1. Summaries of studies with the aim to development and evaluate a web-based intervention

Search strategy: Databases: Pubmed, OVID, ProQuest, Web of science, Elsevier, OT seeker, SID, Magiran, IRAN MEDEX, MEDLIB and Google scholar Keywords: (development, standardization),(validity, reliability, pilot testing, evaluation, formative evaluation, summative evaluation) and (web-based intervention, web-based program, teleintervention)			
Author	**Goal**	**Framework**	**Methods**
Skjoth 2015	Development of a web-based decision aid for participation in down syndrome screening	CeHRes roadmap	– Determine the executive team consists of research group, developers and expert group – Search the database for background information – Interviews with professionals and pregnant women – Field observations – Design model according to the comments – Evaluation by two experts and six pregnant women

Ramadas 2015	Web-based dietary intervention for people with type 2 diabetes	Transtheoretical model's stages of change and user-centered design approach	– Review literature and guideline by research panel includes a nutritionist, behavioral psychologist, public health specialist, endocrinologist and epidemiologist – Prepare twelve lesson plans in a intervention package according to the regime change process for change attitudes, knowledge and behavior in relation with diet – Pilot study to evaluate the acceptability and user-friendliness of the intervention (n=30) – Paper prototype – Mock prototype – Alpha testing web details by webmaster – Beta testing to assess acceptability and user-friendliness web design (n=30)
Poelman 2013	Development and evaluation ofinternet-based interventions to raise awareness of food portion sizes	Transtheoretical model	– Provide content based on relevant text – Content compatibility with transtheoretical model – Observation by eight experts in the prevention of obesity – Pilot study (n=5)
Lee 2013	Development and evaluation web-based self management training and dietary intervention program for the cancer survivors	Life-cycle method	– Determine the needs of users with relevant literature review and interviews with semi-structured questions with cancer survivors and specifying system function requirements with reviewing of other health web-based management programs for cancer survivors and trans-theoretical model strategies such as stage-matched education and feedback – System design – System development – Usability and accuracy evaluation of the content in a group of experts including nutritionist, exercise physiologist, nurse, web designer, web developer. Ease of use evaluation by questionnaire (n=29 breast cancer survivor)

Kelders 2013	Development of web-based intervention to prevent depression	CeHRes Roadmap	– Contextual inquiry with literature review – Value specification with semi-structured interviews with people who had mild depressive symptoms (n=18) rapid prototyping simultaneously and meeting the research team – Design with the evaluation by experts and users
Heckman 2015	Development of Internet intervention to demonstrate behaviors associated with risk of skin cancer in young adults.		– Planning the intervention: interviews with people participated in face to face training (n=25) and focus group interviews to shape content and web application – Web content development: composition of the content resulting from texts and interviews, avatar development and content understandability evaluation by the experts – Preliminary assessment and revision: cognitive interview, acceptability testing with structured interviews, usability testing by questionnaire and interview, quality control testing – Pilot testing: clinical trial (n=53)
Bravender 2013	Web-based intervention Development and use it to enhance the relationship between doctor and adolescents about healthy weights	Social Cognitive Theory Physician-barrier model	– Intervention content and moves development by expert teams – Content revision and edition by four pediatric primary care professionals – Audio clips preparation based on basic information and their code – Website design – Send web address and username and code with an email – Meet face to face and explain intervention

Danaher 2012	Development and process evaluation web-based training program of responsible beverage service		– Programdevelopment includes the design of each program module, its function, information architecture and instructional design – Focus group interviews with curators, managers and employees to determine encouraging factors to use this program and feedback about the type and presentation of content in alpha sample (n=9) – Usability evaluation by think aloud modeling techniques in beta sample (n=3, 7) – Implementation (n=112)
Fledderus 2015	Development and evaluation online Relapse-prevention program based acceptance and commitment therapy for patients with chronic pain	CeHRes roadmap	– Contextual inquiry: focus group session with patients with chronic pain (n=10) and researchers (n=2) – Value specification: based on the needs identified in the previous step. Design a prototype for a website and some prototypes for mobile application with powerpoint. Then presented to participants (n=28) and they were interviewed with semi-structured interviews about usability and clarity of prototypes. – Design of the technology: design were based on the previous steps information. Usability evaluation was done with think aloud modeling technique from user (n=5) and expert (n=9). – Pilot study for two months (n=17), telephone interview about the helpfulness of the program
Ghahari 2009	Development, standardize and pilot study of online fatigue self-management program	Problem solving	– Identify the basic components of face-to-face training for online program with free discussion (deconstruction) – Design a prototype and model (reconstruction) – Formative evaluation in three pilot stage.
Dew 2004	Develop and evaluate web-based intervention to improve the psychological consequences in heart transplant recipients and family caregivers	Problem solving	– Content development with the literature review and focus groups – Web-based intervention for 4 months – Accessibility and user satisfaction evaluation with using information from website and question from users

Springvloet 2014	Development and evaluation protocol of two versions of Web-based nutrition training intervention for adults with cognitive and environment feedback	Intervention mapping protocol	– Needs assessment, determine what is the needs of the study – Determine performance objectives, and change objectives – Determine methods based on theory and practical applications – Development of online intervention: use available commuter version, consumer panel (n=55), pre-test and understandability and ease of use evaluation (n=44)
Gelatt 2010	Development and evaluation of interactive web-based program for step families		
Walters 2014	Development of web-based intervention for substance abuse treatment in criminal justice system	Extended parallel process model Motivational interviewing Social Cognitive Theory	– Content development in the form of questions and answers – Provide audio feedback – Initial assessment (n=21) in the form of application and content
Willems 2015	Systematic development of web-based intervention providing psychological and life style support for cancer survivors	intervention Mapping protocol Problem Solving cognitive behavioral therapy	– Determine the needs, reviewing the literature, focus group interviews and survey – Determine performance objectives, and change objectives – Determine methods based on theory and practical applications – Developing program components – Approval and implementation – Assessment
Martorella 2013	Development and validity of virtual nursing intervention to improve self-management of pain after heart surgery	A nursery model	– Determine the clinical problem – Design general view – Clinical Operations – Production – Pilot study (n=30)

Materials & Methods

Our study applied steps of the CeHRes Roadmap with some modification in accordance with the research conditions. The method was implemented in four main steps. In the first step (determine the needs of users), caregivers of children with CP were asked about information concerning their training needs. In the second step (content development), content for caregivers web-based training was developed by the experts. In the third step (design), website prototype was designed and in the fourth step (operational and evaluation), a pilot study was conducted.

Approval was obtained by the Ethics Committee of the University of Social Welfare and Rehabilitation Sciences IR.USWR.REC.1395.92. Informed written consent was received from participated caregivers.

Determining the needs of users

This step was performed by one of the authors (M, R) through a separate qualitative content analysis study (30). Fifteen in-depth interviews were conducted with mothers of children with CP who participated in face to face training program. The aim was to seek information on barriers and facilitators of the use of the training by mothers. Inclusion criteria include mothers of children with CP with Gross Motor Function Classification System (GMFCS) (31) level III, IV, and V, aged from 4 to 12 yr. They were recruited from Occupational Therapy Clinics in Tehran, Iran. Mothers attended a workshop and received a booklet and then used training for three months. This period was accompanied by an occupational therapist telephone follow-up. After three months, 15 mothers were interviewed individually. The interviews were recorded and then transcribed. To get more information about this step please see the article (30).

Content development

During this step, first a questionnaire -was developed by the research team- was sent by E-mail to a number of experts with the experience of training parents and caregivers of children with CP. Four women and one man, with one of them holding a Ph.D., three being Ph.D. students and one holding a Master with the mean age of 29.6 (SD= 5.46) yr and the mean clinical experience 6.4 (SD= 4.34) yr completed the questionnaire. These researchers had used the content of face to face caring training of children with CP for caregivers in their studies. This questionnaire asked the researcher whether the training topics were helpful or not and are the training topics necessary to be maintained? In this part of the study, two of the researchers received the questionnaire by email and sent it back after completion. The other three completed the questionnaire in a face-to-face meeting. The comments received were discussed in the research team and decisions were made about changes.

In order to seek information on whether the website homepage has particular importance to attract the attention of caregivers to the necessity of the topic, a questionnaire was completed by the experts who took part in the previous step. After explaining the purpose of this questionnaire, the researchers were requested to offer their comments in two parts, first about some statements presented with images in the website homepage and second about some texts for more information. The received comments were discussed by the research team

and decisions were made about necessary changes by expert consensus.

Design

A paper prototype was first designed. Then, in a meeting with a website designer the paper prototype was discussed and requirements for the development of the website were determined. Then, a power point prototype was designed and evaluated by the research team. After that, the website was developed by the designer. The website was developed in HTML, jQuery, and bootstrap (9) and the database management system SQL server (2014). The program was written using Asp.net MVC (4).

Operational and Evaluation

In this step, the web-based training was applied to 10 caregivers of children with CP for four weeks. We decided on 10 to cover caregivers with variety of education and experience of using the internet. Inclusion criteria were included mothers of children with CP with (GMFCS) (31) level III, IV, and V, aged from 4 to 12 yr. They were recruited from occupational therapy clinics in Tehran with convenient sampling. At first, these caregivers were invited to an individual meeting with the researcher to become familiar with use of the website on either mobile phones or personal computers. After registration and user verification by the administrator, they set their educational priorities and downloaded the first priority in their first meeting. During the meeting, discussions, questions, and problems encountered by the caregivers were recorded by the researcher. Then, caregivers downloaded their next four weeks priorities. After four weeks, the usability of the website was tested on these 10 caregivers using WAMMI (32) questionnaire. The questionnaire consisted of twenty statements with a five-point Likert scale (strongly agree to strongly disagree). The scores of statements in negative terms were reversed. Higher scores reflect greater usability of the website.

Results

Determining the needs of users

Facilitating factors in training caregivers were divided into three groups: Factors related to workshops, booklet and persistent relationship between parents and therapists. Caregivers approved the appropriateness of content with their needs.

Caregivers were more motivated to do home care training program if attention was paid to parents' educational needs, their physical and mental health and if parental awareness was increased and also if the parents were counterparts in the network of caregivers with similar experience. Due to the importance of educational needs of caregivers, the possibility of determining educational priorities was considered on the website. Moreover, the possibility to communicate and express similar experiences was provided on the website.

Content development

The summaries of suggestions were discussed by the research team and decisions were made about changes. The topics provided in face to face training were maintained for web-based training. Self-care education (for caregivers) and play were added to the topics. Therefore, web-based training was prepared in nine general topics (Figure 1).According to the experts' suggestions for greater impact, the training was presented weekly.

Training was provided in accordance with the priorities of caregivers. For determining the content of the website homepage, proposed sentences and texts were discussed by the research group and three sentences were selected for presentations to accompany the picture on the homepage including "Do you want to reduce the time it takes to take care of your child?; Do you know after receiving the training program caregiver musculoskeletal pain is reduced?; And do you want your child to be more independent in her/his own care?" Moreover, some texts about CP, motor growth prediction and concepts related to daily care were added to the homepage and user page to enhance the user's personal information. To develop the required texts, the basic content of the texts were prepared by one of the researchers. Then, two experts with Ph.D. and over 20 yr of experience working with children read the prepared texts and presented their suggestions and made corrections.

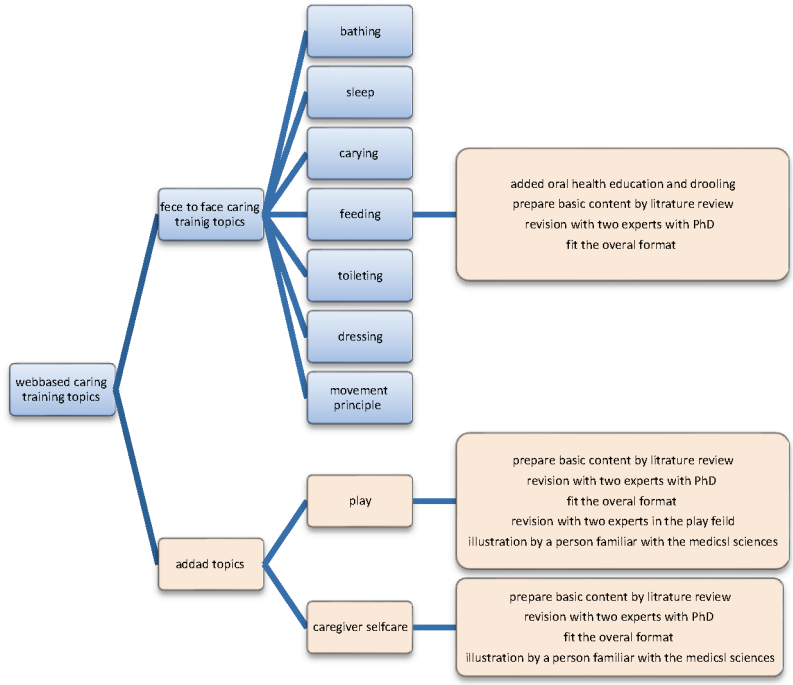

Figure 1. *Web-based caring training topics*

Design

In the first part, the paper prototype was designed and analyzed with a web designer. Some facilities were considered for the user. These facilities included having a personal page, possibility to determine training priorities based on needs, communication among members and the possibility of questions and answers with an expert. Some facilities were considered for the administrator. These facilities included user verification, answers to questions; report lists of the users, number of

entries and downloads, transferring Frequently Asked Questions to the homepage and the potential of providing new information.

In the second part, with the purpose of visualizing ideas, a PowerPoint prototype was designed. In this stage, all content put on the website prepared in the previous steps and information necessary to subscribe (approved by the group of experts) was inserted into a PowerPoint prototype with some pictures for visual attraction. After verification by the research team, the prototype was presented to the web designer to start website development.

Website development was conducted with multiple checks by the research group. In the first modification, website animated images became smaller with more emphasis on their texts by resizing and changing their font color. In the second modification, for explaining the purpose some texts were added to the homepage regarding what is designed, who are the targets groups of the website, what services will be offered on the website and how to use these services. For this purpose, a text was prepared and approved by two experts. In the third modification, children's drawings were used instead of images for the purpose of offering native pictures. Besides, short message service was added to the website to for user verification and to remind the user to download the next priority. The possibility to communicate with similar caregivers and professionals was provided. The accuracy of these conversations was controlled by administration (an Occupational Therapy Ph.D. student) and an expert with Ph.D. The guide for the website was developed. After multiple tests by the designer and the research team, the website was ready for use in the next step (http://www.cpcare.ir). All stages of development all web design standards were noted (33).

Operational and Evaluation

Participants' demographic information is shown in Table 1. In this step, questions asked by the caregivers or difficulties faced by them during the first meeting were summarized and discussed by the research team. For example, pages whose font size was said to be small or whose image size was thought to be large were resized by the designer. Or where the caregivers had to spend time to find the buttons, their access was increased. At this stage, the explanations on the register page were shortened to reduce the time required to complete the registration process. Moreover, to increase the speed and ease of use some explanations were added to the website guide. After completion, the usability questionnaire the average score of 70.5 was observed among caregivers. The average score of all statements was above three.

Discussion

This study aimed to develop web-based intervention for daily care training for caregivers of children with CP and evaluate the process of its development. At first, for decision making on how to develop and evaluate web-based intervention, the researcher reviewed some studies mentioned in Appendix 1. After summarizing the various methods used in the studies for web-based development and evaluation, a method was specified. This method was modified according to different factors including access, finance and time. The process of the development and evaluation was a dynamic process and needed researcher's decision making during the process. In this section, the process is discussed with regard to other studies reviewed in Appendix 1 to determine the factors affecting researcher's decision-making.

Table 1. Demographic information of participants in the usability test

Distribution of participants		
Caregiver age (year)	Mean (sd)	32.6 (5.72)
Caregiver education		
	< diploma	3
	diploma	2
	bachelor	4
	master	1
Caregiver experience of use of internet		
	low	3
	moderate	5
	alot	2
Child age (month)		
	Mean (sd)	80.03 (29.26)
Child sex		
	female	4
	male	6
MACS level		
	Level II	1
	Level III	3
	Level IV	3
	Level V	3
GMFCS level		
	Level III	3
	Level IV	3
	Level V	4

In accordance with research factors that influence researcher's decision, CeHRes Roadmap was used with some changes. For example, the first two steps of this method in our study were conducted as a separate study to determine the user's needs. In the second step, the content was developed. Next steps were based on the roadmap.

In our study, the first step was to determine the user's needdone in a separate qualitative study. Mothers mentioned that they will be motivated if more attention is paid to their educational needs then in our study the possibility of determining educational priorities was considered on the website. In addition, they wanted to have networked caregivers with similar experiences the possibility to communicate and express similar experiences was provided on the website. They approved the appropriateness of content with their needs. The effectiveness of the face to face content was also approved in studies (7-9, 34). The step "determine the needs of the user" has been conducted as a first step in developing a web-based intervention study(22, 23, 25-27, 35). This step was done followed reviewing relevant literature and interviews with the users. Content and related technology requirements in accordance with user

needs were developed in the next step. However, some studies have reported this as a first step (27, 36-40). Considering that the content in of face to face daily care training of children with CP for caregivers was available, and its effectiveness has been examined in various studies, in our study the first step was to determine the user's needs. After that, face to face training content was developed for web-based intervention. Performing a step like determining user requirements or contextual inquiry increases contact between the researcher and users which is a necessary component. The results of this step led to the better use of technology to meet the user's needs. In our study caregivers had the possibility to communicate with caregivers with similar experiences to facilitate greater use of training. If a researcher does not have access to face to face or web-based training, content development must be done before the design. In our study, there was access to face to face training. So it was improved for use in web-based training. All face to face training topics were maintained and some topics were added to them. According to the caregivers' and experts' views, training was provided weekly. It was essential to take these two steps prior to the design phase to consider the website requirements.

In our study modeling and analysis were performed by multiple models with paper, PowerPoint, and prototype. Use of paper and PowerPoint and prototype modeling can be quite helpful because Web-based intervention development in the early stages is abstract. Design was done in the next stages of the studies. Designing a model has been done with paper, PowerPoint or prototype model and then feedbacks from users were received for editing (21, 41, 42). These feedbacks were considered as formative evaluation. Model designing improves evaluation procedures and can help to reduce the time needed for design.

In our study, considering research conditions, evaluation was conducted in two stages including implementation and getting feedback from users and usability evaluation. For evaluating the process of web-based intervention studies have used various methods including assessing acceptability and website usability through a pilot study and getting feedback from users (41), assessing the usability and accuracy of the content in the group of experts, and user-friendliness with completing questionnaires by the user (27), content understandability assessment by experts, acceptability assessment with the structured interviews, usability evaluation by questionnaires and interviews (37), usability evaluation via think aloud modeling technique (43), usability and clarity evaluation with semi-structured interviews and usability evaluation through think aloud modeling technique (23) and accessibility and user satisfaction evaluation using information from website (36). Thus evaluations were done in terms of accuracy, intelligibility, and clarity of content as well as design usability and user satisfaction. The evaluations have been conducted in various ways including interviews, cognitive techniques; think aloud modeling technique, completing questionnaires and meetings with users and experts. Data were also obtained from the website. In our study, after first session implementation feedbacks from users received and after four weeks usability evaluation was done. It shows that our website has acceptable usability and it is easy to use by mothers with different level of education and internet experience.

The process of the web-based intervention development is a dynamic process. In our research, we had to add some possibilities to match the needs faced during development. For instance, users of our website had the possibility to ask their questions of an expert. Hence, when the expert answered their questions, they were not aware of the response. The research team decided to incorporate short message service (SMS) module into the program. The users received an SMS informing that the expert answered their questions. Moreover, this service was used to remember the user to download the next priority and user verification by the system.

The website has the possibilities including registering caregivers of children with CP with the registry form including GMFCS, Manual Ability Classification System (MACS) (44) (was recorded according to the parent questionnaire in website) and IQ level (SPARCLE study)(45), the possibility to confirm registration with an SMS, the possibility to determine the caregiver educational priorities and to remind the caregiver to download priority weekly. The users can share her/his experiences with other users and can ask questions of an expert. The effectiveness of the web-based caring training for caregivers of children with CP must be determined in a randomized controlled trial. We would also suggest assessing parental satisfaction as well as the impact it has on the children.

In the present study, it was not possible to take into account the level of caregiver experiences. Therefore, it is suggested that to pay attention to the amount of caregiver experience in future studies. Effective factors were identified in the use of Internet-based services. These factors included caregivers' needs, factors relating to communication technology, and information use style. Theexperience of caregiver affects the style of using that information (28).

In Iran, the majority of caregivers of children with cerebral palsy are mothers; we provided our training to mothers as the main caregiver. Future studies are presented to the father and other family members.

Limitations

This type of research requires multiple investigations performed by the user at different stages. In this study due to time limited access to users at some steps was limited. It seems better to follow each step in a separate study to spend enough time on every step.

Most of caregivers of children with CP in the study context were mothers. Then caregivers in this study were mothers. This might limit the generalizability of study results to fathers who are also caregivers.

One of the limitations we encountered during the study was the speed of the internet and its interruptions, which user had to reconnect.

In conclusion, for web-based intervention development, it seems more effective to first determine study needs and then proceed with content development. If face to face intervention is available, it can speed up the design process. The main components of face to face intervention could reconstruct for web-based intervention. If there is no access to face to face intervention, content development can be conducted based on the literature reviews and experts' and users' views depending on the objectives of interventions and theories and methods. Then content adaption must be done by specifying technical requirements

and methods for web-based content. In the third step, designing paper or PowerPoint models and receiving users' and experts' comments and designing a prototype model and initial testing can improve the process. Finally, preliminary testing seems to be helpful for summative evaluation (Figure 2). To develop and evaluate a web-based intervention access is essential including access to various experts including website design experts and experts familiar with content, hardware and software accessibility, access to the same people supposed to use certain websites, access to finance. In addition, lack of time that affects the researcher's decision during the research process.

Our website has the possibilities including registering caregivers of children with CP, the possibility to confirm registration with an SMS and the possibility to determine the caregiver educational priorities and also has the usability for training caregivers of children with CP.

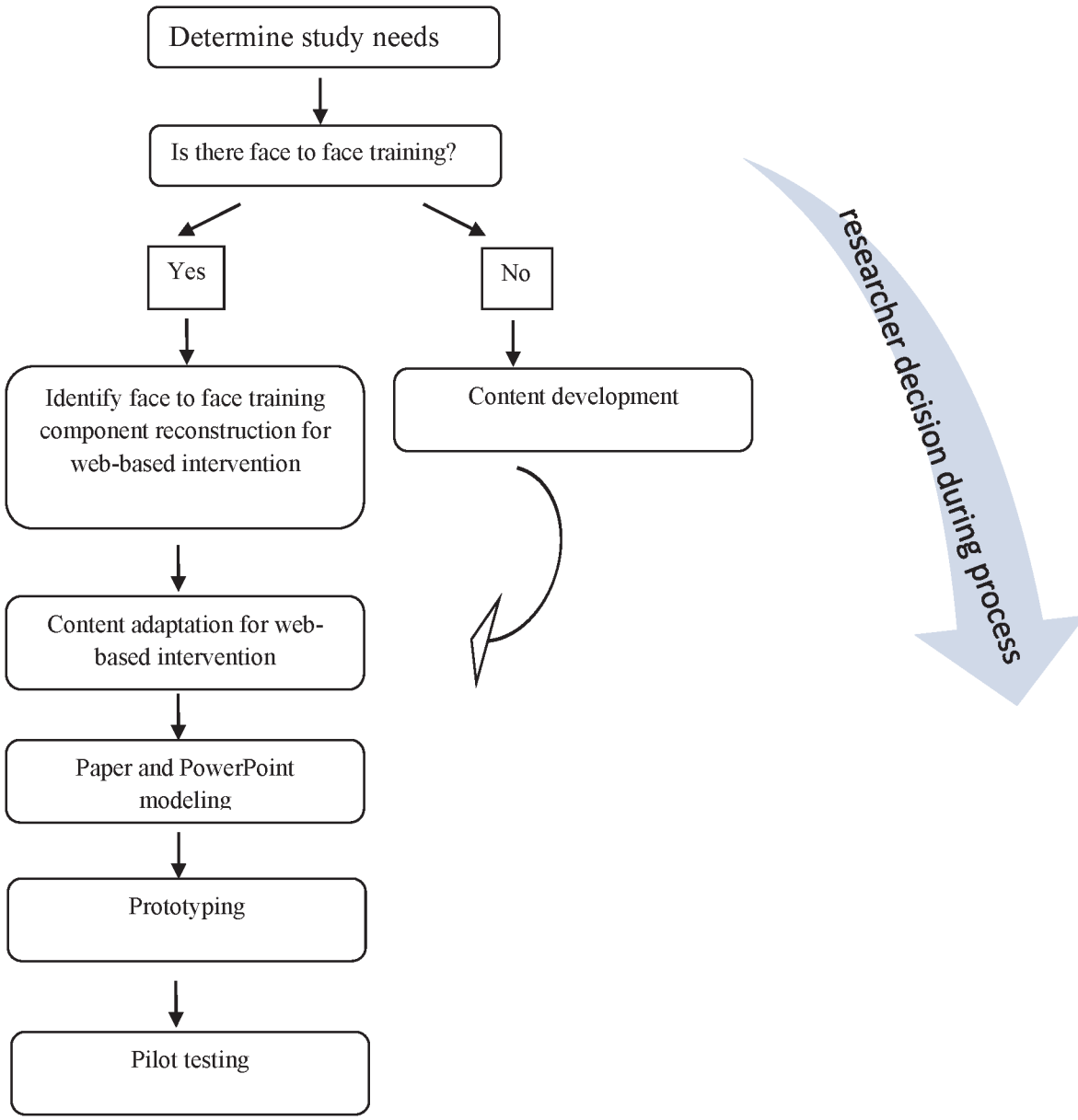

Figure 2. *Researcher flowchart for designing web-based interventions*

Acknowledgement

The project was sponsored by the University of Social Welfare and Rehabilitation Sciences and the Pediatric Neurorehabilitation Research Center.

Author`s Contribution

Nobakhat developed the proposal, data collection and prepare first draft of the article.

Rassafiani developed the idea, designed the study, involved in preparing the article and give the final approval.

Hosseini supervised the research proposal and helped in the first draft.

All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest

The authors declare that there is no conflict of interests.

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ORIGINAL ARTICLE

Comparison of the Effect of Phenobarbital versus Sodium Valproate in Management of Children with Status Epilepticus

How to Cite This Article: Khajeh A, Yaghoubinia F, Yaghoubi S, Fayyazi A, Miri-Aliabad GH. Comparison of the Effect of Phenobarbital versus Sodium Valproate in Management of Children with Status Epilepticus. Iran J Child Neurol. Autumn 2018; 12(4):85-93

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Received: 21-Jun-2016
Last Revised: 24-Jun-2017
Accepted: 02-oct-2017

Abstract

Objectives

Acute prolonged seizure is the most common neurological emergency in children. This research was conducted to compare the effect of intravenous phenobarbital and sodium valproate in control of seizure in children with status epilepticus, referred to emergency ward from Mar to Nov 2013.

Materials & Methods

In this randomized clinical trial, registered with the code number IRCT2015051722300N1, 80 children aged 6 months to 10 years with prolonged seizure and with no response to one dose of diazepam (0.2 mg/kg) administered through IV injection during the five min were selected. Children were randomly divided into two groups, intervention, and control through permutation blocks. In intervention group, intravenous sodium valproate (20 mg/kg) and in control group, intravenous phenobarbital (20 mg/kg) were prescribed. Data such as age, gender, history of previous seizure, seizure type, and recovery time after receiving drug was recorded in the form. Data analysis was done through descriptive statistics, Chi-square and Independent t- test.

Results

Two groups were the same in terms of age and gender and had no statistically significant difference, but they were different in terms of seizure type. In valproate group, 18 patients (45%) and in phenobarbital group, 32 patients (80%) had positive response to the treatment and the chi-square test showed the significant difference.

Conclusion

With regards to this point that in phenobarbital group, patients had more rapid response to drug in comparison with patients in sodium valproate group, phenobarbital is a suitable and effective drug for controlling of seizure in children.

Keywords: Seizure, Sodium valproate; Phenobarbital; Children; Status epilepticus

Introduction

Seizure is defined as paroxysmal and transient changes in motor, behavioral or autonomic activity followed by disturbance in brain electrical activity (1). Seizure is one of the causes of hospitalization in children and acute prolonged seizure is the most common emergency in Pediatric Neurology Emergency (2). In a six-month random sampling of all of the hospitalized patients in Pediatric Emergency Ward in Amin and Al-Zahra hospitals in Isfahan, central Iran, 60% of hospitalized children had seizure (3). Prolonged seizure is associated with high mortality, especially when it leads to complications such as acidemia, hypoglycemia or hypotension. Timely and effective treatment can improve the prognosis of disease and decrease some complications such as metabolic acidosis and aspiration pneumonia (4).

If seizures last longer than 5 min and the patient does not wake up between them, it is a medical emergency. Status epilepticus is a medical emergency that should be anticipated in any patient who presents with an acute seizure. It is defined as continuous seizure activity lasting more than 30 min or two or more seizures without full recovery of consciousness between any of them lasting for more than 5 minutes. In the past, the cutoff time was 30 min, but this has been reduced to emphasize the risks involved with the longer durations. Moreover, febrile status epilepticus is a febrile seizure lasting longer than 30 min (1).

Since the prevalence of seizure disorders in children is higher than in adults, the using of anti-seizure drugs is high in this age group (5). An ideal anti-seizure drug should have suitable performance, reaches the brain quickly and have minimal side effects. Routinely, benzodiazepines are the first-line treatment of seizures in the emergency (6).

When the benzodiazepines are not successful in treating seizure, the long-acting anti-seizure drugs should be used (7). In developing countries, phenobarbital and phenytoin are the most common second-line anti-epileptic drugs (8). Phenobarbital was the first antiepileptic drug introduced in 1912. Nowadays, phenobarbital is commonly used for seizure disorders. Although this drug is less effective than phenytoin or carbamazepine, but it is used for treatment of generalized tonic-clonic and partial epilepsies in all age groups (9). Good efficacy, low toxicity and low cost of the drug have suggested it as an important drug for such applications.

There is evidence that phenobarbital has the most powerful effect in damaging to the behavioral and cognitive activities. The administration of phenobarbital during growth may lead to cognitive impairments such as damage to memory and learning abilities.

Respiratory depression and hypotension are the side effects of rapid phenobarbital infusion, but the most important long-term side effect that limits its use is the impact on children's behavior and learning (10). Sodium valproate as a broad-spectrum anticonvulsant is one of the classic anticonvulsants and is available in our country. This drug is effective in all types of seizures such as absence, tonic-clonic and myoclonic. Besides, it is effective on some kinds of partial epilepsy.

The effect of sodium valproate and phenytoin in patients with status epilepticus were compared and the sodium valproate was more effective than phenytoin (11). Moreover, in a study to determine

the efficacy the sodium valproate versus diazepam in children with status epilepticus, 40 children were studied. Seizure control occurred in 80% of patients' in-group receiving sodium valproate and in 85% in-group receiving diazepam (12).

The efficacy of sodium valproate and phenytoin as the first-line treatment in status epilepticus were compared and showed that there was no significant difference between two groups in terms of seizure control, length of stay in hospital, mortality and serious cardiovascular complications (13).

Considering the importance of these cases, including seizure control and prevention of complications in children, the applicability of the sodium valproate in the treatment of diseases associated with neurologic disorders and also, with attention to side effects of phenobarbital and conflicting results in reviewed studies.

The current study was conducted to compare the effect of phenobarbital versus sodium valproate in management of children with status epilepticus referred to Emergency Ward in Ali-Ebne Abitaleb Hospital in Zahedan, eastern Iran in 2013.

Materials & Methods

This randomized single-blind clinical trial study registered with the code number IRCT2015051722300N1 was conducted in Emergency Ward in Ali-Ebne Abitaleb Hospital in Zahedan, eastern Iran in 2013. The study population was the all of the children with seizure not responded to diazepam within 5 min referred to Emergency Ward. Since the similar study was not found, the pilot study was conducted for calculation the sample size. Based on the results of pilot study with 95% confidence interval and the power of 0.9, sample size was determined as 39 persons in each group. Forty patients were studied in each group.

Patients were selected conveniently and based on inclusion criteria. The most important inclusion criteria were as follows: children aged 6 months to 10 years with seizure lasts more than 5 min with no response to initial treatment to diazepam within 5 min (despite receiving one dose of diazepam 0.2 mg/kg). The second seizure after birth, lack of following conditions: history of serious reactions to sodium valproate, history of uncontrolled bleeding, thrombocytopenia, active liver disease, heart rhythm disturbances, orthostatic hypotension, syncope, history of oral or injectable anticonvulsants, disease that prevents the use of valproate in children such as asthma, chronic liver disease, infection of the central nervous system and the lack of cryptogenic and symptomatic epilepsy. The exclusion criteria of the study included not receiving the full dose of medication for any reason.

The patients were randomly allocated into two phenobarbital and Sodium valproate groups through permuted blocks. Arranging the blocks were randomly and through using random numbers table and the patient entered into two groups based on the blocks.

In intervention group (Sodium valproate), patients were given drug with dose of 20 mg/kg through IV infusion. If their seizure was controlled during 20 min, this was considered as a positive response to drug. The Sodium valproate purchased was constructed of Gerot Lannach Company in Austria.

In control group, phenobarbital was given at dose of 20 mg/kg through IV infusion. If their seizure was controlled during 20 min, this was considered

as a positive response to drug. Phenobarbital was from Chemi Darou Industrial Company.

Data collection tools were the demographic information form including (age, gender, history of previous seizure and type of seizure). Besides, the recovery time after receiving the drug was recorded in information forms in both groups.

Data were analyzed through using SPSS ver. 21 (Chicago, IL, USA), descriptive statistics (mean, SD and frequency), Chi-square test for comparing the qualitative variables in two groups, independent sample *t*-test for comparing the quantitative variables in two groups and Pearson correlation coefficient. In all tests a significance level of 0.05 was considered.

Ethical Considerations

The current study was approved in 2013 by the Research Ethics Committee of the univeristy. All patients' relatives were provided with standardized information about the procedure. Informed consent was sought from patients' relatives and they were guaranteed about the refuse of participation of their patients in the study. All codes of ethics in human research were respected.

Results

Forty patients hospitalized with seizure were studied in intervention group (treatment with sodium valproate) and 40 patients in control group (treatment with Phenobarbital). The mean age of patients in intervention group was 4.15±4.4 and in control group was 4.62±4.96 yr of no significant difference (*P*=0.652).

Moreover, in terms of gender, in intervention group 27 and in control group 25 patients were female. The chi-square test showed no significant difference (*P*=0.639).

The frequency distribution of seizures type showed that in both groups, the most common seizure was status epilepticus. Besides, two groups were similar in terms of type of seizure at the beginning of the study and chi-square test did not show significant difference between the two groups (Table 1).

Table 1: Comparing the type of seizure in two Sodium valproate and phenobarbital groups

Seizure type / Group	FC (%)	SE (%)	Total (%)
Sodium Valproate	15 (37.5)	25 (62.5)	40 (100)
Phenobarbital	18 (45)	22 (55)	40 (100)
Chi-square test	*P*-value= 0.496	df=1	X^2= 0.464

In the phenobarbital group, the higher percent of patients had positive response to drug in compare with Sodium valproate group. Moreover, this difference was statistically significant between two groups in terms of frequency of positive response to treatment (Table 2).

Table 2: Comparing the frequency of positive response to drug in two groups

Group / Response to drug	Sodium valproate (%)	Phenobarbital (%)
Positive	18 (45)	32 (80)
Negative	22 (55)	8 (20)
Total	40 (100)	40 (100)
Chi-square test	X^2= 10.45 df= 1 *P*-value= 0.001	

The mean response time in sodium valproate was higher than the phenobarbital group. In fact, in the Sodium valproate group positive response to drug lasted longer time than phenobarbital group. However, the t-test showed no significant difference between two groups in terms of response time (*P*=0.06).

In addition, the mean response time to drug in both groups was assessed according to type of seizure. In phenobarbital group, response to drug in patients with SE lasted longer time than the patients with FC and this difference was significant (*P*=0.04). Unlike, in Sodium valproate group, response to drug in patients with FC lasted longer time than the patients with SE, but this difference was not significant (Table 3).

Table 3: Comparing the mean response time to drug according to seizure type in two groups

Group	Response time / Seizure type	Number	Mean± SD	Test result
Phenobarbital	FC	18	4.33±1.78	*t*=1.89
	SE	22	5.81±2.71	df= 38
				P-value= 0.04
Sodium valporate	FC	15	5.93±2.46	*t*=-1.99
	SE	25	4.24±2.89	df= 38
				P-value= 0.06

The relationship between age and response time to treatment revealed that with increasing the age of patients, response time to treatment also was increased and Pearson correlation test showed a significant direct relationship between the two variables (r=0.33, *P*=0.018).

Comparison of relationship between response to treatment and gender of patients showed that in the intervention group among the 27 female children, 8 patients had the positive response and among 13 male children, 10 patients had positive response to treatment and chi-square test showed the significant difference (*P*=0.005). However, in the control group, among the 25 female children, 19 patients had the positive response and among 15 male children, 13 patients had positive response to treatment, but there was no significant difference (*P*=0.413).

Besides, comparison the mean and standard deviation of response time concerning the gender in both groups showed that this mean was more in female children than male children in intervention group were, but the *t*-test did not show significant difference. In control group, this time in female patients was more than the male patients and t-test showed no significant difference (Table 4).

Table 4: Comparing the mean and SD of response time in male and female patients in two groups

Response time / Group		Mean±SD	*t*-test result
Sodium valproate	Female	6.25±2.31	*t*=0.102 df=16 *P*-value= 0.92
	Male	6.1±3.57	
Phenobarbital	Female	4.72±2.19	*t*= 0.034 df= 29 *P*-value =0.973
	male	4.69±2.72	

Discussion

The present research aimed to compare the effect of Phenobarbital versus Sodium valproate in management of children with status epilepticus referred to emergency ward. The patients in phenobarbital group had more positive response than the patients in sodium valproate group. This means that the sodium valproate was less effective than phenobarbital for control of seizure in our study sample.

Assessing the mean response time to drug according to seizure type in two groups showed that in phenobarbital group. This time in patients with FC was lower in compared with the patients with SE. In the other words, the patients with febrile convulsion had better response to phenobarbital in compared with patients with status epilepticus.

Unlike, in Sodium valproate group, patients with status epilepticus had more rapid response to drug in compared with patients with febrile convulsion. In fact, patients with status epilepticus had better response to sodium valproate in compared with patients with febrile convulsion. These different responses to drug can be attributed to type of

seizure in patients. The effectiveness of sodium valproate and phenytoin was compared; the mean of response time to drug in sodium valproate was less than in phenytoin. In this study, the patients were suffering from status epilepticus (13) corroborated the results of current study.

The main goal of treating is to completely control seizures during 20 minutes after starting the anticonvulsant infusion. A high percent of patients with status epilepticus had a better response to sodium valproate in compare to phenobarbital (14) that was similar to results of current study. In our study, the patients with SE had a better and more rapid response to sodium valproate in comparison with patients with FC. In patients with status epilepticus, sodium valproate can be more effective than phenobarbital.

The effectiveness of sodium valproate and phenytoin was compared in patients with status epilepticus aged 13 to 60 yr old. The response to treatment was 25% and 79% in phenytoin and sodium valproate respectively (11) corroborated the results of current study.

Furthermore, aim of compare the effectiveness of sodium valproate and phenytoin in patients with seizure aged 15 to 50, seizure was controlled in 66% of patients receiving sodium valproate and in 68% phenytoin. The results of two recent studies indicated the effectiveness of sodium valproate as an anticonvulsant drug for treatment of status epilepticus (15).

The effectiveness of sodium valproate and phenytoin was compared as second-line treatment of seizure control, the positive response in sodium valproate was 88% and in phenytoin group was 84% (16). The effectiveness of sodium valproate was determined on 13 patients with status epilepticus aged 4-12 yr old, 63.3% of patients had positive response to drug (17). Intravenous sodium valproate can be used as the first choice in the treatment of SE and acute repetitive seizures in children (18).

There was a significant direct relationship between the age and response time in all of the patients. In other words, with increasing the patient's age, the response time to drug was increasing that is similar to results that the children with higher mean age had more rapid positive response to drug in compared with younger children (17).

Generally, by comparing the results of various studies with current study, both sodium valproate and phenobarbital are effective drugs in second-line treatment in patients with seizures especially with regard to the type of seizure. The sodium valproate had more effectiveness, the type of seizure was status epilepticus, but the phenobarbital had been more effective, the type of seizure was generalized and partial. In our study, valproate sodium was more effective in patients with status epilepticus.

In conclusion, the phenobarbital in comparison with sodium valproate is a suitable and effective drug for controlling of seizure in children.

Acknowledgment

The authors would like to thank the hospital manager, the nurses and head nurse of Emergency Ward and all the patients who voluntarily and concisely participated in this research.

The authors have no financial relationships relevant to this article to disclose.

Authors' contribution

Ali Khajeh: Conception and design, data collection, final approval of the version to be published.

Saeedeh Yaghoubi: Conception and design, data collection, writing the article.

Fariba Yaghoubinia :Analysis and interpretation, helping in manuscript writing and editing, final approval of the version to be published

Afshin Fayyazi: Conception and design, helping in manuscript writing and editing.

Ghasem Miri-Aliabad: Conception and design, final approval of the version to be published.

All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Conflict of interest

The authors declare that there is no conflict of interest.

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ORIGINAL ARTICLE

Goodenough-Harris Drawing a Man Test (GHDAMT) as a Substitute of Ages and Stages Questionnaires (ASQ2) for Evaluation of Cognition

How to Cite This Article: Baraheni N, Heidarabady S, Nemati SH, Ghojazadeh M. Goodenough-Harris Drawing a Man Test (GHDAMT) as a Substitute of Ages and Stages Questionnaires (ASQ2) for Evaluation of Cognition. Iran J Child Neurol. Autumn 2018; 12(4):94-102

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Received: 15- Jan -2016
Last Revised: 25-Apr-2016
Accepted: 24- Sep -2017

Abstract

Objective

The main aim of the current research was evaluation of concurrent validity of the Goodenough–Harris Draw-A-Man Test (GHDAMT) with the problem-solving subscale of ASQ2 among children between 54-60 months old in Tabriz City, northwestern Iran.

Materials & Methods

In this cross-sectional study, 136 males and 105 females were selected by simple random sampling from nursery schools in Tabriz City, northwestern Iran in 2014 and tested with GHDAMT and ASQ2 to compare the concurrent validity of these tests in evaluation of cognition. Data were analyzed using Pearson or Spearman correlation coefficients and SPSS.16.

Results

The mean Intelligence Quotient (IQ) in girls was 128±18.18 and in boys 118±18.50, and the difference was statistically significant P<0.001. There was no statistically significant correlation between GHDAMT and ASQ2 .The statistical correlation was significant between IQ and mental age among children who had -2SD score in problem-solving subscale, but there was no statistical correlation between children who had -1SD score P<0.002. There was no statistically significant correlation between problem-solving subscale of ASQ2 and mental age and IQ.

Conclusion

GHDAMT did not have acceptable validity and concurrent validity of the test was less than 0.3. So GHDAMT cannot be used as a substitute of ASQ questionnaire. However, the correlation of two tests in children with intellectual and developmental disability was significant. After doing morestudies in further research, it is possible to use GHDAMT as a proper tool for cognition evaluation of these children.

Keywords: Concurrent validity; The Goodenough-Harris drawing A Man Test; ASQ2; Cognition

Introduction

Child development is an interesting and challenging topic for many different scientific disciplines, such as Pediatrics, Psychiatry, and Psychology, In recent years, trials have been conducted to achieve accurately and evidence-based information associated with developmental markers and normal and abnormal developmental processes (1). In this regard, parents are eager to get enough information to know whether or not their child is both developing and growing naturally. This is of particular importance in families with a history of developmental disorders and risk factors during pregnancy, such as preterm delivery, etc. (1).

The assessment of human abilities, including children, has always been one of the areas of interest to professionals in the fields of development and psychometrics. Various tests have been designed to study and evaluate cognitive, social and emotional abilities considering different theoretical perspectives (2). Assessment and diagnosing processes along with labeling the child in relation to his/her development process can have challenging outcomes for the family. If objective and accurate measurement tools are not used in the assessment processes, the delicate developmental points can be ignored on several occasions and planning and intervention processes for treatment can encounter with problem. Only less than half of the mild mental and growth failure and/or mild emotional-behavioral disorders in children can be diagnosed clinically and without the use of tools (3).

Different abilities are assessed in child development including gross and fine motor skills, personal-social skills, language and communication and problem-solving (cognition). Developmental disorders are identified through appropriate tests during the screening process. This is a process which can identify the child suspected to have developmental delays or failures at very early or hidden stages and need further assessment. Many tests and questionnaires aimed at diagnosing developmental delays in children throughout the world have been created and validated accurately and systematically (3).

Among these tests, the Goodenough–Harris Draw-A-Man Test (GHDAMT) and the Ages and Stages Questionnaire (ASQ) are the developmental process tests used by experts to assess children's abilities (4). In the current study, GHDAMT was selected due to being easy, cost-effective and short. The goal was to assess outpatient children referred to the clinic or doctor's office when parents were concerned or the doctor suspected cognitive delays by using this simple, fast and reliable tool.

The formal use of drawing for psychological assessment began with Florence Goodenough, a child psychologist, in 1926. "Goodenough first became interested in drawing when she wanted to find a way to supplement the Stanford-Binet intelligence test with a nonverbal measure" (5). She believed that children draw what they know not what they see and that the nature and content of a child's drawing are related to their mental development rather than other things (5). Many changes can be seen in children's drawings of different ages and these changes are directly related to a child's general intelligence. Her widespread studies on children's drawings led to the first drawing intelligence test which named Goodenough Draw a Man test. Among the other psychologists interested in children's development

was Piaget who did many studies on human drawing (1956-1970) (6).

Over the years, the Goodenough Draw a Man test has been revised many times with added measures for assessing intelligence, but the origin of the test has remained unchanged. In 1949, some tried to introduce it as personality test by making changes on it (7). Harris later revised the test as GHDAMT (8). The test is one of the easiest, most practical and universal tests, the procedure is simple and requires little time and it is feasible in different locations and cost-effective. The test just needs the child's cooperation and parents play no role. The purpose of the test is to assess child's development in cognition scale (4).

Since the image of a man is the same in all cultures and is not affected by educational experiences and family and cultural contexts and with respect to its less bias and lower costs, as it only requires paper and pencil, the test is still in use. In addition, the test is useful and effective for children with hearing damage and developmental and mental disability who cannot respond to instructions of other IQ tests (4).

The Ages and Stages Questionnaire (ASQ) is another developmental test to assess children's abilities designed by specialists at the University of Oregon in accordance with normal developmental processes. This test is easy, affordable and applicable in different locations (3). This questionnaire can be completed by parents at every level of education and except to the scoring and interpretation does not need a specialist. After scoring the answers and summing up, they are compared with pre-determined cut-off points and the child's status is determined. The most important thing about the test is its continuity and the ability to repeat it at different ages and one of the important advantages of the questionnaire is parental involvement in screening their child's development. The psychometric parameters of the ASQ 2 test were assessed in different studies, including studies in Australia and Denmark (9), and the results have been relatively good. The ability of the test to identify the developmental disorder is calculated at more than 96% (3).

One of the most important issues in the field of psychometrics is how to validate and use the ability measuring tests and their assessment in relation to individual's abilities. Concurrent validity is one of the necessary assessments in the validation of the tests. Concurrent validity indicates that one test or measuring tool can be a proper substitute for another test or measuring tool (10). When reviewing the literature no evidence was found on the concurrent validity of the Goodenough - Harris test and ASQ, and, therefore, the present study was done to fill this research gap.

Materials & Methods

Multistage simple random sampling was used to select 241 children aged 54-60 months (136 boys and 105 girls) of whom 10 were mentally disabled from nursery schools of Tabriz, northwestern Iran as the study population in 2014.

The GHDAMT assesses child cognition; problem-solving subscale in the ASQ2 associated with cognition is also taken into consideration.

The researchers chose the age group 54-60 months because if the performance of a 54 months old child in ASQ2 is at – 2SD level (i.e., failed at the area of problem-solving subscale), the performance

is almost equal to a 36 months old, which is the minimum age that children can be measured with the GHDAMT. A 36 months old child acquires the ability to draw a circle and sketch a man and gradually adds body parts and details (11).

In the beginning, in respect to ethical concerns, the purpose of the study was briefly explained to all the parents participating in the study and the participants were promised that their information would be kept confidential in all articles and resources extracted from this study. There would not be any psychological and emotional consequences for them and their children. In addition, participants were free to withdraw at any time. Then the 54 months and 60 months ASQ 2 Questionnaire were given to the parents who had with respect, children at the age of 53-55 months and 59-61 months to complete at home. The Goodenough-Harris test was conducted at each nursery school after completing the questionnaire.

The scores of ASQ2 Questionnaire in the cognitive domain (problem-solving) were calculated and compared with cut-off point values standardized by the Iranian Ministry of Health and Medical Education and classified based on the scores. The passing score was between -1 SD and -2SD and failing score was less than -2SD.

The drawing test, considering the parts and graphic details, based on test instructions was scored between 0-1 (8) and mental age was estimated after summing up the tests based on Table 1, and child IQ was originally computed by taking the ratio of mental age to chronological (physical) age and multiplying by 100.

Table 1. Equivalents of mental age for acquired scores

MA	SCORE	MA	SCORE	MA	SCORE	MA	SCORE
13-0	40	9-9	27	6-6	14	3-3	1
13-3	41	10-0	28	6-9	15	3-6	2
13-6	42	10-3	29	7-0	16	3-9	3
13-9	43	10-6	30	7-3	17	4-0	4
14-0	44	10-9	31	7-6	18	4-3	5
14-3	45	11-0	32	7-9	19	4-6	6
14-6	46	11-3	33	8-0	20	4-9	7
14-9	47	11-6	34	8-3	21	5-0	8
15-0	48	11-9	35	8-6	22	5-3	9
15-3	49	12-0	36	8-9	23	5-6	10
15-6	50	12-3	37	9-0	24	5-9	11
15-9	51	12-6	38	9-3	25	6-0	12
		12-9	39	9-6	26	6-3	13

Children with physical disabilities who have difficulty using pencil were excluded from the study. The obtained data were studied using descriptive statistics methods (Frequency, percentage and mean ± SD). Pearson or Spearman correlation coefficients were used to calculating the correlation between the two tests. Then an independent *t*-test was used to compare the mean of the two groups, and SPSS16 (Chicago, IL, USA) was used for statistical analysis. The *P*-value of less than 0.05 was considered statistically significant.

Results

Assessment of concurrent validity and computing of the two test's correlation by using of Pearson correlation coefficient (Table 2) revealed that statistical correlation between five different subscales of ASQ2 with mental age and IQ obtained from the Goodenough-Harris testis:

Table 2. Statistical correlation coefficients among 5 subscales of ASQ2 with IQ

Variable	Communication	Gross motor	Fine motor	Problem Solving	Personal-Social
IQ Pearson Correlation	.193	.208	.308	.037	.213
***P*-value**	.003	.001	.000	.578	.001

There was a statistically poor significant correlation between the communication domain and IQ (r = 0.19, n= 241, *P* <0.003), the gross motor domain and IQ (r = 0.20, n= 241, *P*<0.001) and the personal-social domain and IQ (r = 0.21, n = 241, *P*<0.001). There was a statistically moderate significant correlation between the fine motor domain and IQ (r = 0.30, n = 241, *P*<0/001). No statistically significant correlation between problem-solving subscale and IQ among children with any mental disability was seen.

The Goodenough-Harris average IQ scores were 128.2 ± 18.18 in girls and 118.2± 18.50 in boys, which was statistically significant (*P* = 0.001).

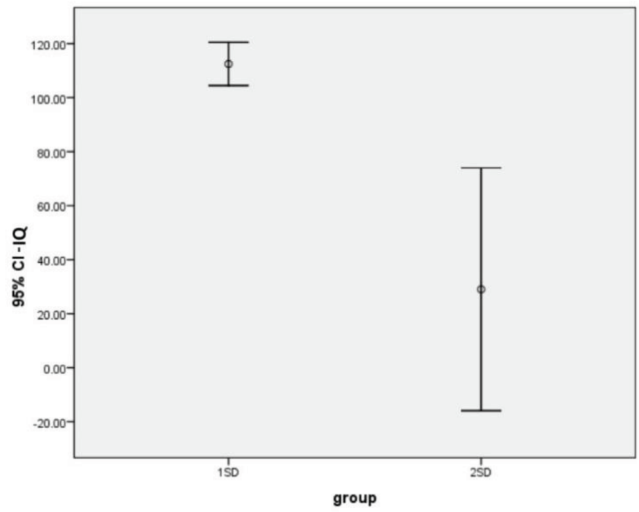

Figure 1. *Error Bar graph. Comparing the IQ in two groups of children -1SD and -2SD*

The results of the *t*-test (Figure 1)revealed that the average IQ scores of children who had -2SD score in solving problem subscale, and in children -1SD the difference was statistically significant (*P* =0.002).

There was no statistically significant correlation between ASQ2 and GHDAMT. A statistically significant correlation between IQ and mental age in the children who failed the problem-solving domain (less than -2SD) was seen *P*<0.002. However, the correlation was not significant in children whose ASQ2 score was higher than -2SD.

The reliability of GHDAMT was not acceptable and concurrent validity was less than 0.3.

Discussion

The aim of the current study was evaluation of the concurrent validity of two tests: the ASQ2 questionnaire and the GHDAMT. In order to compare these two tests, since GHDAMT assess the child's cognition, the problem-solving subscale in ASQ2 questionnaire was selected.

The results of current study suggest that the GHDAMT is not a proper substitute to ASQ2 in assessment of children's cognition and revealed no statistically significant correlation between problem-solving subscale, mental age and IQ in children without mental disability. However, this correlation was significant in children with mental disability.

There are a lot of tests to assess child development that have been universally validated and used. However, they are often time consuming and require a professional to perform the tests and sometimes the high cost of the tests has led pediatricians to avoid using them and only relying on clinical diagnosis which in more than half of the cases, have led to misleading results and/ or delay of early intervention (3). To solve this problem, more practical tests that are easy, short and cost-effective along with sufficient accuracy and validity are taken into consideration.

There are a few studies on the reliability and validity of the Draw a Man test, especially in recent years in Iran, but one was performed in Tabriz. In this study, in addition to GHDAMT, Raven's IQ Test was also done, which revealed acceptable reliability coefficients as well as good reliability and stability (12). The GHDAMT was done on children referred to an outpatient clinic and revealed that the test can be used as a useful tool in screening developmental disorders (13). However, this was not a valid test for assessing children's IQ (4).

The ASQ2 test has been validated in global studies showing high reliability and accuracy (14). Parents re-did the test with 175 children in an interval of 2-3 wk, and this demonstrated the reliability of more than 94% of the results with a 0.1 SD. Re-testing was done on 112 children by an experienced person revealed more than 90% similar results (3).

To warrant concurrent validity, the ASQ2questionnaire was compared simultaneously to the following tests:

Revised Gesell and Amatruda Developmental and Neurological Examination

Bayley Scales of Infant Development

Stanford-Binet Intelligence Scale

McCarthy Scales of Children's Abilities

Battelle Developmental Inventory

There was almost 84% consistency between the results (3). The screening questionnaires completed by parents were as accurate as the ones done by pediatricians (15). The studies carried out on the ASQ2 in Iran verified its validity and reliability (16).

There are other researches questioning the validity of this type of questionnaires filled out by parents in public places (17). The ASQ2questionnaire was used on following up the program of preterm children up to 2 yr (19) and 5 yr (19) and was able to successfully identify the children with severe developmental delays. However, it was not efficient in identifying mild delays. The same test done in India on children of different ages, including high- and low-risk children has shown a sensitivity of 83.3% and specificity of 75.4% (20).

Concurrent validity of this test in following up of very premature children was also consistent with the Wechsler test (21). The efficiency of this easy and cost-effective test in assessment of developmental delay in high-risk children is reported (3).

In conclusion, GHDAMT cannot be a substitute for the ASQ2questionnaire due to the low statistical correlation coefficient. Although the statistical correlation coefficient was higher in children with mental disability but deciding, generalizing and judging in relation to the results is difficult due to the small sample size. The present study can be a starting point for further studies in evaluating IQ and cognition in children with mental disability.

Acknowledgement

The researchers would like to thank Dr. Mohammad Barzegar for his generous assistance in compiling the paper, Ms. Khiabani for preparing the data and the parents and children for participating in the study. This study was sponsored by the Child Health Research Center, Tabriz University of Medical Sciences, Iran.

Author`s Contributions

Baraheni, Nasrin, Coordinator, executive in drawing test, collecting and scoring the tests, writing and editing paper.

Heidarabady, Seifollah, research designer, writing paper.

Nemati Shahrooz, writing and editing paper.

Morteza, Ghojazadeh, consulting and analyzing data.

All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest

The authors declare that there is no conflict of interests.

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ORIGINAL ARTICLE

Oral Levetiracetam as Add-On Therapy in Refractory Neonatal Seizures

How to Cite This Article: Mollamohammadi M, Amirhoseini ZS, Saadati A, Pirzadeh Z,Hassandvand Amouzadeh M. Oral Levetiracetam as Add-On Therapy in Refractory Neonatal Seizures. Iran J Child Neurol. Autumn 2018; 12(4):103-110

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Received: 17-Oct-2016
Last Revised: 18-Sep-2017
Accepted: 26-Sep-2017

Abstract

Objective

Seizure is the most common signs of nervous system disease in neonates. The first line of treatments in neonatal seizures (after ruling out and emergency treatment of electrolyte imbalance and hypoglycemia) are phenobarbital and phenytoin. We aimed to evaluate drugs that are more effective on neonatal seizure.

Materials & Methods

Patients admitted to neonatal wards & NICUs (level IIa&IIb) in Qom hospitals (2015-2017), central Iran with presentation of seizure, were enrolled in this clinical trial study. After ruling out electrolyte imbalance and hypoglycemia these neonates were managed by intravenous phenobarbital, then if no response was seen we added intravenous phenytoin and for remaining neonates with refractory seizure we applied oral levetiracetam as add on therapy. The study was registered as code number of IRCT2016051527896N1.

Results

Initially, 245 neonates were enrolled. According to exclusion criteria, 12 cases were excluded, and phenobarbital was prescribed to the remaining patients. Out of these, 86 patients did not respond, and phenytoin was prescribed for them. Forty two patients who were not responding to phenytoin were finally treated with oral levetiracetam. Finally, 95.3% of seizures were controlled with oral levetiracetam but 4.7% were not cured.

Conclusion:

When the intravenous form of levetiracetam is not available and neonatal seizure does not respond to first line classic drugs, oral levetiracetam as add on therapy maybe effective.

Keywords: Neonatal seizure, Refractory Neonatal seizure, Oral levetiracetam, treatment

Introduction

Seizure is defined as a sudden changes in activity or behavior, sensory or autonomic function, due to paroxysmal electrical activity dysfunction of brain (1-3). Seizure in neonatal age has more prevalence than other period of life (4) that is 1–5 per 1, 000 live births (5). Annual prevalence is 1.8% to 8.6% (6-7), but in children is 0.5-1% (8). Variation in reported rates might be attributed to difficulty in diagnosis, different definitions of neonatal seizures and choosing a different enrolled criteria.

There are different types of neonatal seizures including subtle (More common in preterm), clonic, tonic, spastic, and myoclonic. The incidence of neonatal seizure is different according to age of infants (1-4; 4-14 days; and more than 14 days). The most common leading cause is asphyxia or hypoxic-ischemic encephalopathy that involving 50%-75% of neonatal seizures (9-10). Other causes are infectious diseases, trauma, metabolic disorders, intra cranial &intra ventricular hemorrhage, and structural abnormalities of the brain (11).

Neonatal seizure is one of the common causes of hospitalization that can be present with different patterns (12, 13). Depending on the etiology, different regime of antiepileptic drug could be needed (14-17). For example; if no structural defect detected, the anticonvulsants should be tapered during admission and in other conditions, long term-treatment is recommended (18).

The nervous system of premature neonates, shows nonspecific response. More neonatal seizures are recovered completely and some of them may lead to transient or chronic complications (19). The brain grows and develops in first five years so frequent seizures not only effect on their development and learning capability but also leads to some structural changes in the brain (7). Thus, inhibition of seizure by an effective drugs is essential (20).

Approach to neonatal seizure depends on underlying causes. The first line of treatment in neonatal seizure (after ruling out electrolyte imbalance and hypoglycemia) is phenobarbital followed by phenytoin (7). The potent anticonvulsive effects and low toxicity of phenobarbital, leads to using these drugs in neonatal seizures (20). Thus WHO introduced phenobarbital as a first line therapy in generalized, tonic, clonic and partial seizures (21-23). Some side effects for example are as follows: Sedative effects, behavioral disturbance and neuronal apoptosis of phenobarbital that are more than other similar drugs. But minimal systemic toxicity, long half-life and low cost are the main advantages versus other anticonvulsive drugs (24). In 35%-45% of seizures; phenobarbital and phenytoin as first line therapy were not effective, so other anti-convulsive agents should be added (25-29).

New antiepileptic drugs (for example: topiramate, levetiracetam, lamotrigine, etc.) are recommended in resistant seizure in neonates. Levetiracetam is derived from pyrolidin. This drug is effective in neonatal seizure as add on or first line therapy. In addition, low efficacy towards serum protein, non-hepatic metabolism, absence of drug interaction and serious complications, and no neurotoxic effects, are other characteristics of this drug (27-29).

According to above-mentioned features and because other first line drugs have many sides effects, in this study, levetiracetam is recommended in refractory neonatal seizure as add on therapy. So conducting this study would clarify the dark spots of its utilizing in patients.

Materials & Methods

Overall, 245 neonates presented with seizure in Qom hospitals (in neonatal wards &NICUs (level IIa&IIb)), were enrolled. Exclusion criteria were electrolyte imbalance and hypoglycemia. These neonates were managed by intravenous phenobarbital, then if no any response was seen, we added intravenous phenytoin, and for remaining neonates with refractory seizure, we applied levetiracetam as add on therapy. Because of unavailable of intravenous form, we used oral type.

Neonates were treated with oral levetiracetam, administered in the form of gavage with initial dose of 10-20 mg/kg and gradually increased to 40-50 mg/kg if seizures was repeated (diagnosed according to clinical signs). Then the persistence of neonatal seizures, was monitored after drug administration. According to non-electrophysiological evaluation by subspecialists (in neonatology and pediatric neurology) about 95.3% of clinical seizures were completely controlled.

Informed consent was taken from the parents of the participants before administration of oral levetiracetam. Ethics Committee of the university approved the study. This prospective clinical trial study was registered as code number of IRCT2016051527896N1.

Descriptive statistics (frequency, percentage) and analytical statistics (chi-square test) and SPSS ver. 20 (Chicago, IL, USA) were used to analyze the data.

Results

Initially, 245 neonates were enrolled in this study. According to exclusion criteria, 12 cases were excluded, and phenobarbital was prescribed to the remaining patients. Out of these, 86 patients did not respond, and phenytoin was prescribed for them. Forty two patients who were not responding to phenytoin; were finally treated with oral levetiracetam (Table 1).

Table 1: The relationship between underline disease and response to levetiracetam

Underlying disease	Positive Response to levetiracetam	No Response to levetiracetam	Response to levetiracetam by increasing dose	*P* value
HIE	9(90%)	0	1(10%)	
Brain malformation	7(87. 5%)	1(12. 5%)		0. 838
IEM	6(75%)	1(12. 5%)	1(12. 5%)	
IVH	3(100%)	0	0	
Idiopathic	11(84. 6%)	0	2(15. 4%)	

No significant relationship was found between factors and response to oral levetiracetam.

Influence of factors such as age, sex, type of delivery, gestational age, type and causes of seizure, CNS infections were measured on rate of response to oral levetiracetam. Fifteen patients (35.7%) were delivered by NVD & 27 patients (64. 3%) by C/S. Gestational age of 26 patients (61.9%) was term (over 37 weeks of gestation) and 16 patients (38.1%) preterm. Age of 35 patients (83.3%), was between a few hours to a week, 4 patients (9.5%) between 2 to 3 weeks, 2 patients (4.8%) between 3 to 4 weeks and 1 patient (2.4%) between 1 to 2 weeks. Twenty seven patients (64.3%) were male (Table 2).

Underlying cause of seizure in 10 patients (23. 8%) was HIE (hypoxic-ischemic encephalopathy) and in 8 patients (19%) - brain malformation, in 8 patients (19%) – IEM (inborn errors of metabolism) in 3 patients (7.1%) IVH (intra ventricular hemorrhage) and 13 patients (30.9%) was idiopathic.

Discussion

This clinical trial study showed that oral levetiracetam (in case of unavailability of intravenous form) is useful in controlling neonatal seizures. About 94.5% of neonates that did not respond to first line therapy, completely cured. This study investigates new aspects of the subject because had used levetiracetam after phenobarbital and phenytoin in refractory seizure as oral type and based on the best knowledge of authors, not applied in any other study as oral type. The relationship between basic factors such as age, sex, type of delivery, gestational age, type & causes of seizures and CNS infection with response to treatment were evaluated, but no significant relationships were found. Oral levetiracetam is an effective drug in treatment of neonatal seizures in our study.

In a study on 38 neonates with seizures without hypoglycemia, hypomagnesaemia, hypocalcaemia and pyridoxine deficiency, intravenous levetiracetam was used as first-line therapy with more effectiveness than phenobarbital, without any side effects (30). In our study, the effect of oral levetiracetam has been evaluated in neonatal seizures that was not responding to other anticonvulsant therapy and proven to be effective without any side effects. Khano et al. studied 22 neonates with seizures, treated with intravenous levetiracetam at the dose of 10 to 50 mg/kg. In all cases, seizures were totally subsided after 72 h and 86% of patient were discharged with oral levetiracetam (31). In our study, in order to unavailability of intravenous levetiracetam, we used the oral form of this drug and received to the same results.

A study was conducted on the 8 neonates with resistant seizures to first line anticonvulsant therapy, then they were treated by intravenous levetiracetam. As a result, 6 of them were completely cured, one patient did not respond and one had a partial response to the treatment (32). In our study, the efficacy of oral levetiracetam was evaluated by total cure of 36 neonates out of 42, with initial dosage, 2 neonates were cured by increasing the dose and 4 patient were not responding to oral therapy.

In conclusion, in several studies; intravenous form of levetiracetam was evaluated with f avorable effect without any complication, and in emergency condition it was first line of therapy. We showed in special conditions, oral levetiracetam could be used as an additional therapy with good effect in control of resistant neonatal seizures. Further studies are needed to reach exact conclusion and better results.

Acknowledgement

This study was financially supported by Medical

Table 2: The relationship between response to treatment by oral levetiracetam and demographic data

Demographic data	Positive Response to levetiracetam	No Response to levetiracetam	Response to levetiracetam by increasing dose	*P* value
Gestational age (weeks)				
-Term >=37	21(58. 3%)	1(50%)	4(100%)	0. 382
-Preterm <37	15(41. 7%)	1(50%)	0(100%)	
Sex				
-Male	23(63. 9%)	2(100%)	2(50%)	
-Female	13(36. 1%)	0(0%)	2(50%)	0. 657
Mode of delivery				
-NVD(vaginal delivery)	13(36. 1%)	0(0%)	2(50%)	0. 654
-C/S (cesarean section)	23(63. 9%)	2(100%)	2(50%)	
Post-natal age(days)				
-< 7	30(83. 3%)	2(100%)	3(75%)	
8-14	0(0%)	0(0%)	1(25%)	
15-21	4(11. 1%)	0(0%)	0(0%)	0. 207
22-28	2(5. 6%)	0(0%)	0(0%)	
CNS infection				
Infection	0(0%)	0(0%)	1(25%)	0. 147
No infection	36(100%)	2(100%)	3(75%)	
Type of seizure				
-Myoclonic	8(22. 2%)	2(100%)	1(25%)	
-Tonic	2(5. 6%)	0(0%)	0(0%)	
-Subtle	9(25%)	0(0%)	0(0%)	0. 177
-Spastic	5(13. 9%)	0(0%)	1(25%)	
-Clonic	9(25%)	0(0%)	0(0%)	
-Mixed Form	3(8. 3%)	0(0%)	2(50%)	

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Authors' contribution

Mohsen Mola Mohammadi: Interpreting and discussing results.

Zeinab Sadat Amirhosseini: Interpreting and discussing results.

Ali Reza Saadati: Corresponding author (Project Design, supervise and interpretation of results).

All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

Non-declared

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ORIGINAL ARTICLE

A Novel Splice Site Mutation of the ATM Gene Associated with Ataxia Telangiectasia

How to Cite This Article: Saeidi K, Saleh Gohari N, Mansouri Nejad SE. A Novel Splice Site Mutation of the ATM Gene Associated with Ataxia Telangiectasia. Iran J Child Neurol. Autumn 2018; 12(4):111-119

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Received: 18-Dec-2016
Last Revised: 05-Jul-2017
Accepted: 14-Oct-2017

Abstract

Objectives

Ataxia telangiectasia (AT) is a rare autosomal recessive disorder caused by mutation in the Ataxia telangiectasia mutated (ATM) gene. This disorder is characterized by progressive cerebellar ataxia, telangiectasia, immunodeficiency and a predisposition to leukemia/lymphoma. In this study, we investigated a family with a new mutation in ATM, confirmed by molecular genetic test.

Materials&Methods

Four members of a family including a symptomatic AT patient, his parents and sibling were examined for ATM gene defects at Kerman University Hospital, Kerman, Iran in 2016. DNA was extracted from peripheral leukocytes and the coding regions and exon-intron boundaries of ATM gene were amplified by next-generation sequencing technique. The identified mutation was tested in all members of the family.

Results

Molecular analyses identified a homozygous T to G substitution in c.7308-6 position resulting in a novel acceptor splice site in intron 49 of the ATM gene in the index patient. Parents and sibling of the proband were heterozygous for the same mutation.

Conclusion

The variant c.7308-6T>G is predicted to be pathogenic due to impaired splice site causing exon skipping. This newly found frameshift mutation cosegregated as an autosomal recessive trait as expected for Ataxia telangiectasia syndrome.

Keywords: Ataxia telangiectasia; Cerebellar ataxia; Splice site; New mutation; Autosomal recessive

Introduction

Autosomal recessive cerebellar ataxias (ARCAs) are a heterogeneous group of neurological disorders, characterized by degeneration or abnormal development of cerebellum and spinal cord. In most patients, onset age is before 30 year. The most frequent ARCAs in Caucasian population is Friedreich ataxia, ataxia-telangiectasia (AT) and early onset cerebellar ataxia with retained tendon reflexes. Gait ataxia is the common manifestation of these disorders. Other common findings include nystagmus, dysarthria, and dysmetria. Brain imaging often shows cerebellar atrophy or hypoplasia. Age of onset varies widely but is frequently in childhood. Intellectual disability, peripheral neuropathy, and retinal abnormalities may also occur (1).

Clinical diagnosis is confirmed by magnetic resonance imaging (MRI), electrophysiological examination, and mutation analysis. Recently, molecular genetic has been a powerful approach in investigating inherited ataxias (2).

ARCAs have been divided to (1, 3): 1) Congenital ataxias which include Joubert syndrome (Dysgenesis or agenesis of the vermis and presence of molar tooth sign) and Cayman cerebellar ataxia (Hypotonia from birth, non-progressive truncal and limb ataxia). 2) Metabolic ataxias which include ataxia with isolated vitamin E deficiency (Very low plasma level of vitamin E and normal lipid profile), Abetalipoproteinemia (apolipoproteins B deficiency, multiple fat-soluble vitamin deficiency and abnormal lipidogram), Cerebrotendinous xanthomatosis (Bile acid biosynthesis defect, large deposit of cholesterol and xanthomas) and Refsum disease (Retinitis pigmentosa, deafness, increased phytanic acid level in blood and abnormal blood lipids). 3) Degenerative and progressive ARCAs which include Friedreich ataxia (Ataxia with scoliosis, foot deformity, cardiac symptoms, defective mitochondrial proteins, absence of telangiectasia and normal α-fetoprotein), Mitochondrial recessive ataxia syndrome (Mitochondrial DNA replicative polymerase defect, Infantile onset spinocerebellar ataxia (Mostly Finish heritage disease with hypotonia and vision and hearing problems), Charlevoix-Saguenay spastic ataxia (Early onset, progressive spastic ataxia of all limbs with paraplegia, increased tendon reflexes, progressive distal wasting, atrophy of the superior cerebellar vermis and Retinal hypermyelinated), Marinesco-Sjögren syndrome (Ataxia with congenital cataract, elevation of serum creatine kinase activity, Hypergonadotropic hypogonadism, facial dysmorphism and atrophy of the vermis), Early onset cerebellar ataxia with retained tendon reflexes (Early onset cerebellar ataxia with preservation of deep tendon reflexes), Coenzyme Q10 deficiency with cerebellar ataxia (Reduced levels of coenzyme Q10 in muscle biopsies), and Posterior column ataxia and retinitis pigmentosa (Posterior column ataxia and retinitis pigmentosa). 4) DNA repair defects which include ataxia telangectasia-like disorder (Different from AT based on the genetic data), ataxia with oculomotor apraxia-1 (Limb dysmetria, hypoalbuminemia and hypercholesterolemia), ataxia with oculomotor apraxia-2 (Dystonic posturing with walking and elevated values of gamma-globulin, and creatin kinase), spinocerebellar ataxia with axonal neuropathy (Ataxia with peripheral axonal motor and sensory neuropathy, distal muscular atrophy, and pes cavus), Xeroderma pigmentosum (Ataxia

with skin photosensitivity, early onset skin cancers, photophobia, conjunctivitis, keratitis, ectropion and entropion), and AT (Progressive ataxia, with oculocutaneous telangiectasia, and variable immunodeficiency).

AT is also characterized by sinopulmonary infections, radiosensitivity, early aging, chromosomal instability and a predisposition to leukemia/lymphoma. It is often misdiagnosed in early childhood, before the development of a full clinical picture. The first signs of the disease are movement disorders with different severity. The incidence of AT is 1/40000-100000 cases, but in several populations, the incidence is considerably higher due to founder mutations (4-6).

The initial clinical description of AT disease is reported earlier (7). Three adolescent Czech siblings were described with progressive chorea, dystonia, and ocular telangiectasia. Later, a 9-yr-old child was described with progressive cerebellar ataxia and bilateral oculocutaneous telangiectasia in details (8). The term ataxia telangiectasia was introduced in 1958 and recognized as autosomal recessive mode of inheritance for the disease (9). The disease is sometimes referred to as Boder-Sedgwick syndrome. Different groups have reported case series of AT patients (9-14).

AT is caused by mutations in the Ataxia telangiectasia mutated (ATM) gene, consisting of 66 exons, in chromosome 11 (11q22.3). A 370 kDa protein encoded by ATM gene is an important checkpoint kinase which is one of the most important controllers of cell cycle checkpoint signaling pathways required for cell response to DNA damage and for genome stability. Therefore, nuclear genomic instability resulting from loss of this function is regarded as a major mechanism underlying the pathology of AT (5, 15).

In contrast to ARCAs, autosomal dominant cerebellar ataxias are characterized by late onset spinocerebellar ataxias and episodic ataxias (16).

In this study, we investigated a family with a new mutation in ATM, confirmed by molecular genetic test.

Materials & Methods

In 2016, an 8-yr-old boy born of a consanguineous marriage was admitted to the Kerman University Hospital, Kerman, Iran with the complaints of generalized weakness and difficulty to walk. The patient had one healthy younger sister of 5 yr old. His birth history was uneventful and onset of disease occurred about 2 yr of age with loss of balance. The progression of the ataxia increasingly developed beyond age 5 year. He had ataxic gait, abnormal head movements, chorea, myoclonus, slurred speech, oculomotor apraxia, neuropathy, intention tremor, and hand incoordination. He had drooling and frequent experiences of aspiration because swallowing was not well coordinated. He suffered from frequent respiratory tract infections due to low levels of IgG, IgA, and IgG subclasses. We found congestions in both eyeballs (Figure 1) which appeared between 5 and 6 yr of age and nystagmus. He showed also Café au lait spots. His intelligence was normal and he was cooperative. Writing was affected by age 7 year. Deep tendon reflexes were slight but present.

A genetic counselor explained the objectives and aims of the study to participants. Written informed consents were obtained from subjects.

The 5 ml whole blood from subjects' brachial vein in tubes containing 200 µl EDTA was collected to

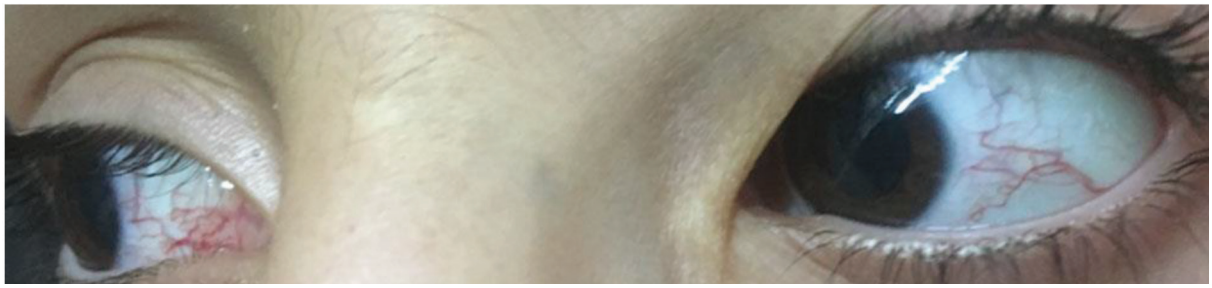

***Fig 1**. Ocular telangiectasia in patient.*

detect any ATM gene mutations. Genomic DNA was isolated from leukocytes of the whole blood using salt-saturation method (17). In AT work-up, the DNA sample of an 8-yr-old affected member of the family was screened for the gene defects using next-generation sequencing technique. The sequencing processes were performed on Illumina Hiseq 4000 platform. Sequence reads were analyzed using BWA –GATK (18, 19). The other family members were screened for the identified mutation by PCR and DNA sequencing methods. To accomplish this, a 572 bp DNA fragment of the ATM gene including intron 49, exon 50 and exon-intron boundaries were amplified using a forward primer

(5'-AGTGTAAGCAGAGGTGTAAGTTA-3') and a reverse primer

(5'-CACTGGACCAAGTGCTAGGAATA-3'). The PCR reaction was performed using the following condition: 30 cycles of denaturation at 94 °C for 45 sec, annealing at the optimal temperature of each primer for 30 sec and extension at 72 °C for 30 sec. PCR products were checked on 1% agarose gel and taken through an ABI automated DNA sequencer (Model: 3730XL).

Results

Complete blood count, lipid profile, LFT, chest X-ray, serum electrolytes, pyruvate, ammonia, lactate, levels of vitamins B12 and E were normal in the proband, he had low level of IgG, IgA, and IgG subclasses, ultrasonogram of whole abdomen and ECG were normal. Serum α-fetoprotein was high and MRI showed cerebellar atrophy. Four members of family including a symptomatic AT patient, his parents and sibling were examined for ATM gene defects.

The screening of the ATM gene in patient revealed T to G substitution in c.7308-6 position. This intronic variant appeared in a homozygous state. The asymptomatic sister of the index patient and his parents were heterozygous for this mutation (Figure 2). Using In Silico Tools for splicing defect prediction (20) and Alamut® Visual software version 2.8, the variant c.7308-6T>G in intron 49 is predicted to be pathogenic due to impaired splice site. Based on the In Silico prediction tools, c.7308-6T>G mutation has moved initial acceptor site by 5 bp upstream from its normal position. This causes an abnormal splicing process by activation of a new cryptic splice acceptor site. The aberrant splicing causes exon skipping (Figure 3).

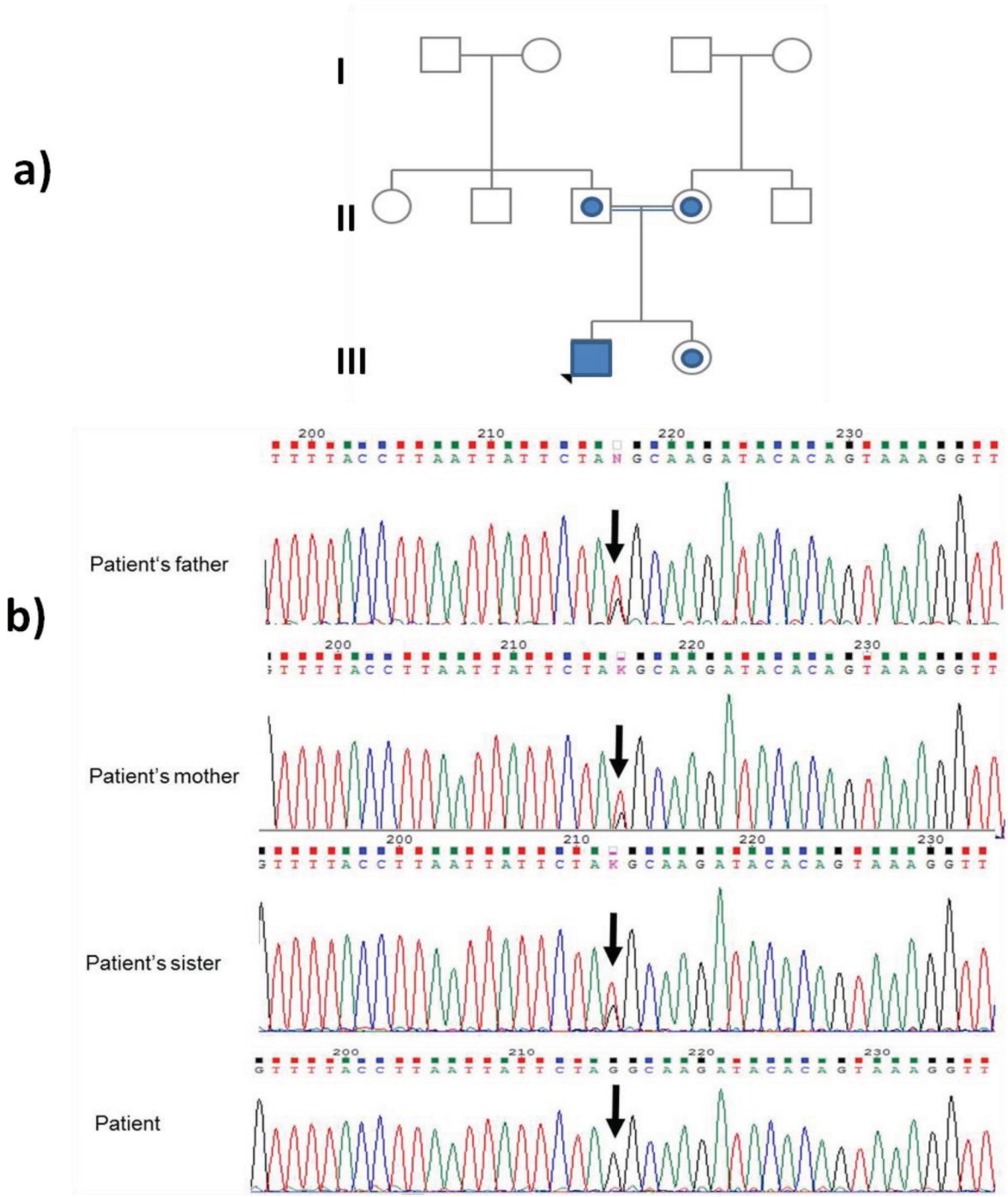

Fig 2. *a) Pedigree of the family with AT. The circle indicates female, the square indicates male, and the filled square indicates the affected individual. b) The homozygous mutation detected in the ATM gene in the patients and heterozygous mutation detected in his parents and sibling. Nucleotide variation is indicated by an arrow.*

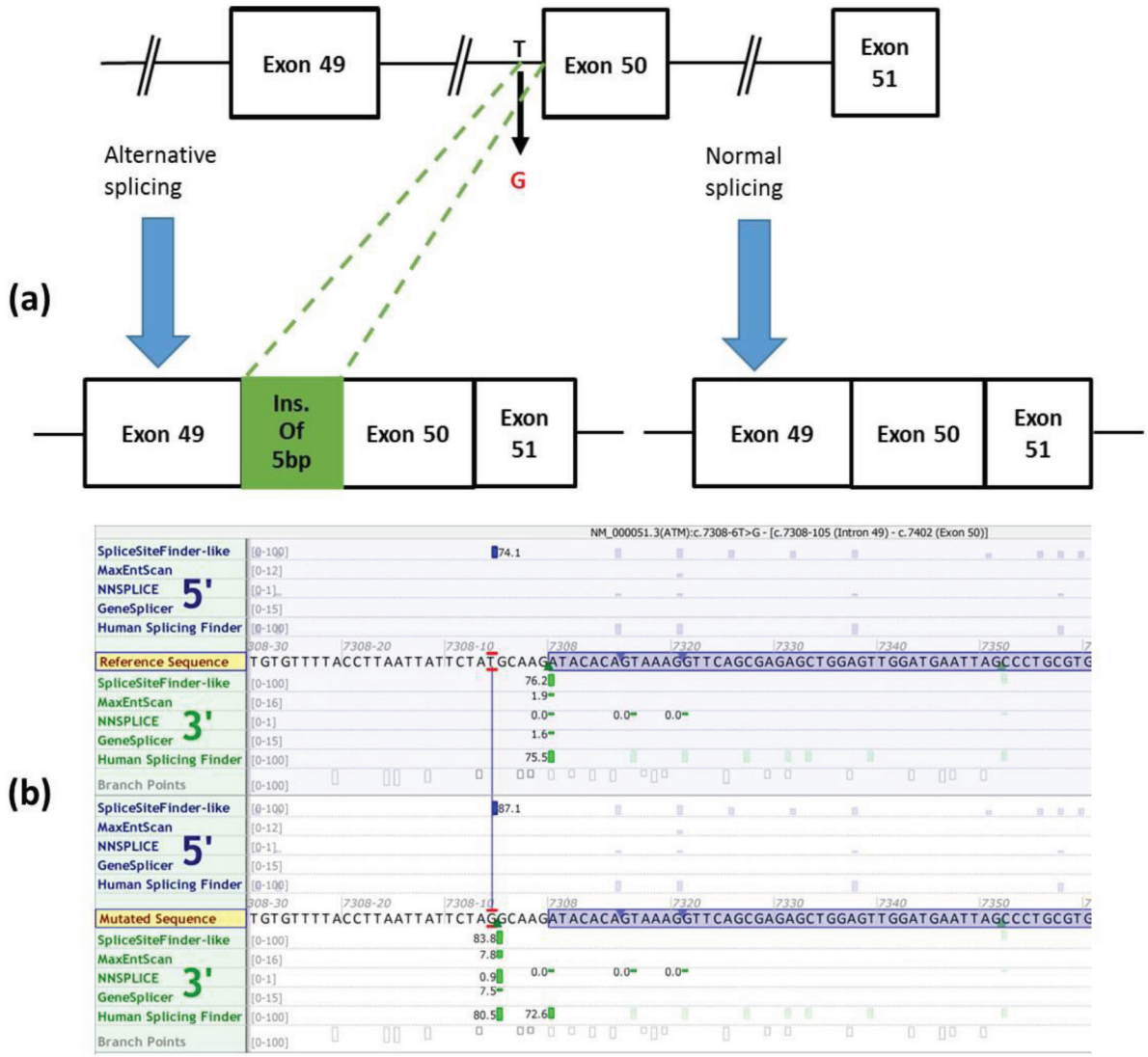

Fig 3. *(a) Ideogram of detected splicing consequences of the c.7308-6 T>G mutation. (b) c.7308-6T>G mutation has moved initial acceptor site by 5 bp upstream from its normal position. The window in (b) displays the reference and mutated sequences and green vertical bars for 3' (acceptor) sites. The height of each bar is proportional to the maximum possible score.*

Discussion

AT is a complex multisystem disorder caused by a mutation in the ATM gene. The ATM gene encodes the protein kinase ATM which expressed is mainly in the nucleus of lymphocytes, fibroblasts, germ cells, and neurons. This protein is the key regulator of DNA damage response (21, 22). The AT gene was mapped to chromosome 11q22.3 (23).

ATM gene was mutated in AT (24). Since then, several mutations in ATM gene including truncating mutations, which result in the total absence of ATM kinase activity, and missense or

splice site mutations, leading to decreased kinase activity have been described (25-29). Up to date, more than 400 mutations in the ATM gene have been described in AT patients (6).

We found a new mutation (c.7308-6T>G) in an 8-yr-old boy with AT who was initially diagnosed with loss of balance. Early diagnosis was delayed due to the rarity of the disease and also lack of obvious clinical symptoms which started at 5 yr of age. Several other neurologic and rare disorders should be taken into account by physicians when aiming for the AT diagnosis (2). Some lab tests such as gene sequencing as well as the clinical features of the disease would assist in differential diagnosis (2). The diagnosis was established on the basis of clinical features such as progressive cerebellar dysfunction, gait and truncal ataxia, telangiectasia, head tilting, impaired eye movement, immunodeficiency and recurrent sinopulmonary infections, dysarthria, slight deep tendon reflexes, elevated serum α-fetoprotein and normal height and intelligence.

We conclude that T to G substitution in c.7308-6 position modifies pattern of splicing leading to a five-base insertion in the transcript, which causes exon skipping. Splicing site prediction tools gave the highest sensitivity scores of 80.5%- 90% for initial acceptor site changing. This skipped exon is located in FAT domain of protein. Of note, the importance of the FAT domain, as a structural scaffold or as a protein-binding domain, has been reported (30). Exon skipping is a very strong evidence (PVS1) of pathogenicity according to the ACMG (American College of Medical Genetics and Genomics) guidelines (31). Moreover, this new mutation also fulfil the supporting criteria pp3 (deleterious effect on the gene or gene product such as conservation has been supported by various computational evidences) and pp4 (patient's phenotype is highly specific for a disease with a single genetic etiology) as well as two moderate criteria PM1 (Located in a critical and well-established functional domain e.g. active site of an enzyme) and PM2 (Absent from controls in Exome Sequencing Project, 1000 Genomes or ExAC) (31).

Therefore, enough lines of evidence are invoked to classify this variant as a pathogenic mutation based on the ACMG variant classification guidelines.

In Conclusion, the variant c.7308-6T>G has not been reported previously and is predicted to be pathogenic due to impaired splice site causing exon skipping. However, as a limitation, we did not have more cases to confirm this. Therefore, further investigation on the functional role and clinical impact of novel alteration are proposed.

Acknowledgement

We thank Najibeh Monami and Zahra Javidan for technical help during this survey.

Author`s Contribution

KS and NSG designed the study. KS drafted the manuscript and performed molecular genetic analysis. NSG contributed in genetic investigation and critically reviewed the manuscript. SEM visited the patients and performed neurological examinations.

All authors have read and approved the final version of the manuscript and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest

The authors declare that there is no conflict of interests.

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ORIGINAL ARTICLE

The Relation between Urinary Tract Infection and Febrile Seizure

How to Cite This Article: Mahyar A, Ayazi P, Azimi E, Dalirani R, Barikani A, Esmaeily S. The Relation between Urinary Tract Infection and Febrile Seizure. Iran J Child Neurol. Autumn 2018; 12(4):120-126

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Received: 05-Jul-2017
Last Revised: 28-Nov-2017
Accepted: 19-Dec-2017

Abstract

Objectives

Febrile seizure is the most common type of seizure among children. Identification of factors involved in febrile seizure is highly critical. The present study was conducted to determine the association between children's urinary tract infection and febrile seizure.

Materials & Methods

In this case-control study, 165 children with simple febrile seizure (case group) were compared with 165 children with fever and without seizure (control group) in terms of urinary tract infection (UTI) in Qazvin, central Iran in 2015-2016. The age of children was between 6 months to 5 yr.

Results

Among 165 children with febrile seizure, 25 (15.2%) had urinary tract infection. In the control group, only 2 patients (1.2%) had UTI. There was significant difference between two groups regarding urinary tract infection (P=0.001). Among 25 children with UTI in the case group, 17 children (68%) had acute pyelonephritis, and the remaining 8 children (32%) had cystitis. The two patients with UTI in control group had cystitis (P=0.055).

Conclusion

Urinary tract infection could be a risk factor for febrile seizure. Therefore, all patients with febrile seizure are examined in terms of urinary tract infection.

Keywords: Febrile seizure; Urinary tract infection; Children

Introduction

Febrile seizure is the most common type of seizure among children. Febrile seizure refers to a type of seizure which occurs if temperature of child's fever is equal to or higher than 38 °C. These patients have not central nervous system infection (such as meningitis, encephalitis, etc.), metabolic

disease and afebrile seizure. The disease is usually observed among children within age range of 6 to 60 months. The age peak of febrile seizure is 18 months old.

The prevalence of febrile seizure ranges from 2% to 5% (1-4). Febrile seizure is divided into simple and complex types. Regarding the simple type, seizures are usually of tonic-clonic type. The seizures do occur once a day and take less than 15 min. Concerning complex type of seizure, it is usually focal and occurs more than once a day and each seizure takes more than 15 min (1-2). Febrile seizure usually has a good prognostic outcome, but it may be lead to epilepsy in 2%-7% of the cases (1).

Although the etiology of febrile seizure is imprecise, some reports point to the role of certain factors such as genetics, infections and deficiency of certain trace elements (5-7). Considering the role of some viral infections in febrile seizure (6), the question is raised for us that "Do bacterial infections such as UTI could provide the conditions for febrile seizure?" Urinary tract infection (UTI) is one of the common diseases of children. In 75%-90% of the cases, *Escherichia coli* is the agent. The prevalence of UTI among females and males are 3%-5% and 1%, respectively (8, 9). Previous studies on the association between UTI and febrile seizure offer contradictory results (9-12).

Considering the high prevalence of febrile seizure and significance of identification of influential factors, the present study was conducted.

Materials & Methods

In this case-control study, 165 children with simple febrile seizure (case group) were compared with 165 children with fever and without seizure (control group) in terms of UTI. The study was conducted in Qazvin Children Hospital, Qazvin University of Medical Sciences, Qazvin, central Iran in 2015-2016. In both groups, children's age ranged from 6 months to 5 year. Sample size was calculated as: =α0.05 1-α=0.95 β=20% 1-β (power)=80%, P_1=1 (Hypothetical proportion of control with exposure), P_2=6.6 (Hypothetical proportion of cases with exposure), OR=7 (least extreme odds ratio to be detected) and following formula:

$$n = \frac{2(Z_{1-\alpha/2} + Z_{1-\beta})^2 \times \bar{P}(1-\bar{P})}{(P1-P2)^2}$$

Sampling was frequently done until intended sample size was achieved. Febrile seizures were defined seizures that occur between the age of 6 and 60 months with a temperature of 38 °C or higher, that are not the result of central nervous system infection or any metabolic imbalance, and that occur in the absence of a history of prior afebrile seizures. A simple febrile seizure was defined a primary generalized, usually tonic-clonic, attack associated with fever, lasting for a maximum of 15 min, and not recurrent within a 24-h period (1-4). The children with complex febrile seizure, epilepsy, developmental delay, abnormal neurologic examinations, central nervous system infections (e.g. Meningitis), electrolyte disorders (e.g. hypocalcemia and hyponatremia), metabolic diseases (e.g. Phenylketonuria) and any factor that justifies seizure as well as uncircumcised children were excluded from the study.

The control group was selected by group matching

from the children with fever and without seizure visited the hospital due to common diseases such as infection of upper respiratory tract and diarrhea. Both groups were local and residents of Qazvin. All male members of both groups had been circumcised. UTI was defined as: positive urine culture (urine culture positive for more than 10^5 CFU/mL of a single pathogen in a midstream urine sample or clean catch method or 10^4 CFU/mL of a single pathogen via urinary catheterization, or presence of any number of colonies of an organism in urine culture taken by suprapubic method (13).

The project was approved by the Ethics Committee of Qazvin University of Medical Sciences (project no: 1121). Then children's parents were briefed on the study objectives and methods. After written parental consent was obtained for the children's participation in the study and verbal consent was obtained from the older children.

The demographic information (e.g. age, sex, height, weight, and perimeter of head), clinical symptoms and laboratory findings (e.g. hemoglobin, type of UTI, and microorganism) of patients were collected and registered. Measurement of height, weight, perimeter of head and temperature of patients was done through available standard methods (14). All of the intended tests were conducted in the laboratory of Qazvin Children Hospital.

The data were analyzed through Chi-square test and *t*-test. To conduct intended analyses, SPSS Software (ver. 20, Chicago, IL, USA) was used. *P*-value of less than 0.05 was considered significant.

Results

Among 165 children in case group, 97 patients were male (58.8%). In the control group, 92 patients were male (55.8%) (*P*=0.65). No significant differences were found between the two groups in terms of age, sex, height, circumference of head, temperature and hemoglobin concentration (Table 1). Among 165 children with febrile seizure, 25 patients (15.2%) had UTI. In the control group, 2 patients (1.2%) had UTI (*P*=0.001) (Tables 2 and 3). There was significant difference between two groups regarding UTI (*P*=0.001). Among 25 children with UTI belonging to case group, 17 patients (68%) had acute pyelonephritis, and 8 patients (32%) had cystitis. In the control group, two patients with UTI had cystitis (*P*=0.055).

The most common organism causing UTI in children was *E. coli*. The most sensitivity was seen to amikacin, gentamicin, ceftriaxone and nalidixic acid, and the highest drug resistance was found to ampicillin, cefalexin, and trimethoprim-sulfamethoxazole.

Discussion

The findings of present study suggested that the prevalence of UTI in children with simple febrile seizure was higher than control group. The findings of studies on the role of UTIs in febrile seizure are contradictory (9-12, 15, 16). A study was conducted on 137 children with simple and complex febrile seizure with age range of 1 month to 5 year. The prevalence of UTI in children with febrile seizure was 6.6%. The author's recommended urinalysis and urine culture test for all patients with febrile seizure so that probable UTI cases could be identified (9). In another study conducted on 228 children with febrile seizure in the age range of 1-71 months (mean age: 24 months), 5%-12% of children had bacteriuria. The authors emphasized the significance of UTI diagnostic tests for children with febrile seizure (10).

Table 1. Comparison of variables between case and control group

Variables	Case group	Control group	*P*-value
	n=165	n= 165	
Sex (male/female) [1]	97/68	92/73	0.65
Age (month) [2]	14±(12)	12±(16.5)	0.55
Weight (kg) [2]	11±(4)	11±(6)	0.79
Height (cm) [2]	76±(10)	75±(15)	0.54
Head circumference (cm) [2]	48±(4)	48±(3)	0.83
Temperature (^{0}C)	38.4±0.8	38.3±0.9	0.2
Hemoglobin (gr/dl)	11.3 ±1.4	11.2±1.5	0.85

[1]Chi-square test, [2]Median(IQR) (Mann–Whitney U test), [3]Mean±SD (*t*-test)

Table 2. Comparison of etiologic causes of febrile seizure in case and control group

Type of disease	Case group	Control group	*P*-value
	n (%)	n(%)	
Acute gastroenteritis	77(46.7)	80(48.5)	0.56
Upper respiratory infection	55(33.3)	60(36.4)	0.92
Pneumonia	6(3.6)	13(7.9)	0.59
Acute otitis media	2(1.2)	10(6)	0.02
UTI	25(15.2)	2(1.2)	0.001
Total	165(100%)	165(100%)	

Chi-square test

Table 3. Comparison of UTI in case and control groups

UTI	Case group	Control group	*P*-value
Yes	25(15.2)	2(1.2)	0.001
No	140(84.8)	163(98.8)	
Total	165(100)	165(100)	

Chi-square test

In contrast to the above-mentioned studies, other studies pointed to insignificant difference between children with and without febrile seizure in terms of prevalence of UTI (11, 12, 15, 16). In a study on 243 children with febrile seizure (mean range: 1.9±-0.96), the prevalence of UTI in such children was 0.7% (11). A similar study was conducted on 171 children with simple febrile seizure (mean age: 21 months) and pointed to 5.9% prevalence of UTI. The prevalence of UTI was reported as 2.6% (15). Among children aged less than 2 yr diagnosed with UTI; only 2 patients (2.6%) had febrile seizure (16). In all of the above-mentioned studies, control group was lacking and the obtained results were compared with mean prevalence of UTI in the public. In the present case-control study, the prevalence of UTI in children with febrile seizure was 15.2%. In addition, a significant difference was found between the group with febrile seizure and the group with fever but without seizure in terms of UTI. The findings of present study are supported by results of two studies (9, 10). Difference in the results of the above-mentioned studies might be due to variable factors such as age of patients, size of sample, type of study, method of sampling and circumcision of male patients.

Based on the our results, diagnosis of UTI in children with febrile seizure is significant due to following reasons: 1- Clinical manifestations of UTI during breastfeeding and early childhood is often accompanied by fever and it rarely has local symptoms such as pain, tenderness of flank, stomachache, as well as explicit urinary symptoms (17). 2- Usually the cause of fever in these patients is viral and is not usually treated with antibiotics. As a result if the febrile patient has UTI, it will not be detected (6). Lack of quick diagnosis and treatment of UTI, especially acute pyelonephritis, could lead to dangerous consequences such as kidney scarring, hypertension and chronic kidney failure (8.17). Probability of kidney scarring in low-age children is higher than older children. In addition, patients with UTI may be inflicted with urinary system abnormalities such as reflux and hydronephrosis. These abnormalities might increase the probability of recurrence of UTI and also add to likelihood of kidney scarring (17).

Among limitations of present study we can point to the following cases: 1) Conducting the study solely in one center; 2) Lack of study on children with complex febrile seizure. The authors recommend further studies in this regard: such as multi-center study, study on complex febrile seizures and study on pathophysiology of this association.

In conclusion, considering the high prevalence of UTI (15.2%), we recommend the urinalysis and urine culture test for all children with febrile seizure, so that UTI cases could be identified.

Acknowledgement

We appreciate Research Department of Qazvin University of Medical Sciences and parents of children for their corporations.

Author`s Contribution

Abolfazl Mahyar**:** design of the work

Parviz Ayazi**:** drafting of the work

Elaheh Azimi**:** collection of data

Reza Dalirani**:** drafting of the work and final approval of the work

Ameneh Barikani: interpretation of data

Shiva Esmaeily: analysis of data

All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest

The authors declare that there is no conflict of interests.

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ORIGINAL ARTICLE

A look at the normal development of Pointing and Reaching Gestures in 12-16-Month-Old Farsi-Speaking Children: A Longitudinal Study

How to Cite This Article: Babaei Z, Zarifian T, Ashtari A, Bakhshi E, Ebrahimipour M. A look at the normal development of Pointing and Reaching Gestures in 12-16-Month-Old Farsi-Speaking Children: A Longitudinal Study. Iran J Child Neurol. Autumn 2018; 12(4): 127-139

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Received: 19- April -2017
Last Revised: 13- Jan -2018
Accepted: 20- Jan -2018

Abstract

Objectives

Human beings can use gestures such as pointing and reaching to communicate with others before they have the ability to use verbal communication to produce speech. Given the importance of children's communication development and the key role of gestures development in communicating, the main purpose of this study was to analyze the normal development of pointing and reaching gestures and their relationship in 12-16-month-old children speaking Farsi.

Materials & Methods

In this prospective, observational and longitudinal study the gestures of 11 monolingual Farsi-speaking children (7 boys and 4 girls, from Oct 2015 to Jan 2017 in the homes of participants across Tehran, Iran) were evaluated via non-randomized sampling method. Child-mother interactions were videotaped monthly in a semi-structured context to capture the emergence and consistent use of targeted gestures. Afterward, the data were coded and statistically analyzed for this purpose Repetitive measured; independent t-test and Pearson correlation were used.

Results

The mean of the pointing gesture increased significantly from 12 to 16 months ($P<0.05$). However, this was not significant for the reaching gesture. Moreover, there was no relationship between pointing and reaching gestures.

Conclusion

Pointing gestures increase with age from 12-16 months in Farsi-speaking children. However, reaching gestures stay the same between 12-16 months of age. The study provided rich details of common gestures that children use to signal their intentions before verbal communication.

Keywords: Gesture; Pointing; Reaching; Development; Iranian children

Introduction

Human beings are social creatures and have a strong tendency to communicate even in the first months of life. This communication can have different communicative functions such as behavior regulation, social interaction and joint attention (1-3). Infants use a variety of gestures to communicate with others. Gestures are movements of parts of the body, especially the hands or head to express a meaning or a need (2-5). Children develop intentional communication around 8 to 9 months and they use gestures to meet their needs (6, 7). Pointing is one of the main gestures which are extending the finger toward something (8). It enables the child to communicate with others before accessing the verbal skills (2, 3). The pointing gesture is a tool to regulate other's behavior results from more primitive gestures known as reaching gesture (9-12). Reaching gesture is extending a hand toward an object except grasping movements (8). "Most basically, infant's acts of pointing are underpinned by: i) motoric prerequisites for index finger extension toward external objects; ii) motivational prerequisites for communicating with others in various ways (e.g requesting things imperatively, or indicating them declaratively); and iii) social-cognitive prerequisites for following, directing, and sharing attention with others" (13). According to classic theories, infants' motivation to point for others begin with their attempt to obtain out-of-reach objects, on the other hand, human beings' fine motor skills develop with increasing the age, and one of the main skills is Index finger extension adapted for pointing gesture. In other hand, by increasing the age, infants imitate their caregivers' pointing gestures for communication and learn to point for achieving their intentions. Therefore, reaching gesture with the imperative function (e.g. Behavior regulation) converts to the pointing gesture with the same function by increasing the age, so decreasing of reaching and increasing of pointing gestures are expected (10, 12-16). Reaching gesture appears first in the development and is the most frequent gesture during the first year of life (17). According to most studies in various societies, pointing gesture increase in the second year of life, especially in 16-20 months of age (3, 8, 18-23).

Because of the time period importance in diagnosis and early intervention, the study of gesture, as one of basic indices of evaluation and early intervention of language disorders and communication problems can guide clinicians to diagnose developmental problems timely (24, 25).

"Using natural gestures in promoting communication and linguistic skills in children with prelinguistic communication disorders has become essential, but it requires deeper knowledge" (20). Although many studies have been done on the development of these gestures, there is contradictory evidence about their developmental stages and their frequency. For instance, the highest frequency of reaching gestures was reported in 9-15 months, while this increase has been reported in 8-12 months in another survey (20, 26). On one hand, this increase in reaching gestures happens in 9.5-12.5 months (18). On the other hand, reaching gestures in Chinese stabilize in 8-14 months and even reduce in some 12-21 month-old infants (19). There are different reports on the pointing developmental process such as reaching gesture. For example, the highest frequency of pointing gesture was reported after 11 months (27), while this increase has been reported in 16-20 months

(22, 23). Pointing gesture frequency increase as children's spoken labeling behavior promote in 18-20 months. Some scientists contribute these differences in the social-pragmatic aspects of communication and the effect of culture on that (28, 29), these attitudes are correlated to system theories, according to these theories a child's development is shaped by the varied systems and human beings develop within a system of relationships that include family and society (30). Therefore, the norms in one society cannot be representative of the norms in another society, and the milestones of these prelinguistic behaviors must be determined in every. That is why gestures have been studied in 30 languages in the world in less than a century (3, 28, 29, 31-33).

Children usually start naming an item 2-3 months after pointing to it. In fact, pointing gesture is a prerequisite for the development of vocabulary and lexical enrichment (18, 34). Moreover, the use of combination of gesture and spoken word can predict two-word utterances in children (35).

The relationship between reaching gesture and the development of language skills, especially the number of receptive and expressive words in the first year of life has been proven (18). In spite of this fact, reaching gesture is negatively correlated with the use of gestures in children with the use of language in older children (20).

Using gesture in children with communication and language impairment is not only different from their normal peers, but also has distinct properties in different developmental disorders (5, 36-47).

Considering the relationship between language development and use of gestures (17), a better understanding of gestures' milestones, stages, and frequency appears to be essential. Consequently, clinicians will be able to diagnose and conduct early intervention more effectively. Although there are numerous studies on the development of gestures (3, 4, 28, 29, 32, 33, 42-47) all of them are conducted in other language and culture, so there is no evidence on this topic in Iranian children.

Therefore, the main purpose of this study was to examine and describe the frequency, developmental process, and relationships of pointing and reaching gestures in 12-16-month-old toddlers in Iran.

Materials & Methods

The study was conducted from Oct 2015 to Jan 2017 in the homes of participants across Tehran, Iran.

This was a prospective, observational and longitudinal study in which the gestures of 11 monolinguals (12-month) Farsi- speaking children (7 boys and 4 girls) were evaluated. Statistical power for this sample size was considered (as) 80%. All participants were medically normal, had normal development, their parents had at least 12 yr. of formal education, and they were monolingual and had a moderate socioeconomic status (48). Ages & Stages Questionnaire (ASQ) was administered to select typically-developed children. Children and their parents who met the inclusion criteria were recruited.

Sampling was initially done through snowball method which is a non-probability sampling technique. Four subjects were recruited from health centers in moderate Socio-economic status areas of the town; four subjects were introduced by other researchers, and three families were referred by other participants in this study.

The data collection instruments included mother-child demographic inventory, ASQ, and handy cam.

Mother-child demographic inventory included general question (child's sex, birth order, medical history and mother education and age), the validity of the demographic questionnaire was evaluated through content validity using scientific resources and expert's opinion. The content validity of questionnaire was qualitatively determined. The questions were revised based on the 14 speech-language Pathologists and then were presented to the parents.

ASQ is the most widely used for developmental disorders determination given to mothers to be filled. ASQ (3rd ed) includes 19 different questionnaires which evaluate communication, gross motor, fine motor, problem-solving and personal-social skills in 4 to 60-month-old children. Each questionnaire has 30 questions, and each domain has 6 questions. ASQ was validated and normalized on Iranian children living in Tehran (49). The Cronbach's alpha for the questionnaire is overall 0.79 and the inter-rater reliability was 0.93. The constant validity of the questionnaire was also confirmed by the factor analysis. The Persia version of ASQ can validly and reliably screen developmental disorders in Iranian children residing in Tehran (49).

The child-mother interactions were recorded using a digital video recorder (Sony.HDR-XR100, Model no:AC-L200C).

After explaining the process of the study and its objectives for the families, a written consent was signed by them, and then the examiner conducted the assessment at the child's home at their convenience. At the beginning of the first session, information about the child's interests and communication methods (behaviors) such as gestures were gathered from the family. Afterward, the mother was explained about how to play and interact with the child in order to evoke the maximum communication act in the child. The mother-child interaction was videotaped by the Sony handy cam (HDR-XR100). The interaction begins with 15-min play with the child's toys and then move to 45-min play with the designed toys (Appendix 1). This procedure continued on a monthly basis for 5 months. Videos of each session were recorded by the researcher through the anecdotal method, and then all the pointing and reaching gestures (during 1-h child-mother interaction) were coded (Appendix 2).

Appendix 1: The designed toys in this study include:

The designed toys
Bubble blower, puppet, baby doll, balloon, hairbrush, cups, spoons, plates, pan, baby bottle, toothbrush, towel, book, blanket or facecloth for peek-a-boo.

Appendix 2: The operational definitions for pointing and reaching gestures

Pointing	- Point with index finger - Point with an object in hand - Touchpoint, when index finger touches the referent - Touchpoint with motion, when index finger touches the referent and moves but remains in contact with the referent. - Touch and tap, when index finger touches the referent-lifts off the referent and touches referent again. - Whole hand touch
Reaching	- Reaching with one or both arms extended toward an object that is out of reach. - Partial reach, when one or both arms are partially extended. - Reach to take - Reach with open hand or opening and closing hand

The coded data were analyzed using SPSS ver. 22 (Chicago, IL, USA) and the descriptive statistics such as mean, and standard deviation. As the data were normal according to Shapiro-Wilk Test, analytic statistics such as repetitive measured (within-subject comparison), independent t-test was used.

In order to validate the coding system, 20% of the recorded samples were coded by two examiners educated earlier on coding and scoring the gestures and had experience in the development of gestures.

This research was confirmed by the Ethics Committee of the University of Social Welfare and Rehabilitation Sciences, Tehran, Iran.

Results

The demographic information of the participants is presented in Table 1.

The frequency of pointing and reaching gestures is shown in Table 2.

Table 1. Demographic information

Child / Data	K.A	R.M	A.M	M.M	A.Sh	P.A	Z.T	Z.A	M.H	Q.H	M.R
Sex	Male	Male	Male	Male	Female	Male	Female	Female	Male	Female	Male
Age (day)	360	361	362	360	363	362	361	363	363	363	364
Birth order	1	3	1	2	1	1	1	3	3	1	2
Mother education	Master of science	Diploma	Bachelor	Bachelor	Bachelor	Bachelor	Master of science	Diploma	Diploma	Master of science	Diploma
Mother age	28	36	27	33	24	27	29	32	33	29	32

Table 2. Descriptive statistics of the pointing and reaching gestures

Age / Gestures	12 months	13 months	14 months	15months	16 months
Pointing gesture frequency	12.000	15.272	29.545	29.272	30.909
(standard deviation)	(9.979)	(14.519)	(28.380)	(22.249)	(21.505)
Reaching gesture frequency	22.545	21.909	25.909	24.636	21.636
(standard deviation)	(4.131)	(8.431)	(10.940)	(8.969)	(9.718)

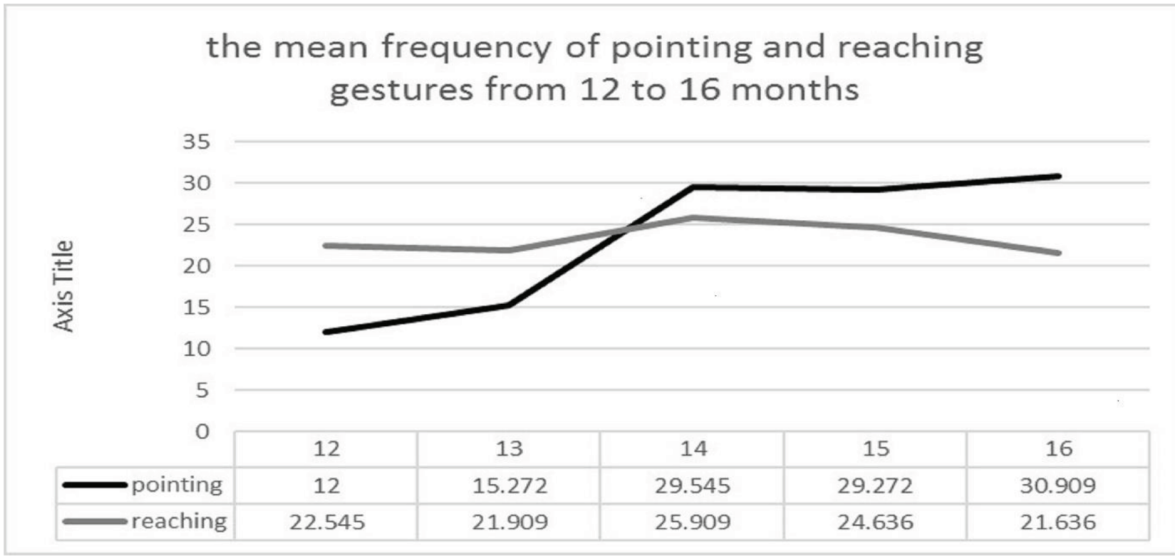

Figure 1. *The mean frequency of pointing and reaching gestures from 12-16 months*

Table 3. Repetitive measurements (within-subject comparison) of the pointing and reaching gestures in 2 successive months

Gesture		Mean Square	F	Sig.
Pointing	12-13	117.818	1.059	0.328
	13-14	2240.818	9.478	0.012*
	14-15	0.818	0.003	0.956
	15-16	29.455	0.049	0.830
Reaching	12-13	4.455	0.066	0.802
	13-14	176.000	1.252	0.289
	14-15	17.818	0.166	0.693
	15-16	99.000	0.870	0.373

* (P<0.05) is significant

Table 4. Independent *t*-test of the pointing and reaching gestures in comparing two consecutive months

Gesture		Df	T	Sig
Pointing	13	17.725	0.616	0.546
	14	12.436	1.934	0.076
	15	13.868	2.349	0.034*
	16	14.116	2.645	0.019*
Reaching	13	14.541	-0.225	0.825
	14	12.796	0.954	0.358
	15	14.061	0.702	0.494
	16	13.501	-0.286	0.780

* (P<0.05) is significant

Another purpose of this study was to determine the developmental process of pointing and reaching gestures. As illustrated in Table 2 and Figure 1, the frequency of pointing gesture incline monthly with age, except in 14-15 months in which no significant difference was observed (P>0.05). The findings from the repetitive measurements in 2 successive months revealed that there is no significant difference, except in 13-14 months in which significant difference was observed (P=0.012). However, if we were comparing two consecutive months, the difference in the mean frequency of the pointing gestures would be significant (12-15 months (P=0.034); 12-16 months (P=0.019)), as it was shown in Table 3 and 4.

According to the Table 2 and Figure 1, the frequency of reaching gesture followed the upward trend monthly, and the findings from the repetitive measurement in two successive months revealed that there was no meaningful difference between the frequency means of reaching gestures. Generally, the comparison of the month 12 with other months revealed that there was no significant

difference in the reaching gestures. Although the chart 2 shows a subtle decline in the frequency of reaching gestures, this decline was not statistically significant.

The third purpose of this research was to study the relationship between pointing and reaching gestures. The results of Pearson correlation indicated that there was no meaningful relationship between these two gestures.

However, inter-examiner reliability was examined on the 20% of the samples by two examiners. The intra-class correlation coefficient (ICC) was 90% (0.9) in this evaluation.

Discussion

The main purpose of this study was to determine the frequency and the typical development of pointing and reaching gestures and their relationship in Farsi-speaking children aged 12-16 months. Pointing and reaching gestures at the child's first communication means prior to the verbal communication stage (6, 7), and can be used by pediatricians and clinicians to screen the developmental problems in children. This, as a developmental milestones scale, can also predict language and communication development (24).

Based on our results, the mean of the pointing gesture increased significantly from 12 to 16 months ($P<0.05$). However, this was not significant for the reaching gesture. Moreover, there was no relationship between pointing and reaching gestures, considering the statistical power of 80%, this might be because of our small sample size.

Our results about pointing gesture consist with another study showing that pointing gesture increase during the second year of life (3, 5, 8, 18, 22, 28, 50). A possible explanation for this phenomenon is that the child's ability (skill) for the three-dimensional interaction (mother, child, object) increases with age and combines with developing the joint attention. Pointing gesture is one of the most common methods of communicating with others; it is expected to increase with age. Another explanation for this might be found in mother's behavior. Mothers as the first and most influential teachers, usually use a combination of pointing gesture and verbal production for naming the objects and events. Children, similarly, 12-month old infants start using a combination form of gesture and word based on their experiences from the environment. The pointing is the most frequent gesture. Children use gestures in combination with their word production, our findings on increasing use of pointing gesture from 12-16 months seems logical (8, 22, 51, 52).

Moreover, we found that although there is a subtle difference in pointing gesture between successive months, these changes are not statistically substantial. This is probably because of a short distance between evaluation sessions. A dramatic change in the pointing gestures during only one month of development is not expected. However, the mean frequency of the pointing gesture increased significantly from 13 to 14 months ($P=0.012$). This change might be because of mother's more inclination toward using pointing gestures during this age (7, 50).

In addition to the pointing gesture, reaching gesture was also examined in this study. The results of our study indicated that reaching gesture did not change from 12 to 16 months of age, which is consistent with a study on reaching gestures in 8-14-month-old children (19). The hypothesis of this study was

that reaching gesture with the imperative function (e.g. Behavior regulation) converts to the pointing gesture with the same function with increasing the age and developing the fine motor movements. Therefore, reaching gestures were expected to decrease with age. However, this hypothesis was not supported by our results. The methodology used in this study might have led us to this result.

Encouraging communication tool was available for the child in this study; that, the child received the object from the mother (communicative partner), and there was no need and no motivation for pointing gesture (10, 12-14). Because the communication context was such that the infants preferred to use easier and faster means of communication and attending to their goals, so they used reaching gestures for imperative functions instead of using pointing gestures. On the other hand, infants learn to point for out-of-reach objects, not for available objects. Our small sample size might be another reason for this observation. Pointing gesture's developmental process was independent of reaching gesture, they developed in parallel to each other. The communication context was the most important component in using communication means (type of gestures), such an account is taken as support for proposal that culture can also have an effect on choosing and designing communication contexts and communication tools and consequently on communication means infants use.

The present study was the first longitudinal in which the development of reaching and pointing gestures and their relationship was analyzed in typical Farsi-speaking toddlers. The small sample size, individual differences between participants and their communicative partners lead us to be cautious about generalizing the findings of this study to all Iranian population.

In conclusion, studying and making conclusions from a much broader population than our sample and examining these gestures in different races are recommended. The relationship between gesture development and communication act be examined in children with communicative disorders. Furthermore, the role of communicative partners, especially mothers, in the development of these gestures should be studied.

Acknowledgement

This article is derived from a master thesis affiliated to University of Social Welfare and Rehabilitation Sciences. The authors would like to offer their sincere thanks to all the families participated in this survey.

Author`s Contribution

Babaei Z: Study concept and design, development of original idea, data collection, statistical analysis, writing the manuscript and finalization.

Zarifian T: Study concept and design, development of original idea, revision of the content, edition of manuscript and finalization, study supervision.

Ashtari A: Study concept and design, development of original idea, revision of the content, edition of manuscript and finalization, study supervision.

Bakhshi E: Study concept and design, development of original idea, statistical analysis.

Ebrahimipur M: Study concept and design, revision of the content, edition of manuscript and finalization.

All authors agreed to be accountable for all aspects

of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest

The authors declare that there is no conflict of interests.

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ORIGINAL ARTICLE

The Relationship between Emotional Content and Word Processing in Normal Persian Speaking Children

How to Cite This Article: Salehi S, Khatoonabadi R, Ashrafi MR, Mohammadkhani GH, Maroufizadeh S, Majdinasab F. Iran J Child Neurol. Autumn 2018; 12(4):140-152

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Received: 18-Dec-2016
Last Revised: 05-Jul-2017
Accepted: 14-Oct-2017

Abstract

Objectives

Emotion is a key component in language processing, but emotional words processing in children is still controversial. We aimed to investigate the relationship between emotional dimensions, arousal and valence, word familiarity, comprehension, use, and emotional content recognition. Eventually, a list of emotional content words for this age was prepared in Persian.

Materials&Methods

The study was conducted in selected elementary schools in Tehran, Iran from April to June 2017. Emotional words, from adult emotional words list, were categorized into 5 groups according to their arousal and valence scores, including neutral, happy, calm, anxious and sad. Evaluation of familiarity, use, comprehension and emotional content recognition of the list was conducted with a checklist in 60 first grade children by speech and language pathologist.

Results

Neutral words gained the highest score in familiarity, use, comprehension and emotional content recognition (the mean=0.74). Afterward, there were the emotional words with high valence, calm (the mean=0.64) and happy (the mean=0.52). Finally, it was found the low score for valence emotional words, sad (the mean=0.46) anxious (the mean =0.43) in end of score rating. There was a significant difference between all word groups in four aspects (P-value<0.001). There were no significant differences between boys and girls in four aspects.

Conclusion

Neutral words are better comprehended and expressed than emotional words. Valence is more effective than arousal in emotional words. Gender was not a determinant factor in all of the aspects. An emotional word list which is comprehensible for children in Persian language was prepared.

Keywords: Emotional content words; Use; Comprehensibility; Familiarity; Persian

Introduction:

Generally, emotion is defined as complicated mental state including three definite constituents: conscious experience related to psychological states, physiological response closed to nervous system reaction, and behavioral or expressive response related to motivation (1, 2). Primarily, emotions were a reflexive response to the stimulus; these responses are motions toward positive and pleasant things and away from negative and unpleasant things. Many of theories of emotion proposed "dimensional organization" for emotion (3). Accordingly, it has bipolar dimensions, including arousal and valence based on evaluative reactions (4). Valence can be defined by bipolar scales that describe constant dimension from pleasantness such as happy and pleased to unpleasantness such as unhappy and annoying (3, 5). The second dimension is arousal described by bipolar scales from an unaroused state such as calming, sleepy and relaxed to high arousal state such as excited and stimulated (3, 5).

There is no gold standard for measuring emotion but Self-Assessment Mankin (SAM) is a widely used assessment technique that precisely measures the arousal and valence. It is a photographic nonverbal approach then it can be used in various language and culture (6).

Emotion in word can be expressed in two ways: verbal or content and non-verbal or prosodic emotion (7). Both of them have an impact on word processing (7). There is debatable data in mutual relationship between emotional aspects including arousal and valence, and emotional word processing. Emotional words processing is modulated by arousal (8, 9), for example, high arousal emotion such as fear had negative effect on information processing in children (9). Similarly, arousing words were better processed (10). On the other hand, valence is more important than arousal in word processing (11, 12). For example, an electrophysiological study indicated that valence and concreteness of word had a key role in emotional words processing (12). Negative emotional words were processed slower than positive and words with high valence slower than low valence, so valence was more important than arousal (13). Therefore, it is still controversial that which dimension of emotion (valence or arousal) is more effective in word processing. This gap in the research will be considered to find out which one is more important in word processing.

Word processing can be assessed by comprehension and expression of words. There are various factors such as frequency of word, age of acquisition and recently emotional content which has influence on word comprehension and expression (11, 14). Comprehension and expression of emotional content words were investigated in some languages. These studies were conducted in Dutch, English, and Chinese languages and they established a list of appropriate words for each age (14-17). Additionally, appropriate emotional and behavioral function in children required language competency (18). Language is a vital tool to express emotion and feelings (19). Children with language disorders experience more emotional and social problems than their peers (20). These language disorders have a wide range, from phonological disorders to pragmatics and limited vocabulary. Then, because of relationship between language and behavior, maybe, these can be the base of behavioral difficulties (21). There is no study to explore emotional content word processing

in Persian speaking children and we have no emotional content words list for children. This list can be useful for language therapy in children.

The main aim of present study was to explore the relationship between emotional dimensions (arousal and valence) and word processing (familiarity, use, comprehension and emotional content recognition of words) words in Persian-speaking children 7-8 yr old. Any difference between boy and girls abilities was considered.

Materials & Methods

The present study had cross-sectional non–experimental research design, including 4 parts as follows:

Preparation of tools

This was a non-experimental descriptive cross-sectional study. Previously, 320 words of the Persian emotional words list were rated according to valence and arousal aspects by 1-7 Self-Assessment-Mankin (SAM) scale by 1200 normal Persian- speaking adult using computer. These words were selected from valid Persian dictionaries based on their frequency and use in daily living (16). As mentioned earlier, SAM is a pictorial measurement of emotion. This approach was developed for assessment of emotional state which used nonverbal graphical representations for feelings. This method has a high correlation with other verbal semantic scales (6).

This technique has a series of pictures which varied in arousal from sleepy calm to arousing state and valence (pleasant) from happy to sad face (Figure 1). It can be done in both computer and pencil-paper ways. Since it is a nonverbal graphical oriented scoring system, it does not depend on language ability. Then, it can be employed with non-English speaking people. However, its validity and reliability should be investigated (6). This instrument became valid and reliable in Iran, and test-retest reliability coefficient was in the range of 0.55-0.78 and concurrent validity ranged from 0.56 to 0.87 for SAM (22). We utilized this emotional word list as resource for our investigation.

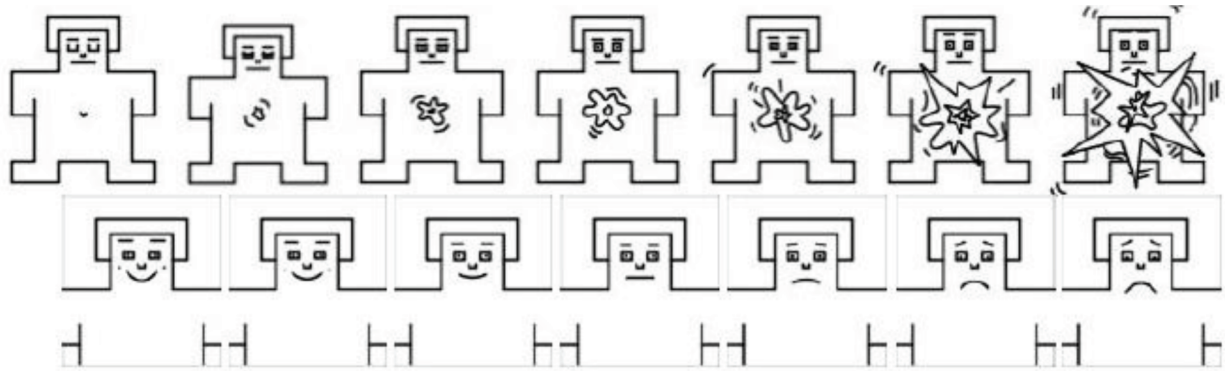

Fig 1. *1-7 SAM scale (19) for arousal (top) and valence (down) (19).*

Emotional words can be categorized by their scores in valence and arousal, into five groups, namely, happy, calm, sad, anxious, and neutral words (16), including:

1. Happy words including words which had scored more than 4 in both of arousal and valence.
2. Calm words consisted of words with score less than 4±S.D. in arousal and more than 4 in valence.
3. Sad words contained words which had score less than 4±S.D. in both of arousal and valence.
4. Anxious words including words which had scored more than 4±S.D. in arousal and less than 4 in valence, and finally,
5. Neutral words with score 4±S.D. in both of arousal and valence.

We categorized the words by their instruction as explained above in a five scoring and prepared the list which contained 40 happy, 78 calm, 28 sad, 80 anxious and 94 neutral words. These words were assessed in four selected dimensions of word processing, namely, familiarity, comprehension, use and emotional content recognition by a checklist which obtained content validity according to six expert speech and language pathologists and one linguist. The checklist was administered by one experienced speech and language pathologist in children for each word and it has yes/no scoring system, 1 for yes and 0 for no. The used question is following:

1. "Familiarity" was evaluated by asking: Is this word heard or not? Yes/no

2. "Comprehension" was evaluated by word definition: Is the definition clear? Yes/no

3. "Use/Expression" was assessed by making a sentence with the words. Is the sentence meaningful? Yes/no

4. Before emotional words were categorized into three main groups based on their scores in arousal and valence, including neutral, positive (calm and happy) and negative (sad and anxious). To describe this categorization to children, we used good, bad and moderate (not good, not bad) for positive, negative and neutral categories, respectively. For example, "family" is a calm category then it is described as a good word for children. Then, for "Recognition of emotional content" evaluation, Child was asking: is this word good, bad or moderate? (If the subject recognize emotional content of words inconsistent with emotional categorization/yes, otherwise/no).

For example, is "family" a good, bad or moderate word? If the child says: good, it is correct because it was a positive word.

Participants

Participants were 60 (30 boys and 30 girls) normal Persian-speaking children, their age ranged from 79-89 months (S.D. =3.46). They were recruited at random from first-grade classes in two public elementary schools from April to June 2017. These schools including a girl's school and a boy's school were selected randomly from central areas in Tehran, Iran which are commonly moderate area. The files of all first-grade students in each school were checked and the names of students who met inclusion criteria were written down. Then, our participants were selected randomly from these written names.

Inclusion criteria of participants were: 1) native monolingual Persian speaking children; 2) middle level of socio-economic status of families based on their family information in their files and teacher's opinion; 3) No history of psychiatric and neurological disorders based on their medical history documents in schools, 4) No reading or other speech and language disorders, according to speech and language pathologist assessment.

All parents included children gave the parental informed consent form. This study has been approved by the Research Council, School of Rehabilitation, Tehran University of Medical Sciences.

Procedure

Four questions in the checklist were asked for 320 words in emotional word list and the score was recorded by 1-0 scoring system. It takes almost 1.5 h for each child. There was a timeout for probable tiredness and finally the children have received a gift for their cooperation. All participants were evaluated in one private quiet classroom individually by one experienced speech and language pathologist.

One expert speech and language pathologist asked the questions for familiarity, comprehension, use, and recognition of emotional content and record the child' response. Their scores were calculated for each word based on their verbal recorded responses. Total score for each word was between 0-4. Questions and response are explained in Table 1.

Table 1: Procedure of the checklist scoring

	SLP' question	Child's tasks	Scoring base	Scores
Familiarity	Is this word (chair) heard or not?	Saying Yes / no	Yes or no	Yes =1 No =0
Comprehension	What is the meaning of this word (chair)?	Defining the word, for example: the thing which sitting on it Or using synonyms	Is the definition clear? Yes/no Is the synonym correct? Yes/ no	Yes =1 No =0
Use / expression	Can you make a sentence with this word (chair)?	Making a meaningful sentence with this word. We have a chair in the room	Is the sentence making sense or not? Yes/no	Yes =1 No =0
Recognition of emotional content	Is this word (chair) good/bad or moderate?	Deciding the word is good or bad or moderate. Chair is a neutral word then correct response is moderate.	Good for happy and calm words is yes Bad for sad and anxious words is yes Moderate for neutral words is yes Otherwise No	Yes =1 No =0

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, ver. 22.0 (IBM Crop., Armonk, NY, USA). The Shapiro-Wilk test was used to evaluate the normality of the data. A Kruskal-Wallis test, followed by the Dunn posthoc test, was used to compare between categories of words. Relationships between dependents variables including familiarity, comprehension, use, emotion recognition and mean of scores were examined by Spearman correlation coefficient. All statistical tests were two-sided and a *P*-value<0.05 was considered statistically significant.

Results

The subjects were 60 first grade school children, their age ranged from 79-89 months (S.D. =3.46). They also were matched in gender and socioeconomic status.

Strong positive correlations were found between all dependent variables including, familiarity, use, comprehension and emotional content recognition (ranging from 0.91 to 0.98) (Table 2).

Table 2: Means, standard deviations, and correlations among study variables

	Mean (SD)	Familiarity	Comprehension	Use	Emotional Content Recognition	Mean of score
1. Familiarity	0.67 (0.38)	1				
2. Comprehension	0.43 (0.29)	0.930[a]	1			
3. Use/Expression	0.62 (0.39)	0.980	0.934	1		
4. Emotional Content Recognition	0.63 (0.38)	0.966	0.910	0.959	1	
5. Mean of score	0.59 (0.36)	0.974	0.973	0.975	0.971	1

SD: standard deviation

[a] All correlations are significant at 0.001 level (*P*<0.001)

All word processing variables had strong relationship. It means these variables for word processing had been selected appropriately. The strongest relationship was between use and familiarity (0.98).

Scores in different dependent variables for five categories of words are exhibited in Table 3.

Values are given as mean (SD)

[†] Kruskal-Wallis test followed by the Dunn post-hoc test

[a-c] Groups followed by the same letter are not significantly different at the 0.05 level.

Table 3. Values of five emotional categories

	Calm	Anxious	Neutral	Happy	Sad	*P*-Value†
Familiarity	0.73 (0.36)^{ab}	0.51 (0.38)^{c}	0.82 (0.31)^{a}	0.61 (0.40)^{bc}	0.55 (0.43)^{bc}	<0.001
Comprehension	0.48 (0.28)^{a}	0.32 (0.28)^{b}	0.58 (0.26)^{a}	0.32 (0.26)^{b}	0.29 (0.26)^{b}	<0.001
Use	0.66 (0.37)^{b}	0.45 (0.38)^{c}	0.79 (0.33)^{a}	0.57 (0.40)^{bc}	0.50 (0.42)^{bc}	<0.001
Emotional content Recognition	0.70 (0.35)^{ab}	0.46 (0.36)^{b}	0.78 (0.32)^{a}	0.59 (0.39)^{ab}	0.49 (0.40)^{bc}	<0.001
Mean of scores	0.64 (0.33)^{ab}	0.43 (0.35)^{c}	0.74 (0.30)^{a}	0.52 (0.36)^{bc}	0.46 (0.37)^{bc}	<0.001

Familiarity**:** Neutral words were the most familiar for children (mean =0.82). Calm words were the next group (mean=0.73), happy words after calm words (mean=0.61). Sad and anxious words did not have marked differences, by mean 0.55 and 0.51, respectively. Generally, the words with high valence were more familiar than low valence, after neutral words. Differences between all groups were significant (*P*-value < 0.001).

Comprehension: Likewise familiarity, neutral words had the most score in comprehension (mean=0.58) which followed by calm words (mean=0.48). Anxious and happy words were at the same level (mean=0.32). Finally, sad words had the lowest score (mean=0.29). Then neutral and high valence words had more score in comprehension variable. There was significant difference between all word groups (P-value < 0.001).

Use: In the case of use, neutral words had been taken as the most score (mean=0.79). Then, calm (mean=0.66) and happy words (mean=0.57) were the next. These words were followed by sad words (mean=0.5) and anxious words (mean=0.45) had the least score of use. Difference between mean score in all word groups was significant (*P*-value < 0.001).

Emotional content recognition: There was the same pattern in emotion recognition variable, first there were neutral words (mean=0.78), next calm (mean=0.7) and happy (mean=59) and following by sad (mean=0.49) and finally, anxious words (mean=0.46). As with other variables, significant difference was in all word groups (P-value < 0.001).

Mean of scores: Overall, mean of scores in neutral words was the most (mean=0.74), next calm (mean=0.64) and happy (mean=0.52) respectively, and then anxious (mean=0.43) and sad words (mean=0.46). In other words, the words without emotional content (neutral words) had the highest mean of score, and then the words with high valence were followed by the words with low valence. Altogether, differences in all word groups were statistically significant (*P*<0.001).

Although there were no significant differences between girls and boys in mean of scores in all word groups (P>0.05), some words in each word category had significant difference between boys and girls. These words included: lover (mæδuq), life (zendegi), waterfall (ʔabδar) and calm (ʔaram) in clam category, in these words boys had more scores. In anxious category, girls had more score in curse (nefrin), disaster (mosibæt) and regretful (pæδiman) and boys had more scores in cartridge (feδæng), bandit (rahzæn), terrorist (terorist), panzer (tank). Considering neutral category, boys were better in ladder (nærdeban), toothbrush (mesvak), steel (fulad), gear or rib (dænde), soil (xak), asphalt (ʔasfalt), and iron (ʔahæn) words. Boys also were significantly better in flight (pærvaz), song (ʔavaz), gift (hedie) and happy (xoδhal) in happy words and cage (qæfæs) in sad words (P-value<0.05).

Conclusively, the words with mean of scores below 0.5 including 138 words in all word groups were omitted from the list, and finally, the children emotional content word list with 182 words was prepared.

Discussion

We aimed to investigate the relationship between emotional content and some aspects of words processing including use, comprehension, familiarity and emotional content recognition of words, by considering two dimensions of emotion including valence and arousal.

Neutral words got the highest score in all dimensions of word processing. As well as, calm and happy words got higher score than sad and anxious. Pleasant had stronger relationship than arousal and furthermore, emotional words with high pleasant were processed more highly accurate than others.

We found that neutral words were the best across other categories in all aspects of word processing, including use, comprehension, familiarity, and emotional content recognition. By contrast, emotional content assists word processing (11). This difference can be explained by the type of these words. In the present study by using Persian emotional words list (16), all neutral words were nouns, thus those appear earlier in development. Additionally, concreteness and frequency are effective factors in word processing (12), it is valid in this word category (23), the neutral words which are nouns are high frequent and concrete/ subjective in compare to emotional words which are usually adjective/objective. Accordingly, it can be reasons why neutral words have the highest scores in our investigation. While valence and arousal are two main dimensions of emotion, just valence is taken to account for word processing based on our analysis. Valence is likely an effectual factor in comprehension and use of words and emotional content recognition. Apparently, it is in contrast to study which declares emotion is adjusted by the arousal of the emotional words (8). Our results are consistent of the results of other studies which argued the valence of the emotional words was more important than arousal in word processing (11, 12). Pleasure (valence) has an important act in word processing in Persian speaking children rather than arousal. In other words, pleasantness facilitated emotional content processing.

Therefore, pleasure (valence) is important in language processing then it could be considered in speech and language assessment and treatment procedures in Persian language.

There was no significant difference between boys' and girls' performance, in consistent with another study (24). However, there is only one study contrary to our findings suggested that girls produced more emotional content words than boys (17). Generally, emotional content word processing is not affected by gender, but we have some girlish and boyish words that mentioned in results.

Additionally, there are researches in developing comprehensible emotion words list for children in other languages (14), at the end of analysis, we prepared a list of emotional words which is suitable for 7-yr-old children (Appendix 1). Since there is not emotional words list in Persian language for children, the list can be a preliminary list for next researches.

Appendix 1: Children emotional words list

Friend (dust)	Snake (mar)	Refrigerator (yæxčal)	Child (bæče)	Cry (gerye)
Car (maδin)	Wolf (gorg)	Table (miz)	Cookies (δirini)	Wrath (qæhr)
Fish (mahi)	Pain (dærd)	Glass (livan)	Laugh (xænde)	Sick (mæriz)
Book (ketab)	Accident (tæsadof)	Spoon (qaδoq)	Money (pul)	Cage (qæfæs)
Day (ruz)	Gun (tofæng)	Nail (naxon)	Heaven (beheδt)	Beggar (geda)
Sea (dæria)	Thief (dozd)	Pencil (medad)	Happiness (δadi)	Arrow (tir)
Home (xane)	Hell (jæhænæm)	Clothes (lebas)	Glee (xoδhali)	Well (čah)
Child (kudæk)	Prison (zendan)	Bowl (kase)	Gift (hedye)	Miserable (bædbæxt)
Boat (qayeq)	Hot (daq)	Hat (kolah)	Flight (pærvaz)	Greed (hers)
Night (δæb)	War (jæng)	Key (kelid)	Celebration (jæδn)	Sad (narahæt)
Mountain (kuh)	Storm (tufan)	Dresser (komod)	Respect (ʔehteram)	Poor (fæqir)
Smile (læbxænd)	Devil (δeitan)	Carpet (farδ)	Song (ʔahæng)	Groan (nale)
Flower (gol)	Enemy (doδmæn)	Hand (dæst)	Wedding (ʔærusi)	Sulky (delxor)
Bazaar (bazar)	Bomb (bomb)	Bracelet (dæstbænd)	Eid (eid)	
Mother (madær)	Earthquake (zæminlærze)	Street (xiabun)	Joke (jok)	
God (xoda)	Ampoule (ʔampul)	Door (dar)	Encouragement (tæδviq)	
Shopping (xærid)	Fear (tærs)	Boot (čækme)	Dance (ræqs)	
Window (pænjere)	Loose (δekæst)	Fork (čængal)	Lucky (xoδbæxt)	
Beautiful (qæδæng)	Cancer (særætan)	Wood (čub)	Marriage (ʔezdevaj)	
Pretty (ziba)	Blade (tiq)	Socks (jurab)	Secret (raz)	

Balmy (xoδbu)	Crazy (divane)	Umbrella (čætr)	Kiss (mač)	
Family (xanevade)	Corpse (jenaze)	Light (čeraq)	Victorious (piruz)	
Rain (baran)	Nightmare (kabus)	Bed (tæxt)	Lover (ʔaδeq)	
Sky (ʔaseman)	Death (mærg)	Ladder (nærdeban)	Melody (tærane)	
Leaf (bærg)	Grave (qæbr)	Bag (kif)		
Music (musiqi)	Flood (seil)	Paper (kaqæz)		
Kind (mehræban)	Punishment (tænbih)	Kettle (ketri)		
Story (dastan)	Regretful (pæδiman)	Glass (δiδe)		
Perfume (ʔætr)	Killer (qatel)	Knob (dæstgire)		
Feather (pær)	Panzer (tank)	Gloves (dæstkeδ)		
Sunlight	Syringe (soræng)	Tooth (dændan)		
Dude (ræfiq)	Curse (nefrin)	Wall (divar)		
Birthday	Execution (edam)	Lesson (dærs)		
Angel (fereδte)		Neighbor (hæmsaye)		
		Chair (sændæli)		
		Chord (tænab)		
		Bucket (sætl)		
		Radio (radio)		
		Dough (xæmir)		
		Bridge (pol)		
		Hole (surax)		
		Chin (čane)		
		Elevator (asansor)		
		Gear or rib (dænde)		
		Ointment (pomad)		
		Glass (ʔestekan)		
		Toothbrush (mesvak)		
		Password (ræmz)		
		Quilt (læhaf)		
		Session (jælæse)		
		Drum (tæbl)		
		Board (tæxte)		
		Agency (ažans)		

The limitation in this study was that the most of neutral words are nouns and the most of emotional content words are adjectives in Persian language. Even if nouns and adjectives were matched in frequency and length, these had different type of word and age of acquisition. Emotional content word processing investigation can be conducted by electrophysiological methods, like Event-Related Potentials which has high temporal resolution and it can illustrate underlying neural mechanism in arousing and pleasant word processing.

In conclusion, neutral words are processing better than emotional words. Valence is more effective than arousal in emotional aspect, in the other words, pleasant words processing is better than other emotional words.

Acknowledgement

The authors wish to thank personals of Fatemeh Zahra and Imam Ali Elementary School and Tehran Education and Training Organization for their corporation and support.

Authors' Contribution

Salehi S, Khatoonabadi A, Ashrafi MR and Mohammadkhani Gh, had basic contributions to theoretical search and research design. Salehi S, Khatoonabadi A, and Majdinasab F had significant contribution in preparing tools for the research, data collection and drafting. Maroufizadeh S, and Salehi S has an essential contribution to data analysis and drafting.

All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest

The authors declare that there is no conflict of interests.

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ORIGINAL ARTICLE

Risk Factors for Hearing Loss and Its Prevalence in Neonates Older than 6 Months with History of Hospitalization in Intensive Care Unit

How to Cite This Article: Keihani-Doust Z, Tabrizi A, Amini E, Sedaghat M, Ghahremani AA, Shariat M, Kavyani Z. Risk Factors for Hearing Loss and Its Prevalence in Neonates Older than 6 Months with History of Hospitalization in Intensive Care Unit. Iran J Child Neurol. Autumn 2018; 12(4):153-161

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Received: 09- May -2017
Last Revised: 27-Dec-2017
Accepted: 28- Feb -2018

Abstract

Objectives

Hearing loss is one of the most important disabilities in neonates. Delay in the detection of hearing loss leads to impaired development and may prevent the acquisition of speech. We aimed to determine the risk factors associated with hearing loss in neonatal patients aged more than 6 months with a history of hospitalization in Neonatal Intensive Care Unit (NICU).

Methods

In this case-control study, screening for hearing loss was carried out on 325 neonates aged 6-12 months referred to Pediatric Neurology Office of Vali-e-Asr Hospital, Tehran, Iran up to 2011. Hearing loss was confirmed using Auditory Brainstem Response screening test (ABR).

Results

The prevalence of mildly and moderately hearing loss in neonates was determined as 3.6%. The most significant risk factors for hearing loss in neonates were neonatal icterus associated with phototherapy, respiratory distress syndrome (RDS) and lower Apgar score.

Conclusion

It seems to quantitative auditory system screening using ABR is necessary for all neonates; because rehabilitation support such as speech therapy and hearing training in this age period is more effective than older ages.

Keywords: Hearing loss; Neonates; Risk factor; Auditory Brainstem Response

Introduction

One of the valuable human senses is hearing that facilitate communication between people through speaking (1). Hearing loss in early life lays a disability that prevents the evolution of speech skill, also language and

hearing difficulties (2, 3). Neonatal hearing loss is estimated at approximately 1 to 3 cases per 100 live births increases to 1%-5% in infants hospitalized in neonatal intensive care units (NICU) (4). The severity of hearing loss defines based on the assessment of threshold in decibels (dB) at various frequencies; normal hearing threshold is 0-20 dB and the severity of hearing loss ranks to 4 categories of mild, moderate, severe and profound loss (5).

The majority of neonatal hearing losses are sensorineural (6), but according to Joint Committee on Infant Hearing (JCIH), neonatal risk factors are risk factors for neonatal hearing loss as follows:

a) family history of hearing impairment, b) intrauterine infections such as cytomegalovirus (CMV), toxoplasma etc., c) neonatal specific disorders as severe hyperbilirubinemia that needs exchange transfusion, d) persistence pulmonary hypertension (PPHN) associated with mechanical ventilation and e) after birth infection like bacterial meningitis (7). By 1998, screening for hearing loss was done in 2.5 years of age in the United States. By implementing public hearing screening program in 2001, the average age of diagnosis was commuted to 3 months and the average age of the intervention determined as 6 months (8).

According to American Pediatrics Academy (APA), the effective test for neonatal hearing screening should detect hearing loss more than 30 dB and be accurate in lower than 3-month neonates; two electrophysiological tests have these properties: Auditory Brainstem Responses (ABR) and Otoacoustic Emission (OAE) (9). ABR measures action potentials from cranial nerve of eight (cochlear nerve) to lower midbrain colliculus in response to the incoming stimulus (3). ABR measures not only the integrity of the inner ear but also the auditory pathway (10). ABR responses are less subjective than common behavioral tests and also can assess mild or unilateral hearing loss. Validity, reliability and predictive efficiency of ABR in neonatal hearing loss detection have been proven already (11, 12).

"Hearing loss causes delays in development of speech and language, and those delays then lead to learning problems, often resulting in poor school performance" (8). Nowadays, in the health centers in Iran, hearing status assessment of newborns is done with OAE qualitative test and ABR in 6-12 month neonates do not perform routinely.

We aimed to evaluate hearing loss in 6-12 months of neonates with a history of NICU admission.

Materials & Methods

This case-control study was conducted for further investigations of hearing loss in 6-12 months neonates referred to Pediatric Neurology Clinic (Tehran, Iran) for 5 years up to August 2011, with a history of hospitalization in Vali-e-Asr Hospital's NICU, Tehran, Iran.

Overall, 325 neonates were enrolled based on the inclusion criteria. Infants clinically and para clinically proved hearing loss assumed as case group and the control group was those who had no hearing impairment. An auditory evoked potential system (Charter ICS, Denmark) was used to record ABR. A click-type stimulus was used twice with rarefaction polarity, with Intensity of 35-80 dB NHL, under 21/1 pulse set based on 1500 trials and analysis time of 10-15 ms. All of the neonates had been sedated by oral chlorate hydrate, 50 mg/kg half an hour before the test.

Four electrodes were applied as follows: two

active ones were placed on mastoid bones, the reference electrode on vertex, and the ground electrode on the forehead. Recorded waves were analyzed and interpreted by an expert audiologist. Measurable and comparable variables consisted of mean latency of V, III and I waves, interpeak interval of I-III, III-V, I-V waves and no waves. Neonates were divided into two groups according to the normal and abnormal results of the ABR. After assessment of hearing status, 12 neonates showed impairment (case group) and 4 times more neonates enrolled as a control group (n=48). Both of groups matched in gestational age (± 2 wk) and birth weight (± 200 gr). Hearing loss detected using ABR test. Recorded variables collected in 3 categories:

Pregnancy variables: A) fetal infections e.g. CMV, rubella, hepatitis B, HIV, syphilis, and chickenpox; B) mothers drug abuse during pregnancy; C) mothers diseases including preeclampsia, gestational diabetes mellitus (GDM), chronic diabetes mellitus, chronic hypertension and heart diseases.

Neonatal variables: mechanical ventilation more than 2 d, low Apgar score (<7), RDS, metabolic diseases (including congenital adrenal hyperplasia, galactosemia, Phenylketonuria (PKU) and hyper/hypothyroidism), sepsis, icterus requiring phototherapy or exchange transfusion.

Independent variables: hearing loss of mothers, fathers or both of them.

Informed consent was received verbally from parents. The name and personal information of the patients remained confidential

Statistical Analysis

Data were analyzed using SPSS software 17.2 (Chicago, IL, USA). Bijective dependent variables analyzed via logistic regression; student t-test used for assessment of correlations among quantitative variables including Apgar score, mechanical ventilation days and qualitative variables including history of icterus, RDS, PPROM sepsis, preeclampsia, thyroid dysfunction and Delivery type analyzed by Chi-square test. A P-value of less than 0.05 considered as significant and for significant correlations, Odd ration with confidence interval of 95% calculated for significant correlations.

Results

Among 325 neonates, 12 infants (3.6%) showed hearing loss according to ABR results as mild (threshold of hearing 15-30 db) and moderate (30-50 db) hearing loss. There was 3 females (25%) and 9 males (75%) in these 12 cases with male to female ratio as 3 to 1. Bilateral hearing loss was shown in 3 neonates (0.92%).

History of icterus, acute RDS and low Apgar score showed significant with impaired hearing screening results (Table 1).

There were no histories of meconium-stained

Table 1. Correlation of impaired hearing screening results with History of icterus, acute RDS and low Apgar score

Variables		Percentage OR	Correlation with Hearing Loss		
			CI 95%	P-value	
Icterus	Case	75	4.5	2.2-9.1	<0.001
	Control	16.7			
RDS	Case	25	0.75	0.54-1	0.006
	Control	0			
Low Apgar score	Case	33.3	5.3	1.3-20.7	0.02
	Control	6.3			

liquor, maternal heart diseases and diabetes in both groups. In the history of any of the members of the two groups, there was no evidence of TORCH. The family history of hearing impairment was negative for members of both groups. Number and percent of not significant variables are listed in Table 2.

No significant differences were noticed between case and control groups in Delivery type, Sepsis,

Table 2. Number and percent of not significant variables

			Number of cases	Percent
Delivery type	NVD	Case	5	41.7
		Control	12	25
	CS	Case	7	58.3
		Control	36	75
Sepsis	Case		1	8.3
	Control		5	10.4
PROM	Case		3	25
	Control		4	8.3
Mothers preeclampsia	Case		2	16.7
	Control		1	2.1
Thyroid dysfunction	Case		0	0
	Control		1	2.1
Mechanical ventilation ≥2 d	Case		1	8.3
	Control		1	2.1

PROM, preeclampsia, thyroid dysfunction and ventilation; NVD: normal vaginal delivery, CS: cesarean section, PROM: preterm rupture of membrane.

Discussion

In the present study, 3.6% of infants showed hearing loss according to ABR result with male to female ratio as 3 to 1. All of infants in case group showed impaired OAE test and 75% of these infants had a history of icterus while only 16.7% of infants in control group had this history. A history of acute RDS showed in 25% of neonates in case group and there was no case of RDS in control group. Low Apgar score was recorded for 33.3% of neonates in case group and 6.3% of cases in control group.

The total cost of education for not screened hard-hearing children imposes high costs on governments (13). The prevalence of congenital hearing impairment determines in neonatal screening, was 2 times more than other disorders characterized by the screening of this age period (14, 15). The frequency of this disorder was 2-6 cases per 100 live births, the figures obtained similar results in Iran which implies that the hearing loss is a health problem in our country (6, 15). In a pilot study of national hearing screening in Iran, 89.7% of newborns proved normal in the primary screening in the maternity ward using OAE test, and 10.3% were abnormal (13). Most of the infants born in hospitals of the project were not referred for follow-up process of hearing screening. Using Poison's distribution for frequency rate of hearing impairment and normal estimate for this distribution and 95% confidence intervals, significant bilateral sensorineural hearing loss was present in ~1 to 4 per 1000 live births in the well-baby nursery population (12 neonates), and in ~2.5 to 4.6 per 100 infants in the intensive care unit (13). The reasons for this situation, especially in Iran are cultural, economic and family health and community awareness of the adverse consequences of hearing impairment in newborns that are discussable from different perspectives.

Our results showed that the prevalence of hearing loss in infants with risk factors before and after birth was 3.6 cases per 100 live births; this figure was almost within the global prevalence (7). In Iran, this prevalence was 8(16), 3.5 (8) and 28 (17) cases per 100 births. Several reports from different regions of the world expressed wide ranges of hearing loss prevalence as 7.8%, 29.1% and 13.5% (18-20). The reason for this variation in results may be using different protocols for screening and also real difference in the prevalence of the disorder in different regions of the world. In a 4 year period, evaluate hearing status 15165 newborns at 15th d after birth using OAE test and the prevalence of hearing impairment showed in 10.8% cases in this stage; ABR test was done for these neonates in next stage and hearing loss confirmed for 6.2% by ABR (10). This study showed that routine screen in the health centers in Iran overestimates hearing loss; so, OAE should be replaced with a more accurate test in early stage.

A research on 1062 infants at risk for hearing loss showed 14 patients with bilateral hearing loss (21). The incidence of bilateral hearing loss was reported as 1-4/1000 newborns (22); however present results showed bilateral hearing loss in 0.9% of infants. Differences in outcome may depend on the type of hospital and its patients. The current study hospital is one of the reference hospitals for women with high-risk pregnancies and infants which may result in higher percentage of neonatal hearing loss

compared to similar studies in Iran.

An important risk factor for hearing impairment in this study was icterus requiring phototherapy (OR=4.5). Nowadays, the importance of icterus, especially severe degrees, is well marked in auditory neuropathy (17, 23). The frequency of hearing impairment in neonates born by normal vaginal delivery (NVD) was significantly more than cesarean section (13). However, in the present results, this correlation was not seen; probably due to low sample size and professionally done NVD in our study population. Low birth Apgar score was significantly correlated with subsequent hearing loss (OR= 5.3), reported as a similar rate already (24, 25); however, this connection was not proven yet (3).

The present study showed that there was no correlation between maternal preeclampsia and neonatal hearing loss, reported already (26). Neonates with hyperbilirubinemia history show higher frequency of hearing loss up to 5 times more than neonates without icterus (27). This relationship also was noticed in our study where 75% of icteric neonates were found with hearing impairment. Low Apgar score was found as a risk factor for hearing loss (28); in line with our results that neonates with low Apgar score showed following hearing loss about 5 times more than normal neonates. There was no correlation between neonatal hypothyroidism and hearing loss (29). Our result showed similar finding on thyroid dysfunction including hyper/hypothyroidism are not related to hearing loss.

The present findings showed correlation between neonatal RDS and hearing loss; however few studies investigate this relationship. RDS was not a risk factor for hearing loss (18); while a case of 2 infants with RDS showed delayed hearing loss at the age of 2.5 yr; who had normal hearing status up to 1-year screening programs (30). These controversial results should be clear by further evaluations.

In conclusion, the newborn hearing screening program is possible, beneficial and justified in terms of scientific and economic principles that provide early treatment interventions that can significantly reduce further costs for patients. Moreover, because the incidence of congenital bilateral hearing loss is higher than the prevalence of other disorder screening, newborn hearing screening is done as soon as possible-preferably before three months of age and early intervention programs and the hearing strengthening tools should be available in health centers. Given the prevalence of hearing impairment 3.6% and risk factors such as phototherapy treated icterus, RDS and low birth Apgar score and also the cost of hard-hearing patients training, it seems necessary considering of these risk factors in hearing screening. Nowadays, neonatal hearing status screening performs routinely using OAE in Iran; however, ABR is a more accurate test to replace with OAE in the first step of screening.

Acknowledgement

This study was a general practitioner thesis approved ethically and financially by Tehran University of Medical Sciences. We appreciate pediatric and NICU staff of Vali-e-Asr Hospital who cooperated in performing this project.

Author`s Contribution

Zarrin Keihani-Doust designed the study and

supervised sampling implementation.

Idin Tabrizi and Elahe Amini participated in study design and checked the correctness of the implementation of the study.

Mamak Shariat participated in study design and performed the statistical analysis.

Mojtaba Sedaghat and Amir-Ali Ghahremani conceived of the study, and participated in its design and helped to draft the manuscript.

Zeinab Kavyani collected data and drafted the manuscript. All authors read and approved the final manuscript.

All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest

The authors declare that there is no conflict of interests.

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Cockayne Syndrome Misdiagnosed as Cerebral Palsy

How to Cite This Article: Vafaee AR, Baghdadi T, Norouzzadeh S. Cockayne Syndrome Misdiagnosed as Cerebral Palsy. Iran J Child Neurol. Autumn 2018; 12(4):162-168

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Received: 25-Jun-2017
Last Revised: 24-Oct-2017
Accepted: 21-Nov-2017

Abstract

A 7-yr-old patient was referred to pediatric orthopedic clinic of Imam hospital (2016) with the diagnosis of cerebral palsy (CP). His parents were concerned about some inconsistency of his disease progression. After initial evaluations, the diagnosis of CP was incorrect. The true diagnosis was suspected and confirmed with molecular genetic analysis. A rare autosomal recessive disorder -Cockayne syndrome- was diagnosed. Although untreatable, it can be prevented by appropriate prenatal diagnostic tests for their future children.

Keywords: Cockayne syndrome; Cerebral palsy; Prenatal diagnosis

Introduction

Cerebral palsy (CP) is a relatively common disorder with clinical presentation that predominantly becomes obvious after the first year of life (1, 2). The combination of spasticity, developmental delay, and positive birth history are the mainstays of the diagnosis. Of these, none is specific for the diagnosis and any doubt arising from clinical or history should be carefully noticed and appropriate measures are warranted.

In fact, some neurometabolic and hereditary disorders share the similar clinical characteristics with CP and only careful physical examination and detailed birth as well as developmental history could make differential diagnosis possible (3).

Here we represent a 7-yr-old boy referred to our clinic. He had been diagnosed with CP.

Case presentation

This study was approved by the Ethics Committee of Orthopedic Surgery Department, Imam Khomeini Hospital, Tehran, Iran and a written consent was signed by the parents.

A 7-yr-old boy, the only child of otherwise healthy parents was referred the Pediatric Orthopedic Clinic, Imam Khomeini Hospital, Tehran, Iran

on July 2018 with the diagnosis of CP. The reason for referral was the parents' concern about the increasing severity of disease despite regular occupational therapy.

On physical examination, the patient was developmentally delayed, unable to walk or stand, with obvious cognitional and gross and fine motor retardation. Flexion contractures were noted in elbows, wrists, knees, and hips. There was bilateral equinovarus deformity of feet and increased popliteal angle. Plantar reflexes showed extension response and DTRs were exaggerated. Spastic response of muscles was recorded after continuous stretching. Sitting balance was extremely unstable (Figure 1).

Figure 1. *Unstable sitting balance at the age of 7 years*

The patient was the result of a consanguine marriage and normal pregnancy. Birth weight was 2950 gr and head circumference and height were 35 and 47, respectively. The few first months of his life showed normal weight gaining and development. He was able to hold his head in 5 months and roll over at 7 months age. The first time the parents had been told about the possibility of an abnormality was in a routine screening at 5 months age. The pediatrician noticed a decreased head circumference growth. Further investigation showed the head circumference reached a plateau (40 cm) in its growth around 12 months age (Figure 2). His general and developmental condition seemed to experience a sudden pause with progressive delay in growth and development since then. He lost his ability to rolling over and never gained any gross motor milestones. His face became expressionless and his eyes started to sink into the orbits (Figure 3). Other findings were: apparent cachectic dwarfism, microcephaly, loss of facial adipose tissue, pigmented retinopathy, thoracolumbar kyphosis, multiple joint contractures, senile appearance, photosensitivity,

and thin and dry hair.

Although physical examination had a lot of similarity to a patient with CP, the history was inconsistent with the diagnosis of CP in its almost all aspects. This made us reevaluate the diagnosis. After a thorough history taking, some clues were added to our knowledge which was critical to the correct diagnosis. These include rapid regression of all motor functions, regression of language and fine motor functions and facial changes which are not compatible with CP.

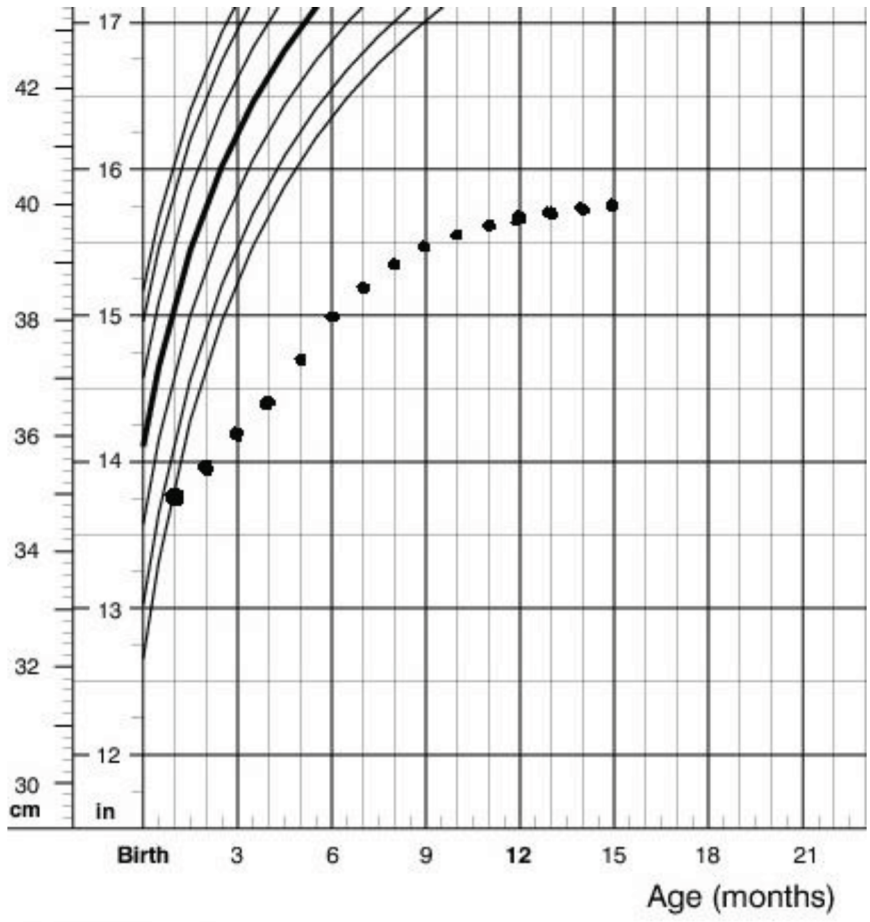

Figure 2. *Head circumference of the patient during the first 15 months*

At 7-yr-old age, he was in a cachectic dwarfism condition. The progeroid appearance narrowed our differential diagnosis.

Our first diagnosis based on clinical findings and progression of the disease was Cockayne syndrome. The diagnosis was later confirmed by molecular analysis for Cockayne syndrome. The patient was homozygous for ECCR6 gene (genotype: c.2551 T>A /p.W851R- c.2551 T>A /p.W851R). The parents were also heterozygous for the same gene. This was also true for the patient's only sister.

Figure 3. *Patient face at 9 months and 7 yr old*

Discussion

First described by Dr. Edward Alfred Cockayne (1880-1956) in 1936, called Cockayne syndrome (CS) was initially characterized by dwarfism, retinal atrophy, and deafness (4). Through the years, many additional clinical, laboratory and genetic features are added to the disease spectrum. The fibroblasts of CS patients had an increased sensitivity to UV irradiation. The hypersensitivity was absent when these cells were exposed to X-ray radiation (5). These cell responses were also different from what is seen in patients with xeroderma-pigmentosum (6). Cells from patients with Cockayne syndrome failed to recover RNA synthesis after UV irradiation. The ERCC8 gene mutations were introduced as the molecular genetic basis of this syndrome (7). ERCC (Excision repair cross-complementing) are a group of proteins involved in DNA repair. There are different genes responsible for synthesis of these proteins. The so-called ERCC8 was the first with correlation to CS. About 80% of the CS patients have mutation in ERCC6 gene-another member of the ERCC gene family (8).

CS has been clinically classified into 4 groups (9). CSI also known as the classic CS, manifest in the first years of life. The prodromal signs and symptoms include gradual deterioration of neurodevelopmental functions, growth failure, followed by visual and hearing abnormalities, skin photosensitivity, characteristic facial changes, dental caries and eventually death in the first and second decades of life (9). CSII which is a severe form of the disease appears at birth with severe neurological findings, extensive involvement of the brain including white matter abnormalities, calcifications and atrophy. The mean age of death is 7 yr old (9). CSIII is a milder form with patients capable of living into adulthood (10). Finally, xeroderma pigmentosum-Cockayne syndrome (XP-CS) was considered with clinical characteristic of both disorders.

Another classification based on genetic abnormality classified CS into 3 groups: CSA caused by defective ECCR8 gene and CSB with ERCC6 gene abnormalities. CSC is an intermediate form combining the genetic features of XP and CS.

Whatever classification used, the basic defect in CS is the inability of cells to repair the UV induced damages to their DNA (11). Accumulation of defective DNA eventually causes cell death. Interestingly the rate of skin malignant changes does not seem to increase in CS patients (9).

Table 1 represents the main organ systems affected by Cockayne syndrome and their presence in our patient.

Table 1. Cockayne syndrome signs and symptoms

Organ system	Abnormality	Presence in the patient
CNS	Developmental/Cognitive retardation	+
	Inability to walk	+
	Decreased/increased muscle tone	+
	Increased reflexes	+
	Hearing loss	+
	Cranial nerves dysfunction	-
	Muscle weakness	+
	Seizures	-
EYES	Cataract	-
	Retinopathy	+
	Strabismus	-
	Photophobia	+
FACE	Dental caries	+
	Deep sunken eyes	+
	Fat atrophy	+
MUSCULOSKELETAL	Kyphosis	+
	Joints contractures	+
	Limb atrophy	+
	Cachectic dwarfism	+

Clinical relevance

CP is a common disorder with diverse clinical features. Although there is no specific test to prove the diagnosis, a thorough history, and physical examination could be used to rule out the less common but important diagnoses. In this case, the parents are offered to have prenatal screening test for next pregnancies. This would help them to prevent experiencing another emotionally and economically disastrous.

In conclusion, the diagnosis of CP must be made with caution. There are many metabolic or neurologic conditions which mimic the clinical presentation of CP with different clinical course and prognosis.

Author`s Contribution

Dr Baghdadi supervised the scientific contents and designed the study. Dr Vafaee coordinated and wrote the draft. Ms Norouzzadeh managed the genetic study and confirmed its authenticity.

All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest

The authors declare that there is no conflict of interests.

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CASE REPORT

Enterobacter Meningitis Due To Dermoid Cyst Manipulation

How to Cite This Article: Rafiei Tabatabei S, Azma R, Kahbazi M, Farzan A, Kazemi Aghdam M, Seifi K, Nahanmoghaddam N. Enterobacter Meningitis Due To Dermoid Cyst Manipulation. Iran J Child Neurol. Autumn 2018; 12(4):169-177

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Received: 12- Feb -2017
Last Revised: 23-Aug-2017
Accepted: 28-Aug-2017

Abstract

Gram-negative meningitis can occurssubsequent to dura-arachnoid barrier disruption because of trauma, surgery and rarely an infected dermoid cyst. Association of neurosurgical procedures with Gram-negative meningitis was described for the first time in 1940. Intracranial infections from gram-negative bacilli like Enterobacter are serious and difficult to treat as many antibiotics fail to achieve bactericidal concentrations in the cerebrospinal fluid. Here in, we report a rare case of pediatric Enterobacter meningitis in a patient with a dermoid cyst that had been manipulated. She was managed with antibiotic therapy plus surgical removal of the infected cyst.

Keywords: Meningitis؛ Enterobacter؛ Antibacterial agents؛ Dermoid cyst

Introduction:

Enterobacter is a genus of Enterobacteriaceae that is an increasingly frequent cause of healthcare-associated pediatric infections. It can cause infection of postsurgical wounds, gastrointestinal, urinary and respiratory tracts and meningitis.

E. cloacae and E. aerogenes are the most common species recovered from clinical specimens. Additional Enterobacter species rarely recovered from human infections include E. amnigenus, E. asburiae, E. gergoviae, E. cancerogenus and E. kobei. E. ludwigii is a new species isolated from clinical specimens closely related to the E. cloacae complex (1).

Gram-negative bacilli may cause meningitis, but it is rare beyond neonatal period and history of impaired immune system or infected brain cyst due to neurosurgical manipulation that lead to CSF contamination are prerequisites to the infection (2, 3).

Risk factors for Enterobacter meningitis have not been clearly defined yet

(4) but prolonged antibiotic administration and cyst manipulation over the scalp are the two main factors associated with Enterobacter meningitis (5, 6). Meningitis due to Enterobacter species is an uncommon infection after neonatal period without underlying risk factors so a search for risk factors must be done in all cases of Enterobacter meningitis (6).

Intracranial fossa dermoid cysts are congenital benign masses with a prevalence of 0.1%-0.7% of all intracranial neoplasms (7, 8). The presence of dermoid cyst in the posterior fossa is uncommon and surgery is the treatment of choice. Manipulated dermoid cyst should be resected by surgery in addition to antibiotic therapy (8, 9).

Case Report

An 11-year old girl was admitted Mofid Children's Hospital, Tehran, Iran in 2015 and we took her family informed consent form template for case report studies. She had high-grade fever, severe headache, and vomiting since four days before admission. She had been diagnosed with meningitis in another hospital and had received dexamethasone and antibiotics including ceftriaxone and vancomycin. No improvement had been seen in her status, and her high-grade fever had remained uncontrolled. The patient was referred to Mofid Hospital with complaints of high-grade fever, severe headacheand photophobia. Her mother reported that she had a history of common cold, sinusitis and pharyngitis few days before her first admission.

In addition, she had a history of right knee arthritis last year; she also had a congenital occipital mass with occasional purulent discharge. It had been manipulated by her father because of pain and edema 2 weeks before her admission leading to oozing of pus.

On physical examination, the patient was lethargic; vital signs included body temperature of 39 °C, blood pressure120/80 mm Hg, pulse rate 90/min, and respiratory rate 25/min. Meningeal irritation was present (positive nuchal rigidity, Kernig and Brudzinski signs) with photophobia; pupils midsize and were reactive to light. Erythematous occipital mass (1×2 cm) was palpated in the midline, with no discharge. The range of motion of right hip was decreased with tenderness without erythema, warmth and edema. The rest of the physical examination was normal.

Because of continuation of fever despite antibiotic administration, lumbar puncture was done. CSF analysis in previous hospital admission showed; WBC=132(p=70%,L=28%), Glucose=10, Protein=27, RBC=180 and with a gram-negative bacilli (Enterobacter) in CSF culture.

Laboratory evaluations showed WBC=17000/mm3 (PMN=87%), Hemoglobin=12.6 g/dl, and Platelets=197000/mm3. Biochemistry tests including Na, K, P, amylase, lipase, and LDH were normal and serology for hepatitis b, hepatitis Cand CMV viruses was reported as negative. The erythrocyte sedimentation rate, (ESR) was 67 mm in the first hour and CRP 124 mg/l. NBT, Immune Globulins (Igs) and CD flow cytometry were also in normal range. Mild TR, Mild AIand Mild PI were reported in echocardiography without any vegetation. Audiometry also was normal.

CSF analysis in our hospital showed WBC=1000/mm3 with 90% PMN and 10% lymphocyte, Glucose=18mg/dl, Protein=30 mg/dl, RBC=10/mm3and CSF culture was negative.

Antibiotics were changed to vancomycin and meropenem in our hospital. After 3 days, the patient was not responding and had leukocytosis and fever, so chloramphenicol was added to vancomycin and meropenem. Five days later, CSF analysis showed WBC=100/ mm3 with 80% PMN and 20% lymphocyte, Glucose=25 mg/dl, Protein=18 mg/dl, RBC=60/mm3Blood culture was negative. Vancomycin and meropenem were discontinued and intrathecal amikacin was added to chloramphenicol. After five days, CSF analysis showed WBC=30/mm3with40% PMN and 60% lymphocyte, Glucose=29mg/dl, Protein=95mg/dl, RBC=10/ ml. The second CSF culture 8 days after admission showed gramnegative bacilli Enterobacter by BACTEC (Becton Dickinson Microbiology Systems, Model No. B9120). According to the antibiogram, microorganism was sensitive to chloramphenicol and cotrimoxazole and resistant to ampicillin- sulbactam, amikacin, gentamicin and cefepime. Therefore, antibiotics were changed based on antibiotic sensitivity test (Amikacin was discontinued, chloramphenicol continued and cotrimoxazole added). Patient responded to the new antibiotic therapy clinically and CSF culture became negative.

Brain CT scan with and without contrast was performed for the patient which showed an extra-axial hypo dense relatively round lesion in posterior mid aspect of posterior fossa along with calcified foci in its superior aspect. A subcutaneous lesion was also noted in the overlying scalp. After contrast administration, rim enhancement was seen in both intracranial and subcutaneous lesions (Figure 1). The lesion was suspected to be an infected intracranial and subcutaneous dermoid cyst with a connecting tract through the occipital bone, Brain MRI with and without contrast was performed subsequently which revealed CSF signal in the lesion and rim enhancement as well as prominent restriction in DWI sequence (Diffusion weighted imaging) which confirmed the diagnosis in the CT scan (Figure 2).

She was referred to the Neurosurgical Department for removal of the infected dermoid cyst. After neurosurgery, Brain CT revealed an evidence of posterior craniotomy in occipital bones with mild pneumocephalus. Small subdural effusion was detected in the right side of the posterior fossa with normal ventricle sulci; no infarction, hemorrhage, mass, midline shift or herniation was seen.

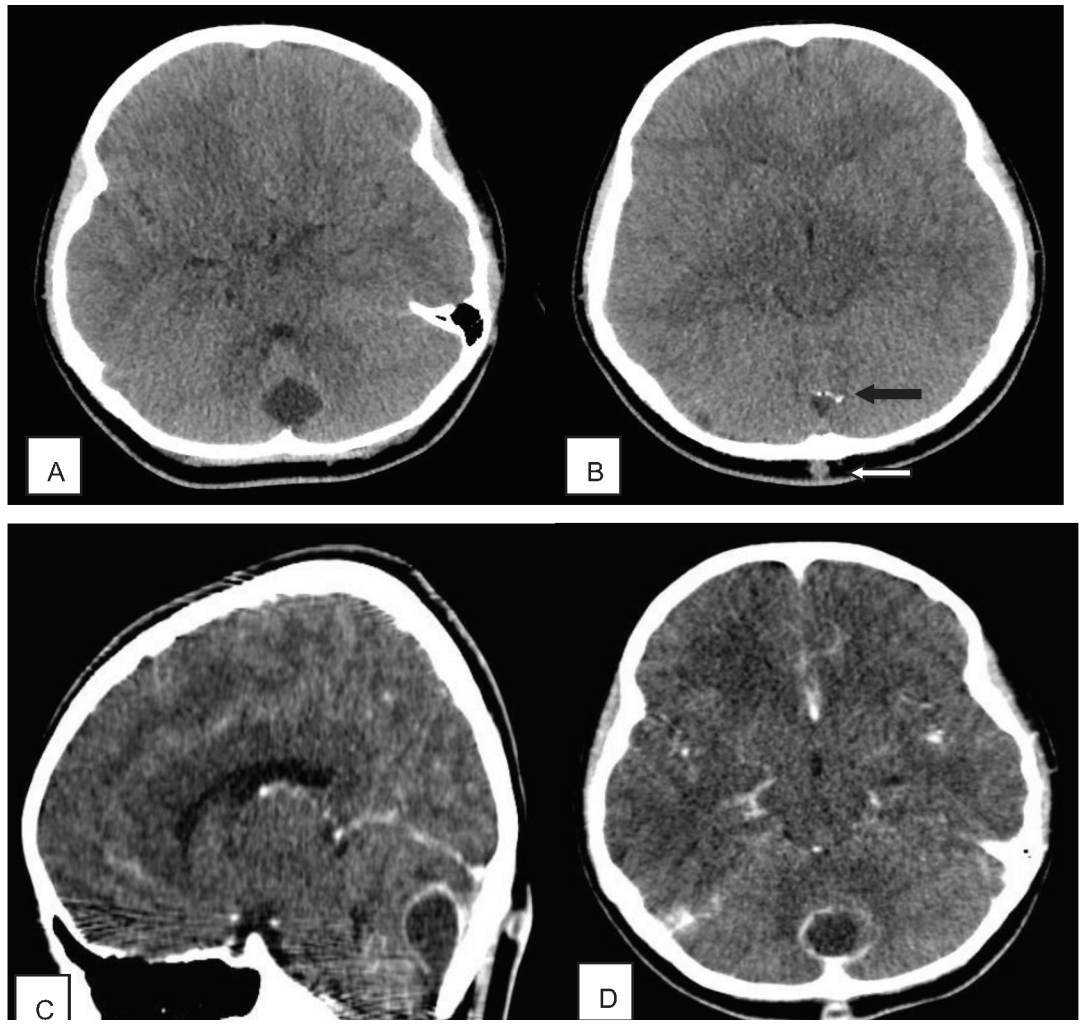

Figure 1. *A and B axial non-enhanced brain CT scan show an extra-axial hypodense relatively round lesion in posterior mid aspect of posterior fossa. Note the calcified foci in superior aspect of the lesion(black arrow) as well as a small subcutaneous lesion in the overlying scalp(white arrow)*

C. Coronal contrast-enhanced and D. axial contrast-enhanced brain CT scan reveal rim enhancement of both intracranial and subcutaneous lesions.

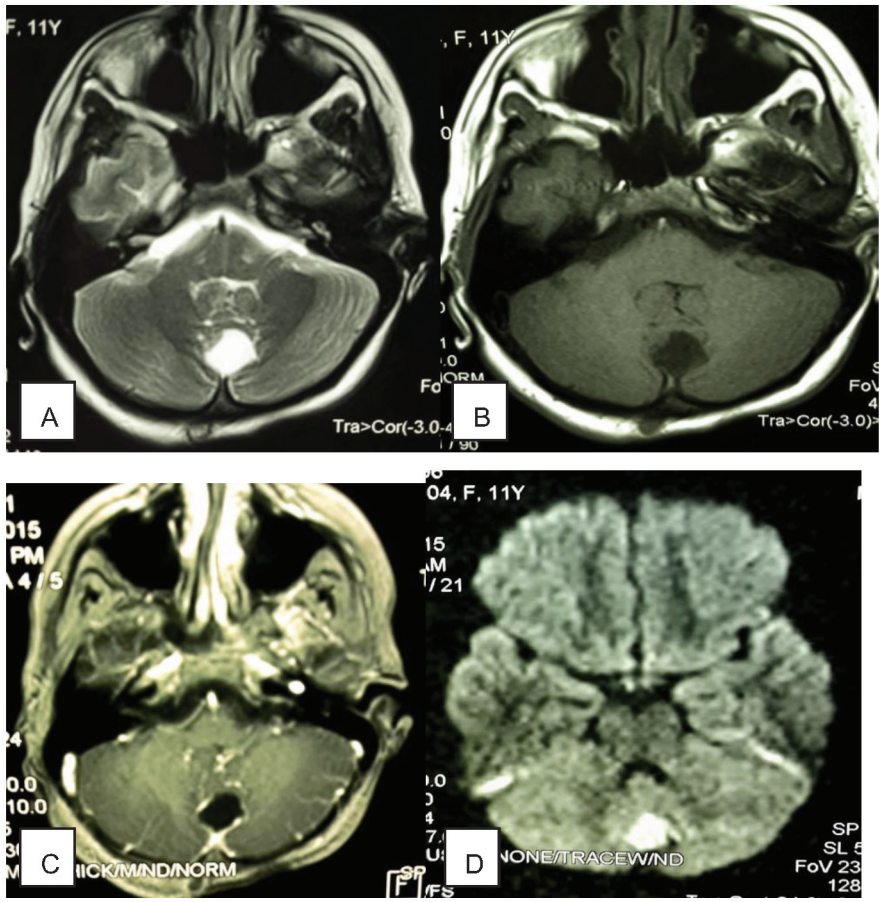

Figure 2. *A. Axial T2 Weighted brain MRI and B. Axial T1weighted brain MRI shows an extra-axial CSF density lesion in posterior mid aspect of posterior fossa. C. Axial T1 Weighted contrast enhanced brain MRI reveals rim enhancement of the lesion. D. DWI (Diffusion Weighted Imaging)sequence demonstrates restriction in the lesion.*

The histopathology findings of brain mass showed a cyst lined by keratinized squamous epithelium containing hair shafts and keratinous material. Severe mixed inflammation and foreign body type reactions well as foci of calcification with hyalinization and congestion in the periphery are seen with no evidence of malignancy. It confirms the diagnosis of an infected dermoid cyst (Figure 3).

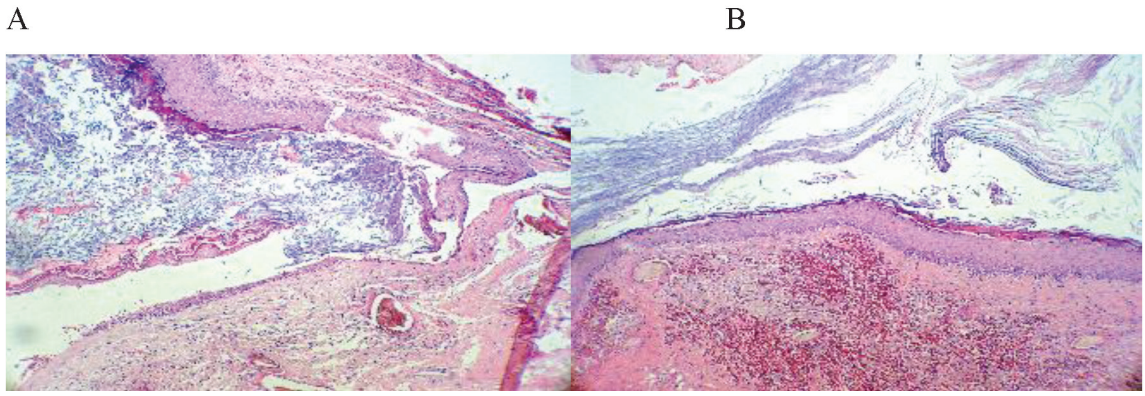

Figure 3. *Cyst wall and intracystic keratinous material (A), squamous epithelium of the cyst wall and hair shafts in underlying tissue (B).*

She was discharged with final laboratory results of normal CBC, CRP=23and ESR=60. Her final CSF analysis showed negative smear and culture. Meningitis was treated by chloramphenicol and cotrimoxazole. Patient responded to our treatment and was well on discharge and on follow-up one month after discharge with normal CBC, ESR and CRP.

Discussion

Infected idiopathic and congenital brain lesions can cause meningitis, following a defect through the defense barrier of brain(2).As it provides an entry of organisms to invade the meninges (10). Although gram-negative bacilli are the most common cause of nosocomial meningitis, it still remains an unusual cause of meningitis in adults and children (4). Major risk factors include cerebrospinal fluid leak, immunosuppressed patients, history of immunosuppressive drugs consumption, presence of infected brain mass and head trauma or history of neurosurgery (11). Gram-negative bacillary meningitis has mortality rates of 40 to 80% among adults and children (12).Enterobacter meningitis dominantly occurs in cases with neurosurgical brain mass manipulation and trauma (13).

Intracranial dermoid cysts are rare, usually located in the posterior fossa and are slow growing (14, 15).These presents with headache and seizure and are usually reported in the first and second decades of life (16). Dermoid cyst of the posterior fossa may be occurring accompanied with Staphylococcus epidermidis abscess. It cured with radical excision of the occipital cyst followed by antibiotics therapy (17).

Enterobacter may be found in manipulated mass in the brain. It is a serious infection and resection of the mass and appropriate antibiotic therapy based on culture is the treatment of choice (18). Enterobacter was one of the rare and important causes of nosocomial bacteremia in hospitalized children (19). Our patient presented with Enterobacter meningitis at age 11 year. Gram-negative bacilli meningitis is a causative agent in the neonatal period but occurrence in adults without immunologic risk factors is very rare (20).

Antimicrobial regimens for treatment of Enterobacter meningitis iscontroversial. The efficiency of cefepime in postoperative meningitis attributable to Enterobacter has been described (17). In the United States, 15 patients who had positive cultures for Enterobacter were evaluated (4). The main treatments of these patients included intravenous (I.V) carbapenems (60% of cases were treated with carbapenems with both I.V. monotherapy and combined I.V- protocols). In addition, one patient was treated with a third-generation cephalosporin, 1 patient with piperacillin and 2 patients with ciprofloxcacin. Patients treated with combined I.V. therapies received the following regimens: (6 patients) were given aminoglycoside in addition to intravenous carbapenem (5 patients) or third-generation cephalosporin (1 patients), and 1 patient was treated by intravenous carbapenem and a third-generation cephalosporin. Among all, one patient had died in I.V combination therapy (4). A 22-year-old patient underwent neurosurgical manipulations developed Enterobacter meningitis who was treated with tobramycin, I.V. ceftriaxone, vancomycin, and metronidazole (10). However, in our study, the cultured bacteria were resistant to aminoglycosides and beta-lactam antibiotics that led to the lack of response tointrathecal amikacin and I.V. vancomycin and meropenem. On the other hand, chloramphenicol and cotrimoxazole aresusceptible against gram-negative bacilli and also achieve high concentrations in CSF (21), which the case of which our patient was finally cured with combination of chloramphenicol and co -trimoxazole.

Korinek et al. designed a prospective trial of 3,000 patients reported Staphylococcus aureus was found as a most common cause of meningitis in infected brain masses and the second common pathogen was Enterobacter in 24% cases (22). Enterobacter was isolated from CSF in 16% of patients who enrolled in Parodi's study (4).

Dermoid cyst of the posterior fossa is described in a 16-yr-old man; who presented with clinical signs of intracranial pressure and cerebellar symptoms (8). They showed there is no risk of infectious complications without manipulation similar to our patient showed the symptoms and signs of meningitis due to dermoid cyst manipulation.

In conclusion, effective antibiotic therapy is crucial for the treatment of Enterobacter meningitis. Although the first step is initiating antibiotics but with the presence of an infected mass, surgery is necessary for removal of the mass. Our patient identified with dermoid cyst, which had been infected owing to manipulation. Appropriate antibiotic therapy cured our patient beside neurosurgery removal of cyst to eliminate the underlying factor.

Acknowledgement

We thank the parents of the girl described for allowing us to share her details.

Authors' Contribution

Sedigheh Rafiei Tabatabei : Case finding, Drafting, designing of the work and final approval of the work

Negin Nahanmoghaddam : Case finding, Drafting, designing of the work and final approval of the work

Roxana Azma : Radiological diagnosis

Manijeh Kahbazi : case finding and Referring

Abdonaser Farzan : Neurosurgen

Maryam Kazemi Aghdam : pathological diagnosis

Kimia Seifi : Final approval of the version to be published

All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest

The authors declare that there is no conflict of interests.

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