CASE REPORT

Occupational Therapy in Kleefstra Syndrome

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Keywords:

Kleefstra Syndrome

Case Report

EHMT1 Gene

Rare Syndrome

Occupational Therapy

Received:
28-Oct-2023
Accepted:
14- May -2024
Published:
22- Jun -2024

ABSTRACT

Objectives

Kleefstra Syndrome (KS) is a rare genetic neurodevelopmental disorder caused by a microdeletion in chromosomal region 9q34.3 or a mutation in the euchromatin histone methyltransferase 1 (EHTM1) gene. Patients with KS show a range of clinical symptoms, including delay in motor and speech development, intellectual disability, autistic-like features, childhood hypotonia, and distinctive facial dysmorphic features. The patient is a four-year-old girl who was initially diagnosed with developmental motor delay by a pediatric neurologist and referred to an occupational therapy clinic at the age of six months. The initial assessment showed hypotonia and difficulties with rolling. Occupational therapy intervention was based on principles of neurodevelopmental treatment and sensory integration (SI) with cognitive integration and activities of daily living (ADL) training. With continuous occupational therapy services over more than three years, she overcame many disabilities and improved in occupational performance skills such as gross and fine motor skills as well as cognitive abilities, although her verbal communication skills were not effective. The patient's progress was as follows: she began rolling over at seven months, achieved independent sitting at ten months, crawled at eighteen months, stood with support at twenty months, and took her first steps at twenty-six months. The predominant problem was speech delay, which was noticeable in this syndrome. When a patient is being referred because of KS, occupational and speech therapy assessments should be accurately implemented.

How to cite this article: Ghaffari SH, Kalantari M. Occupational Therapy in Kleefstra Syndrome: A Case Report. Iran J Child Neurol. Summer 2024; 18(3): 143-149. https://doi.org/10.22037/ijcn.v18i3.43716

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Introduction

The core phenotype of developmental delay, intellectual disability, childhood hypotonia, and distinct facial features characterize Kleefstra syndrome (KS). The cause of KS is a submicroscopic deletion in the chromosomal region 9q34.3 or an intragenic mutation of the euchromatin histone methyltransferase 1 (EHMT1) gene. In April 2010, Dr. Tjitske Kleefstra, a clinical geneticist at the Department of Human Genetics, Radboud University Nijmegen Medical Centre, officially recognized the syndrome as KS, which was previously known as 9q34.3 deletion syndrome (1).

To date, over one hundred patients have been reported (2). The diagnosis is established by the characteristic facial morphology, including brachycephaly, middle face hypoplasia, widely spaced eyes (hypertelorism), short nose with anteverted nares, open mouth with a fleshy everted lower lip, large tongue, thickened ear helices, arched eyebrows with synophrys, and a protruding jaw (prognathism)(3). Most affected individuals have severe expressive speech delay with hardly any speech development, whereas general language development is usually at a higher level. Behavioral issues include sleep disturbances, stereotypies, mild self-injurious behaviors, and autism spectrum disorder. Motor development is impaired due to childhood hypotonia, but independent walking is typically achieved between the ages of two to three years (4, 5). Structural CNS abnormalities such as agenesis or hypoplasia of the corpus callosum and subcortical white matter anomalies are observed. Additionally, patients may experience epileptic seizures, hearing loss, visual impairment, congenital hypothyroidism, and a tendency to develop severe respiratory infections (5). Presently, only two cases of KS have been reported in Iran, the first one in May 2017 and another in September 2020 (7, 8). There is a significant need for information on rehabilitation in KS, as most studies focused on medical and genetic symptoms (1, 9). This report emphasizes the importance of occupational therapy interventions for the child diagnosed with KS.

Case report

The patient is a four-year-old girl whose parents were not relatives. Data from medical records, family reports, and occupational therapy sessions were used for case description, and informed consent was obtained. The mother was twenty-six at the time of pregnancy. During the mother's pregnancy, there were abnormal signs, and the patient was part of a twin pregnancy, with one twin being lost at 13 weeks. The surviving twin was born vaginally with the assistance of a vacuum at thirty-nine weeks, weighing 2900 grams. At birth, the baby's head circumference was 33cm, and her height was 43cm. After three months, her parents visited the pediatric neurologist due to the child's lack of head control, and the physicians informed them that the child's head size had grown slowly. She was referred to the occupational therapy clinic after she had achieved head control at five months and started receiving occupational therapy interventions at the age of six months. The parent's primary concern was the child's inability to roll over. Initial observations revealed lower muscle tone and a lack of eye contact. The child had difficulty grasping and holding objects for more than a few seconds. Dysmorphic facial features were also seen. The studied patient with KS at the age of 12 months is presented in Figure 1.

On Oct 4, 2020, when she was two years old, Whole Exome Sequencing (WES) confirmed the

Fig 1. *Some phenotype abnormalities include a flat face, midface hypoplasia, coarse faces, synophrys, upslanting palpebral fissures, anteverted nostrils, arched eyebrows, and a short nose*

syndrome. There was a heterozygous mutation in the EHMT1 (c.2811delC:p.I937fs) gene. Pathogenic mutations in this gene are shown to lead to KS. MRI showed a mild dilatation of the lateral ventricle. Subcortical hyperintensity, measuring 2-4 mm in diameter, was observed in both cerebral white matter on T2 and FLAIR images. Hypoplasia of the splenium of the corpus callosum was also reported. The cortex and the white matter showed normal intensity. In both cerebral white matter, some tiny subcortical lesions and mild dilation of both lateral ventricles were reported.

After a comprehensive evaluation, the occupational therapist decided to focus on mobility and play as her main activities, considering her age and family requests. According to the Occupational Therapy Practice Framework (OTPF), occupational therapy evaluation and interventions can be implemented at three levels: occupational performance (including activities of daily living (ADL), play, and leisure), occupational performance skills (motor skills, process skills, social interaction skills, etc.), and occupational performance components (such as muscle tone, attention, and memory)(6). In this regard, among the performance skills, the occupational therapist turned to the motor and sensory skills, which were more related to the disability of the child in play and mobility.

Before treatment

She had hypotonia in her muscles, which limited her ability to roll over and sit. She had difficulty grasping and holding objects and only touched or gazed at them by chance. When an object rarely attracted her, she just glanced at it for a few seconds without trying to grasp it. Whenever the therapist put small toys with various textures in her hand, she immediately refused them. At first observation, she never turned when her name was called and rarely produced vocal sounds. She could not keep eye contact, especially when her mother or therapist spoke with her. Sometimes, she seemed to be interested in auditory objects, such as a rattle or harness bell, but she did not try to catch them. Fortunately, breathing and feeding disorders or hearing loss and eye problems were not observed.

After treatment

Over more than three years, the patient underwent occupational therapy interventions. Occupational therapy intervention to achieve gross motor developmental milestones included neurodevelopmental treatment (NDT) and sensory integration (SI). As she progressed, cognitive rehabilitation, focusing on attention, sequencing, and learning alongside ADL training were incorporated (10). OT intervention has been done in three sessions per week and 45 minutes per session. Worth mentioning that throughout the COVID-19 outbreak, a number of therapy sessions were performed via online sessions.

Significant progress was achieved throughout the treatment. At seven months, the patient

could roll over to both sides and sitting without support was attained by ten months. To challenge the child's balance, she was made to reach for objects of interest while sitting on the equilibrium board and Swiss ball. Crawling was achieved at sixteen months using proprioceptive input with weight-bearing exercises and joint compressions. Transitions from supine to sit, sit to stand, and half kneel to stand were facilitated by the appropriate placement of the therapist's hands (11). The swing system gave vestibular input to improve balance. As the child reached twenty months, she began unsupported standing and utilized a walker under close supervision to facilitate walking (Figure 2). Over time, her gait improved from a wide-based gait to a more normal gait pattern. Balance training involved standing on a balance board and stability disc with minimal support, accompanied by multidirectional reaching and pushing-pulling activities. Walking was then practiced on different surfaces and across the obstacle course to improve balance. The parents were educated about the home exercise program. With the regular individualized occupational therapy program, the child could gradually walk, climb stairs, run, and she could jump at forty-eight months of age.

The therapist also focused on sensory and fine motor skills. Most of the time we used play as a means of reaching our therapy goals (12). To encourage her to participate in manual activities this study provided tactile and proprioception stimuli through playful and meaningful activities (13), for example, messy play, sand table, water play, and sponge bombs (Figure 3). The child used her hands more functionally and actively manipulating and exploring objects. She appeared to be motivated to engage in motor skills and interested in the environment especially after she reached walking skill. Between the ages of two and three, progress was reached in terms of intentional object watching, eye contact, eye tracking, voluntary grasping, and object exploration. By the age of four, she could manipulate most objects, although slowly or with reduced quality of performance, her participation in ADL was quite active.

She also showed interest in ADL training. Activities such as using a spoon and fork, drinking

Fig 2. *The child walks with the assistance of a walker during clinic sessions*

Fig 3. *The child actively engages in sensory play and uses her hands with functional grasp*

water from a cup, using zippers and velcro, and taking off shoes were performed using task analysis approach until she became independent, other activities such as taking off coat and pants were performed with assistance and guidance based on her age and ability in occupational therapy sessions.

The patient's cognitive development also improved. In order to increase visual attention, occupational therapist tried to strengthen the child's visual tracking by using colored lasers in the dark room. To enhance the auditory attention in the child, the authors provided a variety of hearing stimuli. For example, the therapist called her name as well as using different musical instruments in different directions to make her react to the sound (14). Between the ages of one to two, she could move her gaze from one object or person to another, localize sounds, and engage in cause–and–effect relationships. The pointing-touching gesture, although still rough, appeared. She could push buttons on toys to listen to music. At present, the child can shift her attention between tasks and focus her attention on two components of an activity. The expression of this ability was not limited to the therapeutic setting but also appeared in other contexts.

Currently, the therapist uses perceptual-motor activities to improve her attention, sequencing, eye-hand coordination, and balance. Tools such as stairs, foot ladders, and a lacing beads game are used to make activities fun and meaningful. She can walk up and down small steps, follow activity stages, and draw circles and lines with an immature tripod pencil grip.

The most concerning aspect was the delay in speech development. In this regard, she was referred to a speech therapist at 12 months, and began speaking single words at about 18 months. The patient is undergoing speech therapy. However, her verbal communication skills are still poor, meaning that she is seldom an effective sender or receiver, even with familiar partners.

Discussion

The present article reports the first case report of occupational therapy in a child with KS syndrome. the pesent study presented a four-year-old girl with KS who has been receiving occupational therapy since she was six months of age. The 9q34 microdeletion has a critical role in KS, resulting in the insufficiency of the EHMT1 gene.

The girl has facial dysmorphic features which are characteristic of the KS reported in many studies, such as hypoplasia of the middle part of the face, arched eyebrows, a short nose with anteverted nares, an open mouth with fleshy everted lower lips, a large tongue and thickened ear helices (2, 3, 15). She has been reaching the milestones with a delay in almost all skills, has a mild intellectual disability, and is expected to attend special education classes. The girl was regularly consulted with her neurologists every three to six months. According to the neurologist's reports and the parents, there were significant differences in physical and mental functions before and after treatment. In this case, occupational therapy interventions were planned to facilitate her developmental skills. Our experience showed that the NDT and SI approaches, along with using cognitive rehabilitation and ADL training, were effective in the rehabilitation of the studied child. Some studies indicated that these interventions were useful in some other rare syndromes with similar symptoms (10, 14). The occupational therapy program has enabled her to actively participate in activities both inside and outside of the clinic.

Early intervention had a great impact on her significant progress. The child's mother, who was always present and particularly attentive to the therapeutic program, had a very important role in the generalization of skills since she was trained to use the same strategies at home and generalize them to everyday life situations. Regarding the child's moderate intellectual disability (16), she has not learned to control her bowel and bladder completely. The main purpose of the rehabilitation team, specifically occupational therapists, is to achieve maximum independence and improve the quality of life of the referring patients and their caregivers (17). Therefore, occupational therapists need to be familiar with rare disorders, as well as the prognosis of the treatment process and interventions to provide the best possible treatment services for their clients. As most individuals with KS have severe expressive speech delay with limited speech development, speech therapy interventions are necessary in these cases. Due to the lack of some standardized and valid assessment scales in the clinic and the long duration of occupational therapy interventions (more than three years), the researchers could not record and document scores before and after treatment.

In Conclusion

Since KS is a rare genetic disorder, there is a need to raise awareness among neurologists and rehabilitation teams about the importance of early diagnosis and intervention to choose and implement better approaches, preventing further problems and promoting greater participation in activities at home, school, and society.

Acknowledgment

In the end, our appreciation is for the help of Dr. Hamid Nemati for his prompt referral and the parents of the studied patient. No funding was received to support this report.

Author's Contribution

This work was carried out in collaboration among all authors. Shakiba Ghaffari designed the study, collected information, and wrote the first and final draft of the manuscript. Dr. Minoo Kalantari managed the literature searches, edited the final draft of the manuscript. All authors read and approved the final manuscript

Conflict of Interest

The authors declare no conflicts of interest.

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