ORIGINAL ARTICLE

Investigating the Prevalence of Neurological Soft Signs in Children with Autism Spectrum Disorder and their Siblings: A Cross-Sectional Study

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ABSTRACT

Objectives

Autism is determined by children's inability to communicate with others through language. More studies have shown that neurological soft signs (NSS) can be one of the symptoms of psychiatric disorders, including schizophrenia. However, complete and proven evidence regarding the role of NSS in the pathogenesis of autism has not been determined. For this purpose, this research investigated the prevalence of NSS in children with autism spectrum and their siblings and compared it with the control group.

Materials & Methods

The current study was cross-sectional. In this study, thirty-two children aged 7-17 who had been referred to the pediatric psychiatry clinics of Imam Hossein Hospital and the Autism Charitable Association in Tehran, Iran, were entered; they were diagnosed with an autism disorder by a child and adolescent psychiatrist based on the DSM-5 diagnostic criteria. Furthermore, thirty-two siblings of children with autism in the age group of 7-17 years who did not have any neurological and mental disorders were included; thirty-two healthy individuals (controls) who did not have any disorders were evaluated with the K-SADS checklist. Gilliam Autism Rating Scale 3rd Edition (GARS-3) was also used to confirm the diagnosis and severity of the disease.

Results

The results showed that the incidence of NSS in the patient group was higher than in the other two groups, which was statistically significant ($p<0.05$). Furthermore, the results indicated that these signs had a high diagnostic value in identifying patients from healthy people.

Conclusion

In general, using the NSS score in patients with autism can be considered a prediction factor compared to their siblings. In addition, the score had no effect on the prediction between sibling and control subjects.

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Introduction

Autism is one of the neurodevelopmental disorders in children. It is a neurobehavioral disorder that causes patients to have problems interacting with others, as well as verbal and social skills (1). Research indicates that autism occurs in approximately 20 out of every 10,000 live births. Additionally, it is more frequently diagnosed in males than females (2). The main factors involved in the pathogenesis of autism have not been identified. However, studies have shown that hereditary factors, environment, and other risk factors can play a role in the occurrence of the disease (3, 4). On the other hand, more studies have shown that neurological soft signs (NSS) can be one of the causes of neurological diseases, including schizophrenia. Nevertheless, complete and proven evidence regarding the role of NSS in the pathogenesis of autism has not been determined (5). The occurrence of NSS in patients can be accompanied by a sign of disturbance in sensory, motor, and communication symptoms and indicates a poor prognosis (6).

A study conducted by Manouilenko et al. examined the connection between neurological soft signs (NSS) and cerebral blood flow in individuals with autism. The research revealed that these neurological disorders are linked to metabolic changes and variations in cerebral blood flow. As a result, NSS could potentially serve as a diagnostic indicator for autism patients (7).

Given the significance of employing efficient educational approaches to enhance the quality of life, numerous researchers have endeavored to create intervention programs to foster mental health across various aspects (8-11). The number of children with autism is growing. Although no definitive treatment is available for autism, severe and timely treatment of autism makes significant changes in the lives of the involved children. Autism causes impairment in social behaviors and communication skills. Children and adults with autism have problems in verbal and non-verbal communication, as well as fun activities (7). Considering that the definitive cause of autism spectrum disorder (ASD) is still unknown and the only proven case is the higher prevalence of symptoms of the disorder in their siblings of children with autism, it is possible that the presence of NSS in co-sisters of autistic children is a sign of danger symptoms in these high-risk children, or is one of the symptoms that help diagnose autism in a suspected child. Currently, no definitive studies exist on this topic, and existing research often presents conflicting results or has limitations. Therefore, this study aimed to investigate the prevalence of NSS in children with ASD and their siblings, comparing these findings to a control group.

Materials & Methods

The current study was cross-sectional. This study included thirty-two children aged 7-17 who had been referred to the pediatric psychiatry clinics of Imam Hossein Hospital and the Autism Charitable Association in Tehran, Iran; they were diagnosed with an autism disorder by a child and adolescent psychiatrist based on the DSM-5 diagnostic criteria. GARS III was also used to confirm the diagnosis and severity of the disease. Moreover, thirty-two caregivers of children with autism in the age group of 7-17 who did not have any neurological and mental disorders were included, and thirty-two healthy individuals (controls) who did not have any disorders were evaluated with the K-SADS checklist. The participants were selected from Shahrtash School in Tehran, Iran.

The method of data collection was an interview.

In order to select the sample of IQ patients participating in the study, based on the information that was registered when they entered the school and passed the entrance test for normal schools, it was set as a criterion.

Inclusion and exclusion criteria

The inclusion criteria were obtaining informed consent from parents after being informed about the purpose of the research, age between 7-17 years (for all participants including patients, siblings, and control group), and autism level 1, who did not have verbal disabilities and being a student (based on DSM-5 and GARS III diagnostic criteria). Exclusion criteria were the presence of any mental retardation disorders (IQ<70), Tourette's disorder, chronic tic disorder, psychosis, seizure disorders, cerebral palsy, and any obvious neurological disorders that could distort the results of the study.

Procedure

After selecting the study participants, the questionnaires were provided to the participants corresponding to each of the three groups. Subjects were asked to answer the questions carefully. After completing the questionnaire, the analysis was done using SPSS version 23 software.

GARS III Questionnaire

Gilliam Autism Rating Scale, Third Edition (GARS-3), is a norm-referenced screening tool designed to identify people aged 3-22 with ASD. This questionnaire consists of 58 items divided into six sub-scales; it can be used to identify specific observable and measurable behaviors. It is completed according to the child's speech status: Four indicators are used for children who cannot speak, and six indicators are used for children who can speak. This questionnaire was used to determine the level of severity in the group of patients (12).

NES Questionnaire

This questionnaire contains 28 NSS that indicate three main functional areas. These three areas are:

1- Sensory coherence

2- Movement coordination and sequence of complex movements

3- Predominance of hemispheres, frontal lobe symptoms, and eye movements.

Each symptom is given a numerical score of 0 (no problem), 1 (mild disorder), or 2 (prominent disorder). Except for the sucking reflex and the chin, which get a score of 0 to 2. The process for determining the score for each mark is clearly explained to ensure consistent grading. Scores range from a minimum of zero to a maximum of 56 (13).

K-SADS questionnaire

The K-SADS questionnaire is a semi-structured interview designed to assess current and previous episodes of mental illness in children and adolescents based on the DSM. Searching and objective criteria are available to evaluate each symptom. As the interview is semi-structured, there is no need to repeat the questions verbatim. These questions are only a guide to obtaining the necessary information for scoring each question, and the examiner can ask the questions according to the child's level of development. It is completed according to the interviews with parents and children and summarizing information from all available sources. Completing the K-SADS questionnaire requires filling in the following sections: 1) a preliminary unstructured interview,

2) a diagnostic screening interview, 3) a supplementary checklist attached, 4) attached diagnostic appendices, 5) a checklist summary of lifetime diagnoses, and 6) a child's overall assessment scoring scale (14).

Statistical Analysis

The quantitative and qualitative data were analyzed using SPSS version 23 software. The ROC curve was used to evaluate the diagnostic value of NSS. $p<0.05$ was considered as a significant level.

Results

Demographical information of patients

The demographic information of the patients is shown in Table 1. The percentage of females in the control and patient groups was lower compared

Table 1. Demographic and clinical information of the control, patient, and siblings

Variables		Groups			P Value
		Control (n=32)	Patient (n=32)	Siblings (n=32)	
Age (Mean ±SD, years)		10.84 ± 2.81	12.03±3.4	11.25±4.12	0.221
Gender (N, %)	Females	8 (25)	4 (12.5)	19 (59.4)	<0.001
	Males	24 (75)	28 (87.5)	13 (40.6)	
Birth order (N, %)	First	18 (56.7)	24 (75)	7 (21.9)	<0.001
	Second	11 (34.4)	8 (25)	23 (71.9)	
	Third and above	3 (9.4)	0 (0)	2 (6.3)	
Age of neonate (N, %)	< 37	2 (6.3)	8 (25)	10 (31.3)	0.083
	37-42	29 (90.6)	24 (75)	22 (68.8)	
	>42	1 (3.1)	0 (0)	0 (0)	
Mother's health status (N, %)	Health	32 (100)	28 (87.5)	27 (84.4)	0.07
	Patient	0 (0)	4 (12.5)	5 (15.6)	
Birth weight (N, %)	<2500 mg	4 (12.5)	5 (15.6)	6 (18.8)	0.789
	>2500 mg	28 (87.5)	27 (84.4)	26 (81.3)	
Neonate's health status (N, %)	Health	32 (100)	25 (78.1)	27 (84.4)	0.024
	Patient	0 (0)	7 (21.9)	5 (15.6)	
Childhood health status (N, %)	Health	0 (0)	8 (25)	--	0.002
	Patient	32 (100)	24 (75)		
Drug using (N, %)	Yes	0 (0)	8 (25)	1 (3.1)	0.001
	No	32 (100)	24 (75)	31 (96.9)	
Tourette's disorder (N, %)	Yes	0 (0)	3 (9.4)	0 (0)	0.045
	No	32 (100)	29 (90.6)	32 (100)	
OCD disorder (N, %)	Yes	0 (0)	1 (3.1)	0 (0)	0.364
	No	32 (100)	31 (96.9)	32 (100)	
ADHD disorder (N, %)	Yes	0 (0)	6 (18.8)	3 (9.4)	0.037
	No	32 (100)	26 (81.3)	29 (90.6)	
Developmental delay (N, %)	Yes	1 (3.1)	18 (56.3)	3 (9.4)	<0.001
	No	31 (96.9)	14 (43.8)	29 (90.6)	

Abbreviations: OCD: obsessive-compulsive disorder; ADHD: Attention deficit hyperactivity disorder

to the siblings group, which was statistically significant (p<0.001). When considering birth order, most individuals in both the control and patient groups were first-born. In contrast, those in the siblings group were predominantly second-born. This difference was statistically significant (p<0.001). In addition, some other variables such as neonate's health status, childhood health status, Tourette's disorder, attention deficit-hyperactivity disorder (ADHD), and developmental delay were statistically significant between the three groups (p<0.05). There was no significant relationship with other variables between the three groups (p>0.05) (Table 1).

Evaluation of neurological symptoms based on NES score between three groups

Based on the Tandem walk variable, the results showed that in the control group, all people had zero scores, while in the group of patients, six individuals (18.8%) had a score of 1, and 2 (6.3%) had a score of 2., In the sibling group, four people (12.5%) scored 1 (p=0.03). Regarding the audiovisual integration variable, in the control group, one person (3.1%) scored 2. In the group of patients, eight people (25%) scored 1, and one individual (3.1%) scored 2. Besides, in the sibling group, four individuals (12.5%) scored 1 (p=0.03). According to the Fist ring test in the control group, one individual (3.1%) scored 1. In the group of patients, 12 cases (375%) scored 1, and three (9.4%) scored 2. In the sibling group, four people (12.5%) scored1, and one person (3.1%) scored2 (p<0.001). Additionally, a statistically significant relationship existed among the three studied groups concerning the variables: Fist Edge Palm Test, Ozeretski Test, Memory (5 minutes), Memory (10 minutes), Rhythm Tap (A), Rhythm Tap (B), Rapid Alternative Movement, Right-Left Confusion, and Gaze Persistence. (p<0.05) (Table 2).

Table 2. Comparison of neurological symptoms in three groups

Variables		Groups			P Value
		Control (n=32)	Patient (n=32)	Sibling (n=32)	
Tandem walk	No	32 (100)	24 (75)	28 (87.5)	0.03
	1	0 (0)	6 (18.8)	4 (12.5)	
	2	0 (0)	2 (6.3)	0 (0)	
Romberg test	0	32 (100)	30 (93.8)	32 (100)	0.131
	1	0 (0)	2 (6.3)	0 (0)	
Adventitious overflow	0	32 (100)	31 (96.9)	32 (100)	0.364
	1	0 (0)	1 (3.1)	0 (0)	
Tremor	0	32 (100)	31 (96.9)	32 (100)	0.169
	1	0 (0)	1 (3.1)	0 (0)	
Cerebral Dominance	0	28 (87.5)	26 (81.3)	27 (84.4)	0.851
	1	2 (6.3)	2 (6.3)	3 (9.4)	
	2	2 (6.3)	4 (12.5)	2 (6.3)	
Audiovisual integration	0	31 (96.9)	23 (71.9)	28 (87.5)	0.03
	1	0 (0)	8 (25)	4 (12.5)	
	2	1 (3.1)	1 (3.1)	0 (0)	

Continued Table 2.

Stereognosis	0	31 (96.9)	27 (84.4)	31 (96.9)	0.085
	1	1 (3.1)	5 (15.6)	1 (3.1)	
Graphesthesia	0	23 (71.9)	18 (56.3)	26 (81.3)	0.222
	1	7 (21.9)	12 (37.5)	4 (12.5)	
	2	2 (6.3)	2 (6.3)	2 (6.3)	
Fist ring test	0	31(96.9)	17(53.1)	27(84.4)	<0.001
	1	1(3.1)	12(37.5)	4(12.5)	
	2	0(0)	3(9.4)	1(3.1)	
Fist edge palm test	0	29(90.6)	17(53.1)	28(87.5)	<0.001
	1	3(9.4)	13(40.6)	4(12.5)	
	2	0(0)	2(6.3)	0(0)	
Ozeretski test	0	27(84.4)	28(87.5)	15(46.9)	<0.001
	1	5(15.6)	2(6.3)	13(40.6)	
	2	0(0)	2(6.3)	4(12.5)	
Memory 5 minutes	0	25(78.1)	27(84.4)	18(56.3)	0.03
	1	7(21.9)	3(9.4)	13(40.6)	
	2	0(0)	2(6.3)	1(3.1)	
Memory 10 minutes	0	28(87.5)	27(84.4)	17(53.1)	0.01
	1	3(9.4)	3(9.4)	10(31.3)	
	2	1(3.1)	2(6.3)	5(15.6)	
Rhythm tap (A)	0	31(96.9)	30(93.8)	21 (65.6)	0.003
	1	1(3.1)	2(6.3)	9(28.1)	
	2	0(0)	0(0)	2(6.3)	
Rhythm tap (B)	0	32(100)	30(93.8)	24(75)	0.01
	1	0(0)	2(6.3)	5(15.6)	
	2	0(0)	0(0)	3(9.4)	
Rapid alternative movement	0	32(100)	27(84.4)	32(100)	0.03
	1	0(0)	4(12.5)	0(0)	
	2	0(0)	1(3.1)	0(0)	
Finger thumb	0	32(100)	30(93.8)	32(100)	0.39
	1	0(0)	1(3.1)	0(0)	
	2	0(0)	1(3.1)	0(0)	
Mirror movements	0	14(43.8)	22(68.8)	15(46.9)	0.15
	1	18(56.3)	10(31.3)	16(50)	
	2	0(0)	0(0)	1(1)	
Extinction	0	32(100)	28(87.5)	30(93.8)	0.28
	1	0(0)	3(9.4)	2(6.3)	
	2	0(0)	1(3.1)	0(0)	
Right- left confusion	0	29(90.6)	26(81.3)	17(53.1)	0.006
	1	3(9.4)	5(15.6)	10(31.3)	
	2	0(0)	1(3.1)	5(15.6)	
Synkinesis	0	32(100)	28(87.5)	30(93.8)	0.11
	1	0(0)	4(12.5)	2(6.3)	

Continued Table 2.

	2	0(0)	0(0)	0(0)	
	0	31(96.9)	26(81.3)	30(93.8)	
Convergence	1	1(3.1)	6(18.8)	2(6.3)	0.07
	2	0(0)	0(0)	0(0)	
	0	31(96.9)	19(59.4)	31(96.9)	
Gaze impersistence	1	1(3.1)	9(28.1)	1(3.1)	<0.001
	2	0(0)	4(12.5)	0(0)	
	0	32(100)	32(100)	32(100)	
Finger-to-nose test					1
	1	0(0)	0(0)	0(0)	
	2	0(0)	0(0)	0(0)	
	0	32(100)	28(87.5)	29(90.6)	
Glabellar reflex	1	0(0)	4(12.5)	3(9.4)	0.13
	2	0(0)	0(0)	0(0)	
	0	32(100)	32(100)	32(100)	
Snout reflex	1	0(0)	0(0)	0(0)	1
	2	0(0)	0(0)	0(0)	
	0	32(100)	32(100)	32(100)	
Grasp test	1	0(0)	0(0)	0(0)	1
	2	0(0)	0(0)	0(0)	
	0	32(100)	32(100)	32(100)	
Suck reflex	1	0(0)	0(0)	0(0)	1
	2	0(0)	0(0)	0(0)	

Note: P < 0.05 *, P < 0.01 **, P <0.001 *** show significant p-value. P > 0.05 indicates a non-significant p-value. 0= absent, 1= present–mild intensity, 2= present–high intensity

Evaluation of the total neurological symptoms between three groups

Based on the results, it was shown that the incidence of neurological symptoms in the patient group was higher compared to the other two groups; this difference was statistically significant (p<0.05) (Figure 1).

Evaluation of diagnostic value of total neurological symptoms in three groups

The figure below shows the diagnostic value of total neurological symptoms evaluated in three groups. The results showed that these symptoms had a high diagnostic value for identifying patients from healthy individuals. In addition, their siblings can also be used to diagnose autistic patients (Figure 2).

Discussion

NSS is one of the neurological signs that is observed in many patients, including schizophrenia patients (15). The presence of NSS in patients can cause behavioral and movement disorders and many other abnormalities (16). This study investigated the prevalence of NSS in autistic patients and their siblings. Nevertheless, in recent studies, NSS has been mainly investigated in autism patients. However, the prevalence of NSS in the siblings of patients has been limited.

Although in a disorder like hyperactivity, it seems

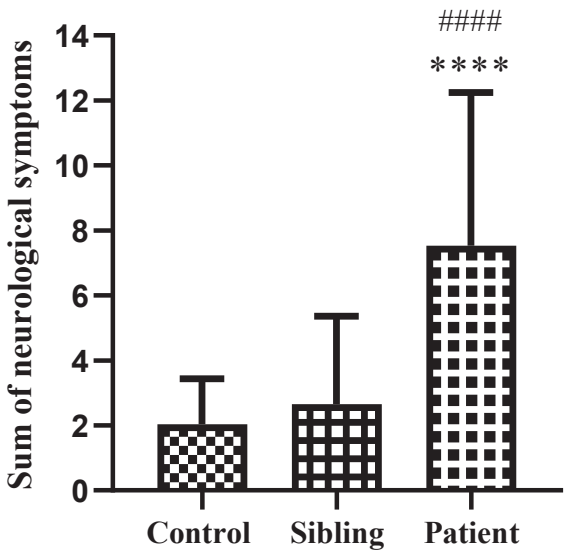

Figure 1. Comparison of total neurological symptoms in three groups
Note: P <0.0001 **** (Control vs. Patient), and P< 0.0001 #### (Siblings vs. Patient) show significance

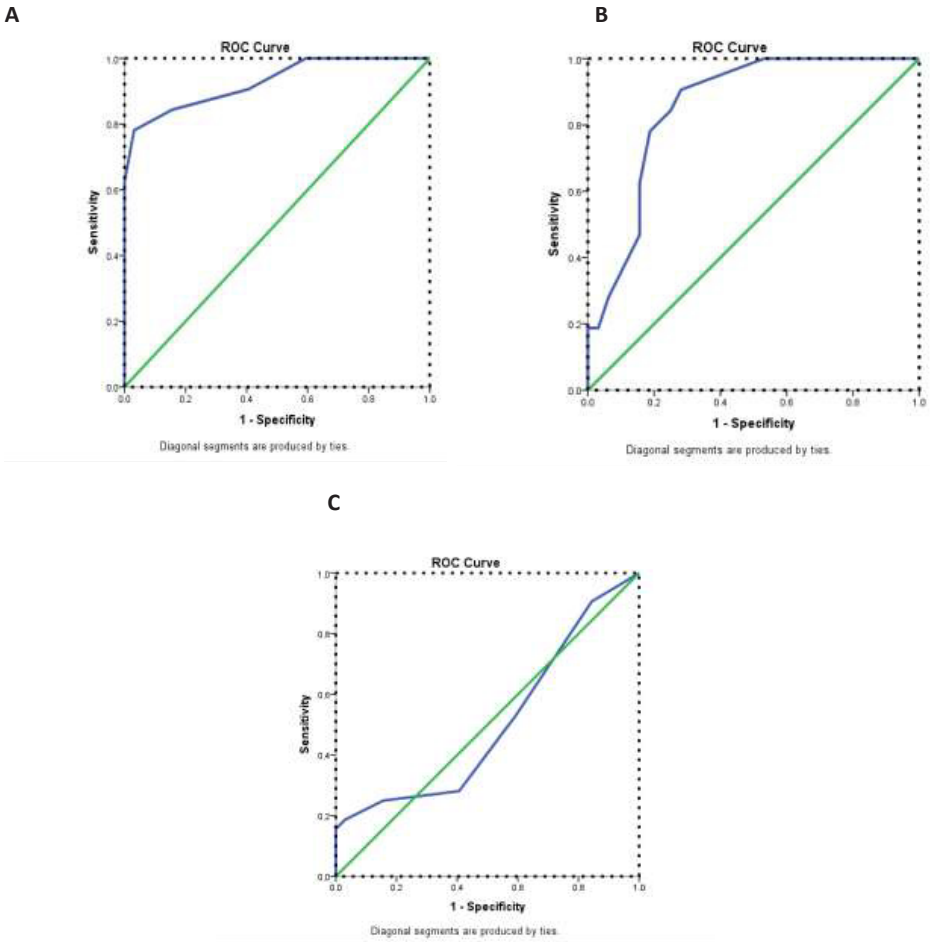

Figure 2. Receiver operating characteristic (ROC) curves for models to predict autism. (A) AUC showed a higher value in the model for the sum of neurological symptoms as a new marker for ASD (ASD) detection (Control vs. Patients) (P<0.0001, AUC=0.92). (B) AUC showed a higher value in the model for the sum of neurological symptoms as a new marker for ASD detection (Siblings vs. Patients) (P<0.0001, AUC=0.85). (C) AUC showed a weak value in the model for the sum of neurological symptoms as a new marker for ASD detection (Control vs. Siblings) (P>0.05, AUC= 0.50)

that the soft neurological symptoms can have a genetic basis and are more common in siblings, this is not true in autism. Seemingly, it is not a disorder that can be seen in their healthy siblings. The reason is unknown, and it may be due to the complexity of genetic factors in autism.

In this study, 28 NSS symptoms were examined and compared among three control groups: Siblings and patient group. The results showed that total NSS was higher in autism patients compared to their siblings and control subjects ($p<0.05$).

Malviya et al. showed that NSS exists in autism patients, and therefore, patients need to be evaluated concerning their symptoms. Further investigations showed that 71% of patients had errors in the finger-nose tests, 70% had difficulty in tandem walking, and 78% had errors in the Ozeretski test (5). However, NSS symptoms were increased in patients in the study of Malviya et al., unlike this study, which was conducted on patients and was not compared with the control group.

Focseneanu's study indicates that using the NSS score can help differentiate patients with schizophrenia from obsessive-compulsive disorder (OCD). Their results showed that the NSS score was higher in schizophrenia patients compared to OCD and healthy people (17). Razjouyan et al. reported that the prevalence of NSS was higher in patients with ADHD compared to the control group. On the other hand, their results showed that the prevalence of NSS-related symptoms in the siblings of ADHD patients was also higher compared to control subjects (18). In the study of Gong et al., it was exerted that the overall average NSS score was higher in ADHD patients and their parents compared to the control group. In addition, it was found that the evaluation of the NSS score of fathers compared to mothers can be more helpful for disease prediction (19).

The above studies investigated the NSS score in other mental disorders. However, the present study found that the NSS score in these diseases was higher in patients compared to healthy people. Gong et al. showed that NSS in ADHD patients can be transmitted from father to child through genetic inheritance. Further investigations showed that each parent's disease alone could cause a series of differences in the incidence of NSS in children. This could be due to genetic changes in them (19).

Another study revealed that examining NSS alongside other diseases can result in various overlaps. In other words, the extent of these overlaps often depends on the tools employed in the analysis (20).

In the present study, the average NSS score in autism patients was higher compared to their siblings' counterparts. In addition, it was shown that using NSS in patients compared to healthy people can be considered a suitable prediction factor. The critical point in this study was the comparison of neurological symptoms in autism patients and their caregivers. Based on this, it was revealed that using NSS scores in patients compared to their nurses can have a predictive value. However, these symptoms had no predictive value for nurses of patients compared to healthy people.

Overall, there have been very few studies conducted on NSS concerning autism based on current evaluations. However, studies have shown that NSS appears exclusively in patients and is not found in their siblings. Meanwhile, considering that NSS is a hereditary disease and there is a possibility of its transmission through heredity, more studies are needed in this field.

This study has several limitations. Future studies must conduct more statistical studies on the population in future studies. In addition, the relationship between the incidence of NSS in patients and their parents should be determined through genome sequencing. It is also necessary to compare NSS scores in autism patients with those of other patients.

In Conclusion

Overall, using the NSS score to compare individuals with autism to their siblings can be beneficial. Additionally, the score does not influence predictions between siblings and control subjects.

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Authors' Contributions

Katayoon Razjouyan: contributed to study conception.

Abbas Babazadeh dezfoly: contributed to clinical investigation and data collection,Rozita Davari Ashtiani: contributed to clinical investigation, Mojgan Khademi :contributed to design and drafted the article , Fariba Arabgol: contributed to design and drafted the article,Mohammad Javad Nasiri: contributed to statistical analysis,Nahid Piri :contributed to data collection,Mohammad Ali Miri :contributed to data collection.

Conflict of Interest

The authors declared no conflict of interest.

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