AFMN BIOMEDICINE

CASE REPORT

NIZON-ISIDOR SYNDROME, A RARE GENETIC DISEASE WITH LATE DIAGNOSIS PRESENTING WITH AUTISM SPECTRUM DISORDER : A CASE REPORT

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Nizon-Isidor syndrome (NIZIDS) is a rare genetic disorder associated with mutations in the MED12L gene and is usually characterized by a distinctive facial appearance, neurodevelopmental delay, autism spectrum disorders (ASD), and chronic gastrointestinal symptoms (GIS). In this case report, we emphasize the importance of early evaluation of genetic tests and diseases with Nizon-Isidor syndrome in our patient, who had characteristic facial findings, ongoing GI symptoms since birth, diagnosed with ASD at the age of 2, and diagnosed with Nizon-Isidor at a late stage (age 4) in an 8-year-old girl. In particular, it has been demonstrated once again that early genetic testing in patients with similar clinical features plays a critical role in reaching the correct diagnosis and treatment planning. These findings indicate the importance of a multidisciplinary approach in the recognition of rare syndroms of genetic origin.

Keywords: Nizon-Isidir syndrome, autism spectrum disorder, neurodevelopmental delay, genetic diseases

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INTRODUCTION

Nizon-Isidor syndrome (NIZIDS), associated with mutations in the MED12L gene, is a rare genetic disease first reported by Nizon Isidor et al. (1) in 2019. This syndrome usually presents with prominent facial dysmorphia, neurodevelopmental delay, and gastrointestinal symptoms (GIS) (1). Genetic diseases are the etiological factor in a significant portion of autism spectrum disorder (ASD). ASD, which is a polygenic disorder, is also associated with monogenic syndromes and chromosomal anomalies. In particular, clues such as neurodevelopmental delay, characteristic facial findings, and chronic GIS symptoms that persist from birth reveal the importance of early referral to genetic testing in these children (2, 3). In this case report, the importance of early genetic diagnosis is discussed through the case of a pediatric patient diagnosed with NIZIDS.

CASE REPORT

An 8-year-old girl was admitted to our clinic with a diagnosis of ASD and characteristic facial findings for cognitive training. Physical examination revealed a height of 130 cm (50-75 percentile) and a weight of 30 kg (75-90 percentile). Hypertelorism, a bulging nasal tip, a flat nasal bridge, an everted lower lip, an enlarged earlobe, an inward squint in the right eye, and fullness in the upper eyelids were found (Figure 1). Her medical history included GIS such as chronic vomiting and diarrhea that had persisted since birth. Neurodevelopmental delay was noted at the age of 1.5 years, and she was diagnosed with ASD at the age of 2 years. Her family history was not significant in terms of genetic diseases. As a result of genetic tests performed at the age of 4 years, the diagnosis of Nizon-Isidor syndrome with a mutation in the MED12L (NM_053002.5:c.4898A>T, p.(Asp1633Val), Chr3:g. 151,385,106>T) gene was confirmed.

DISCUSSION

There is very limited information about NIZIDS syndrome, which was first reported in the literature in 2019. It is possible to discuss three main points from this case. First, it is necessary to draw attention to the relationship between ASD and genetic diseases. Genetic factors are essential for understanding the clinical presentation of ASD. Genetic disorders such as fragile X syndrome, Rett syndrome, and tuberous sclerosis are the main diseases associated with ASD (2) (Table 1). Considering that rare genetic disorders, such as Nizon-Isidor syndrome, are also involved in the etiology of ASD, early genetic testing in children with ASD may positively affect the diagnosis and treatment processes.

Secondly, characteristic facial findings provide a critical guide in the differential diagnosis of genetic diseases (4). The distinctive dysmorphic features present in NIZIDS, such as hypertelorism, a flat nasal bridge, and a thin upper lip, provide important clues for guiding the genetic testing. Clinical observations suggest that such dysmorphic findings should be evaluated together with neurodevelopmental and other systemic symptoms (4).

Finally, the role of the genetic diagnostic process and MED12L gene mutations in Nizon-Isidor syndrome should be emphasized. Genetic confirmation not only provides a definitive diagnosis but also guides patient management in the long term (3, 5). This case demonstrates once again that early application of genetic testing in children with ASD and GIS symptoms is critical to reaching a diagnosis.

In conclusion, rare genetic diseases such as NIZIDS may be overlooked due to clinical variability. However, as seen in this case, genetic testing in patients with ASD, neurodevelopmental delay, and characteristic facial findings may guide clinicians in the diagnostic process. This approach will allow for the creation of an appropriate treatment and counselling plan for both the patient and the family at an early stage.

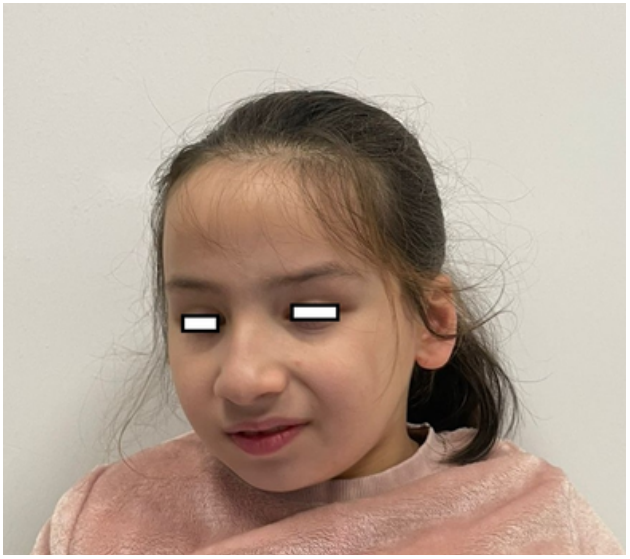

Figure 1. *Characteristic facial and head findings of the patient** *Hypertelorism, a protruding nasal tip, a flat nasal root, an everted lower lip, enlarged earlobes, right-sided esotropia, and fullness of the upper eyelids are observed.

Table 1. *Important known genetic diseases that progress to autism spectrum disorder*

Disease	Affected gene	Location description
Fragile X syndrome	FMR1	Associated with mental retardation and ASD-like behaviors.
Rett syndrome	MECP2	Usually seen in girls; neurodevelopmental delay and ASD features.
Tuberous sclerosis complex	TSC1, TSC2	Tumor formation in the brain, skin and other organs; ASD prevalence is high.
Angelman syndrome	UBE3A	Associated with mental retardation, speech difficulties, and ASD-like features.
15q11-13 duplication syndrome	15q11-13	Associated with ASD, epilepsy, and developmental delays.
Phelan-McDermid syndrome	SHANK3	Difficulties with social interaction and symptoms of ASD are common.
Smith-Magenis syndrome	17p11.2	Associated with sleep disorders, learning disabilities, and ASD features
CHARGE syndrome	CHD7	Sensory-motor deficits and ASD-like behaviors may be seen
Neurofibromatosis type 1	NF1	Neurofibromas are associated with learning disabilities and a predisposition to ASD.
PTEN hamartoma tumor syndrome	PTEN	Macrocephaly, tumor risks, and ASD symptoms are common.
Nizon-Isidor syndrome	MED12L	Prominent facial dysmorphia, neurodevelopmental delay, and gastrointestinal symptoms (GIS).
Williams syndrome	7q11.23	Associated with social extremism and some behaviors that may be on the ASD spectrum.
Prader-Willi syndrome	15q11-q13	Eating disorders, developmental delays, and ASD features may be seen.
Down syndrome	Trisomy 21	Mental retardation may be associated with an increased prevalence of ASD.
Dup15q syndrome	15q11.2-q13	Duplication associated with epilepsy and distinct ASD features.
Klinefelter syndrome	XXY	Chromosome social interaction difficulties and ASD-like features may be seen.
DiGeorge syndrome	22q11.2	Deletion is associated with mental retardation, psychiatric disorders, and ASD symptoms
Sotos syndrome	NSD1	Developmental delays, macrocephaly, and increased prevalence of ASD may be seen.
SYNGAP1-associated encephalopathy patients	SYNGAP1	Seizures, mental retardation, and ASD symptoms are common
Joubert syndrome	AHI1, PHP1, TMEM67	Associated with brain developmental disorders and ASD-like behaviors.
ADNP syndrome	ADNP	Associated with developmental delay, language delay, and autistic features.

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Author's contribution

Conceptualization, M.S.D.; Investigation, M.S.D.; Resources, Y.K.; Writing - original draft preparation: Y.K. and M.S.D.; Writing - review & editing, M.S.D.; Visualization: M.S.D. and Y.K.; Supervision: M.S.D. Both authors have read and approved the published version of the manuscript.

Statement of Ethics

The study was conducted in accordance with the Declaration of Helsinki. Complete written informed consent was obtained from the patient's parents for the publication of this study and accompanying images.

Statement of Competing Interest

The authors declare no relevant conflicts of interest.

Statement of Data Availability

Not applicable.

Statement of Generative AI Use

No generative AI was used.

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