MEDICAL RESEARCH REPORTS

Med Res Rep 2024;7(3):177-182
https://doi.org/10.55517/mrr.1439712

CASE REPORT

X-Linked Intellectual Disability with NEXMIF Gene Mutation and Developmental Delay with GNAO1 Gene Mutation: Case Report

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ÖZET

X'e bağlı zihinsel engellilik (XLID) genetik olarak heterojen bir bozukluktur. Şu anda XLID ile bağlantılı 162 gen bulundu, ancak XLID'nin nedeni hala belirsiz. GNAO1 geni hipotoni, epilepsi, gelişimsel gecikme ve hareket bozuklukları için önemli olsa da, KIAA2022 olarak da bilinen NEXMIF geni XLID, otizm ve epilepsi ile ilişkilidir. Çalışmanın konusu olan 5 yaşında bir kız çocuğunun yarık damak, anal atrezi, alt ekstremitelerinde hipotoni ve baş parmağının olmaması gibi birçok doğuştan kusuru vardır. Skolyoz, parmak malformasyonları ve kraniyofasiyal dismorfizm gibi çeşitli göz anormallikleri vardır. Radyolojik testler önemli kalp sorunları, bilateral böbrek hipoplazisi ve beyin anormallikleri ortaya koydu. Çağdaşlarından daha geç dönüm noktalarına ulaştı ve bu da açık gelişimsel eksiklikleri gösteriyor. NEXMIF (NM_001008537.2) ve GNAO1 (NM_138736.2) genleri, yeni nesil dizileme kullanılarak genetik araştırma yoluyla keşfedilen heterozigot çerçeve kayması varyantlarını içerir. Bu vakada XLID ve gelişimsel gecikmenin karmaşık ve çeşitli klinik belirtileri gösterilmiştir. Klinik tablo, NEXMIF ve GNAO1 genlerindeki mutasyonların birlikte görülmesiyle daha da karmaşık hale gelir ve bu da uygun tedavi çözümleri sunmak için bir yaklaşıma olan ihtiyacı vurgular. Bu genler arasındaki karmaşık etkileşimleri ve XLID ve gelişimsel gecikmeyle ilişkili semptomları nasıl etkilediklerini anlamak için gelecekteki çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: GNAO1, Mikrosefali, NEXMIF, Vaka raporu, XLID

ABSTRACT

X-linked intellectual disability (XLID) is a genetically heterogeneous disorder. Currently, 162 genes linked to XLID have been found, but the cause of XLID is still unclear. While the GNAO1 gene is crucial for hypotonia, epilepsy, developmental delay, and movement disorders, the NEXMIF gene, also known as KIAA2022, has associations with XLID, autism, and epilepsy. The subject of the study, a 5-year-old girl has lots of congenital defects, including a cleft palate, anal atresia, hypotonia in her lower limbs, and thumb missing. A variety of eye abnormalities, such as scoliosis, finger malformations, and craniofacial dysmorphism. Radiological tests revealed substantial heart problems, bilateral renal hypoplasia, and brain abnormalities. She met milestones more later than her contemporaries, indicating clear developmental deficits. The NEXMIF (NM_001008537.2) and GNAO1 (NM_138736.2) genes both include heterozygous frameshift variants discovered through genetic research using next-generation sequencing. The complex and varied clinical signs of XLID and developmental delay are shown in this case. The clinical picture is further complicated by the co-occurrence of mutations in the NEXMIF and GNAO1 genes, which emphasizes the need for an approach to offer suitable therapy solutions. Future studies are necessary to understand the complex interactions between these genes and how they affect XLID and developmental delay related symptoms.

Keywords: GNAO1, Microcephaly, NEXMIF, Case Report, XLID

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Mail: gulam.hekimoglu@sbu.edu.tr Received: 19.02.2024 ; Accepted: 04.10.2024

Cite this article as: Aygun T, Yener S, Yucel N, Hekimoglu G, Eser M, Ilce Z. X-Linked Intellectual Disability with NEXMIF Gene Mutation and Developmental Delay with GNAO1 Gene Mutation: Case Report. Medical Research Reports 2024; 7(3):177-182

INTRODUCTION

X-linked intellectual disability (XLID) is a genetically heterogeneous condition that affects more than 10% of males with intellectual disability (1). Since then, the relationship of 162 genes on the X chromosome with XLID has been described. According to the 2022 update; Another 21 new genes associated with XLID have been added to the literature. In addition, 199 syndromes with XLID have been described in cases, but 42 of them could not be explained at the molecular level (2). The NEXMIF gene (KIAA2022) (OMIM number: 300524) is expressed extensively in the cerebral cortex and cerebellum, with minor amounts in some tissues in fetal life and adult individuals (3). Mutations in this gene have been associated with XLID, autism, and epilepsy (4) However, the GNAO1 gene encodes the α subunit of G proteins involved in the transduction and modulation of neurotransmitter release (5). It is involved in conditions such as hypotonia, epilepsy, developmental delay, and movement disorders (6).

The NEXMIF gene was first associated with XLID in 2004 (7). Carrier females generally show a wide phenotypic variation, ranging from a completely asymptomatic prognosis to severe intellectual disability and drug-resistant epilepsy (8). The phenotypic variability in female carriers is thought to be due to skewed X-inactivation or cellular mosaicism (9). We described a case of a young girl with XLID and developmental delay identified as a heterozygous frameshift variant of both NEXMIF (NM_001008537.2) and GNAO1 (NM_138736.2) genes.

CASE DOCUMENTATION

Our patient was 5 years old, she was born in February 2018, weighing 2010 grams, by cesarean section at 41 weeks of gestation. The Apgar score was recorded as 6/8. It was noted that there was no consanguinity between the mother and father and there was no history of disease in the family.

Physical Examination

Physical examination revealed cleft palate, anal atresia, hypotonic lower extremity, and absence of thumb. Eye examination revealed biparietal stenosis with an upward-sloping palpebral space, choroidal coloboma, and periorbital edema in the lower periphery of the right eye. She had retrognathia in her jaw. While the left hand was normal, the 4th and 5th fingers on the bilateral feet were smaller than normal, and facial dysmorphism findings such as partial cutaneous syndactyly, right hemifacial microsomia, plagiocephaly, bilateral epicanthus, and scoliosis were observed.

Radiological Examinations

MRI imaging showed that she has semi-lobular holoprosencephaly, advanced corpus callosum hypoplasia, incomplete formation in the hippocampus, dissociated lateral ventricles (separation in the occipital and temporal horn), hypoplastic cerebellar vermis, microcephaly, absence of septum pellucidum and the presence of interhemispheric fissure (Figure 1, 2). Abdominal ultrasonography revealed bilateral renal hypoplasia and accessory spleen. Echocardiography revealed patent ductus arteriosus (PDA), atrial septal defect (ASD), and ventricular defects.

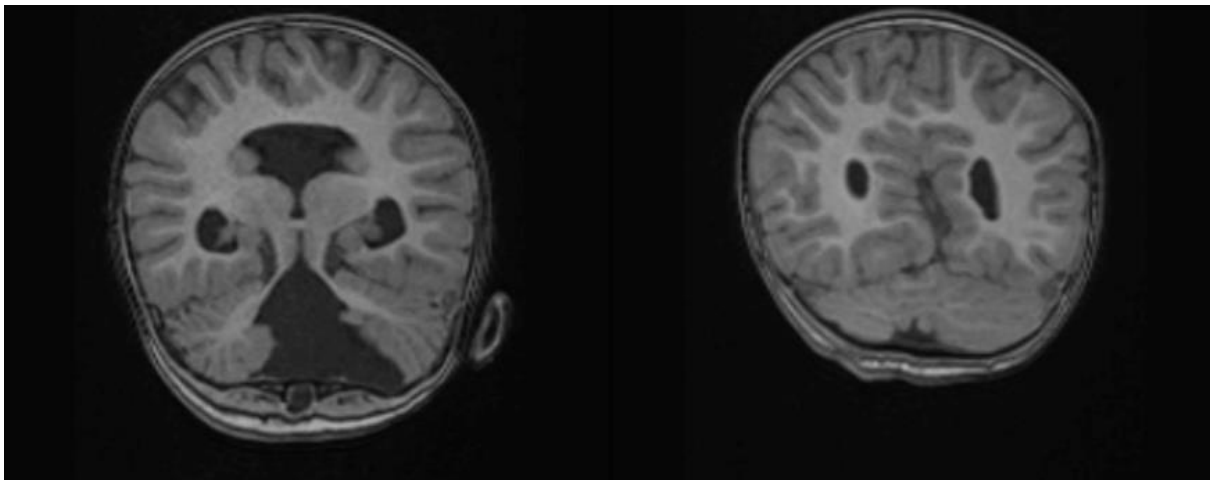

Figure 1: Coronal T1AG image shows that there is no fronto-parietal fusion, corpus callosum agenesis, thalamic fusion, or interhemispheric fissure.

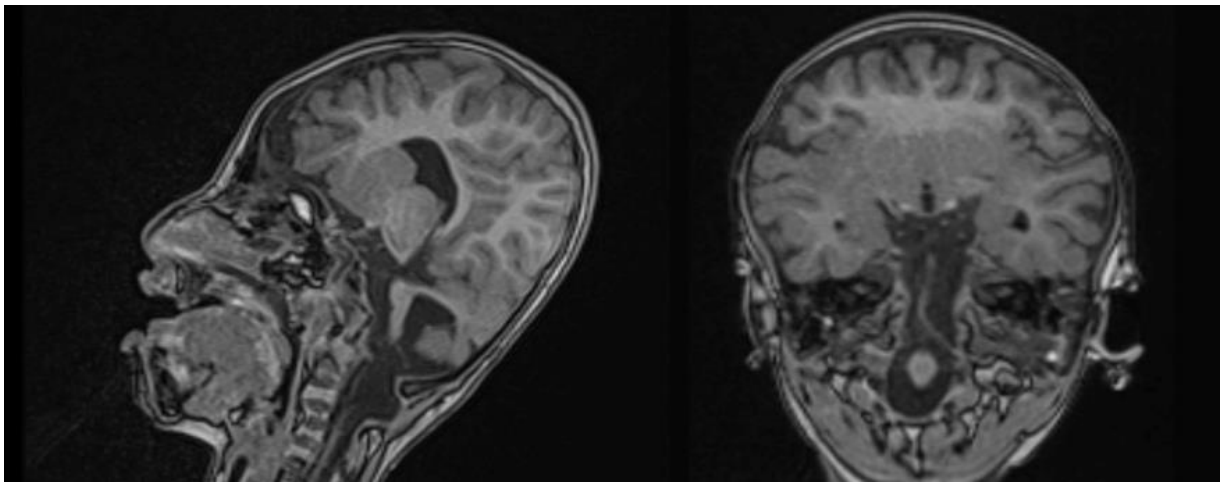

Figure 2: The anterior corpus callosum is not visible in the sagittal T1AG image, and its posterior part is clearly atrophic and dysgenetic.

According to the Denver 2 Developmental Test conducted at the age of 12 months; Personal and social development was noted at 3.5 months, fine motor development at 4 months, language development at 2.5 months, and gross motor development at 2.5 months. It was observed that the patient was calm, followed objects with her eyes, made eye contact, and started symmetrical extremity movements.

Genetic Analysis

Next Generation Sequencing technology (NGS) is used in genetic testing. DNA was isolated from peripheral blood samples with the QIAA mp DNA mini (Qiagen) kit and analyzed using the Twist Human Core Exom v2 kit. The sequencing reaction was performed using the Illuminanovaseq® system. Bioinformatic analyses and variant calling were performed against the hg19 human reference genome using the Sophia DDM® bioinformatics analysis platform. The coding regions of 21378 genes were included in the study. According to the test results, nucleotide change (c.45512_4513del p. Phe1505*), annotation (frameshift), and ACMG classification [likely pathogenic (PVS1, PM2)] in the NEXMIF (NM_001008537.2) gene and nucleotide change (c.950_951del p. Lys317Argfs*20), annotation (frameshift), ACMG classification [VUS (PM2)] in GNAO1 (NM_138736.2) gene were observed as heterozygous.

DISCUSSION

MRI image results of our case showed delay and abnormalities in brain development. There were studies suggesting that the NEXMIF mutation leads to a marked disruption in neuron growth, including dendrites and axons, thus NEXMIF plays an important role in neuron development and brain function (10).

In our report, the presence of microcephaly was detected in brain examinations. This was in line with the findings in the case report of Panda. Panda et al. showed that the presence of microcephaly was more common in males in a study conducted with 24 female and 21 male patients with the pathological NEXMIF variant (8). In addition, cases of cerebral atrophy, ventricular enlargement, and enlarged Wirchof-Robin space were also reported (10).

Findings such as facial dysmorphism, developmental delay, late appearance of motor milestones, dystonia, and mental retardation in this case all support the case records available in the literature (3). In addition, the presence of scoliosis in our patient was an important physical disability, and similarly, case reports were reporting the presence of scoliosis (3).

Important data was revealed in radiological examinations. Advanced corpus callosum hypoplasia was detected in our case. This was in concordance with the recent study that diffuse cerebral atrophy and corpus callosum hypoplasia were observed in cases with GNAO1 mutation (5).

Our patient was a girl in 5 years old and did not show any epileptic seizures. De Lange

et al. reported that 12 of the 14 female patients they examined in their study had epilepsy (9). There were different cases presented in terms of the age of onset of epileptic seizures. De lange et al. also reported different ages of seizure onset as 7 years and 16 years of age, and Van Maldergem et al., as the first month or 14 years of age (9, 10).

In addition, divergence in the occipital and temporal horns of the lateral ventricles and hypoplasia in the cerebellar vermis were observed in this patient. The most important MRI finding in our patient was the presence of semi-lobular holoprosencephaly. It was unique to our report. In the studies, no holoprosencephaly cases were found with NEXMIF or GNAO1 gene mutations.

CONCLUSION

This paper reveals a striking case report of a young girl with NEXMIF gene mutations, a disorder that is less frequent in females and causes phenotypes that are remarkably variable with a challenging prognosis. Interestingly, this followed in all procedures carried out for this study. The patient's parents or legal guardians provided written permission for the case report example may be the first incidence of simultaneous mutations in both the NEXMIF and GNAO1 genes in the history of scientific literature. Given the wide range of onset ages, the importance of regularly monitoring this patient's epileptic seizures cannot be emphasized. We strongly advise undertaking a family segregation study to see whether this mutation is de novo, in order to better comprehend it. These findings highlight the crucial relevance of ongoing investigation and monitoring in the field of genetic disorders, offering prospective understandings and better patient outcomes in the future.

Source(s) of financial support: None.

Conflicts of interest: The authors have no conflicts of interest to declare.

Ethical Statement: The writers are responsible for all parts of the work and must see to it that any concerns about the truthfulness or integrity of any portion of the work are duly investigated and addressed. The Helsinki Declaration and institutional and/or national research committee(s) ethical requirements were both and photographs to be published. The editorial office of this journal has a copy of the written consent on file for examination.

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