Academic Journal of
Pediatrics & Neonatology
ISSN 2474-7521

Juniper Publishers
key to the Researchers

Case Report
Volume 14 Issue 2 - June 2024
DOI: 10.19080/AJPN.2024.14.555936

Acad J Ped Neonatol

A Comprehensive Case Report of OPHN1 X-Linked Intellectual Disability and a Hazardous Association with Familial Mediterranean Fever Heterozygote Mutation

Hadi Fakih M[1]* and Abdallah Dbouk[2]

[1]*Pediatrics, Faculty of Medical Sciences, Lebanese University, Beirut, LBN, Pediatrics, NICU Division, Sheikh Ragheb Harb University Hospital, Toul, Lebanon*

[2]*Pediatrics, Faculty of Medical Sciences, Lebanese University, Beirut, LBN, Pediatrics, Sheikh Ragheb Harb University Hospital, Toul, Lebanon*

Submission: June 13, 2024; **Published:** June 20, 2024

***Corresponding author:** Hadi Fakih M, Pediatrics, Faculty of Medical Sciences, Lebanese University, Beirut, LBN, Pediatrics, NICU Division, Sheikh Ragheb Harb University Hospital, Toul, Lebanon

Abstract

OPHN1 X-linked intellectual disability (XLID) is a rare genetic disorder characterized by moderate intellectual disability and various neurological and developmental manifestations. This report describes a 4-year-old male with multiple clinical features consisting of dysmorphic facial features, external ear protuberance, failure to thrive, short stature, hypothyroidism, cerebellar and periventricular gliosis and wide based gait with delayed milestones development The case highlights the importance of considering a broad differential diagnosis and the utility of genetic testing in patients with complex multisystem presentations. Early diagnosis and intervention can significantly impact the management and quality of life for affected individuals and for the appropriate genetic counseling for the family.

Keywords: OPHN1; Intellectual; Disability; Cerebellar; Gliosis

Abbreviations: XLID: X-linked Intellectual Disability; PICU: Pediatric Intensive Care Unit; FMF: Familial Mediterranean Fever; MRI: Magnetic Resonance Imaging

Introduction

OPHN1 encodes oligophrenin 1, a Rho-GTPase activating protein involved in synaptic morphogenesis and functions through the regulation of the G protein cycle [1], OPHN1 is related to syndromic X-linked intellectual disability (XLID), it contains 25 exons, located in the Xq12 region, encoding an 802 amino acid Rho GAPs domain [2]. This protein is observed both in glial cells and neurons where it coexists with F-actin, especially at the tip of rising dendrites and at both parts of the synapse [3]. The recognizable phenotype includes intellectual disability, a distinctive facial appearance with vision problem, brain anomalies such as cerebral ventricular augmentation and cerebellar hypoplasia preponderant in the vermis, ataxia, seizures, and endocrine disorders [4]. We report the case of a 4,5 years-old boy diagnosed as having OPHN1 mutation with full clinical and diagnostic investigations that directed us to the final diagnosis.

Case Presentation

The case was a 4,5 YO boy, born on 2019, by an elective cesarean section from no -consanguineous parents with normal first male sibling, he was admitted on March 2024 to the pediatric intensive care unit (PICU), for severe sepsis and pneumonia, with a history of multiple hospitalization due to recurrent fever and infections. given his special features and clinical findings that consist of (Table 1) & (Figure 1). Giving the complex clinical disorders that

involved multiple organs and system like the brain, endocrine and the immune system which correlated with positive findings on the MRI imaging of the brain that showed periventricular and cerebellar chronic gliosis (Figure 2).

Associated with a severe bone age delay and resistant hypothyroidism, despite an appropriate hormonal replacement therapy, we decided to perform a comprehensive genetic test that could lead to the likely syndrome or genetic disorder that combines the above cited various features. The whole exome sequencing (WES) confirmed the clinical diagnosis and explained the periodicity of fever that the patient complained of (Figure 3).

Figure 1: Facial characteristics and wide based gait of the boy (with the courtesy of parents).

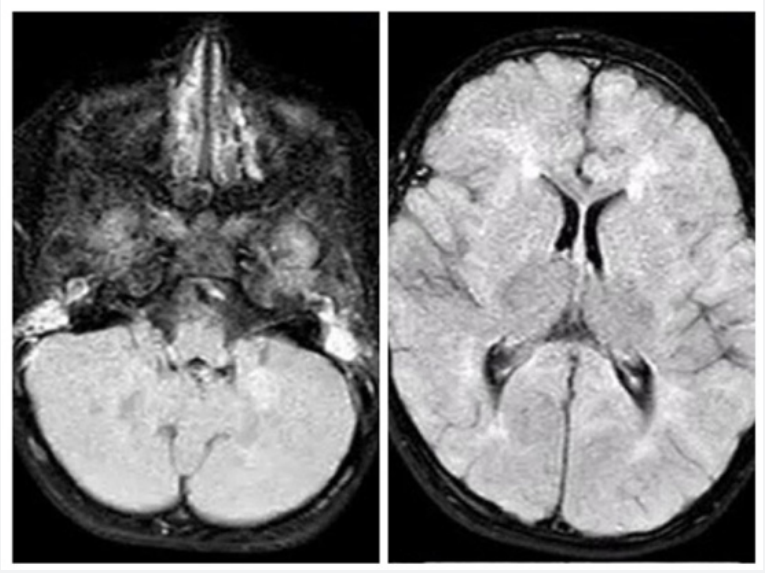

Figure 2: Axial 2 FLAIR cuts of brain MRI showing Diffuse severe bilateral periventricular FLAIR matter hyperintense changes, and FLAIR white matter hyperintense changes in bilateral centrum semiovale and cerebellar white matter, reflecting gliosis versus leukomalacia.

How to cite this article: Hadi Fakih M, Abdallah Dbouk. A Comprehensive Case Report of OPHN1 X-Linked Intellectual Disability and a Hazardous Association with Familial Mediterranean Fever Heterozygote Mutation. Acad J Ped Neonatol 2024; 14(2): 555936. DOI: 10.19080/AJPN.2024.14.555936

Variant Details		
Gene ID	OPHN1	MEFV
Transcript	NM_002547.3	NM_000243.2
Location	ChrX:67421509	Chr16:3293310
HGVSc and HGVSp	c.977C>T p.Thr326Met	c.2177T>C p.Val726Ala
Coverage	0:35	35:38
Zygosity	Hemizygous	Heterozygous
Inheritance Pattern	X-Linked Recessive	- Autosomal Recessive - Autosomal Dominant
Disease	Intellectual Developmental Disorder, X-Linked, Syndromic, Billuart Type	Familial Mediterranean Fever (FMF)
Classification	Likely Pathogenic	Pathogenic
Classification Database	ClinVar, Franklin, Varsome	ClinVar, Franklin

Figure 3: Result of Whole Exome Sequencing.

Table 1: Clinical and Laboratory findings.

Clinical Finding	Description
Dysmorphic Facial Features	Large forehead
	Long and narrow face
	Deep-seated eyes
	Peaked nose
	Short philtrum
	Protuberant ears
Short Stature and Failure to Thrive	Weight: 10 kg (below -3 SD)
	Height: 92 cm (below -3 SD)
	Bone age: Estimated at 2 years
Delayed Developmental Milestones	Speech Delay
	Delayed Fine and Gross Motor milestones
Ataxic Walk	Wide-Based Gait
Hypothyroidism	TSH: 27 mU/L (normal range: 0.45 to 4.12 mU/L)
History of Recurrent Infection	Multiple Hospitalizations and Neutropenia

Figure 3 findings:

i. A hemizygous missense variant (c.977C>T, p. Thr326Met) has been detected in OPHN1 gene located at exon 11 out of 25 total exons. This variant has been classified as likely pathogenic variant in Clin Var by single submitter in 2023 (1-star) as it is not observed at significant frequency in large population cohorts (gnom AD); In silico analysis supports that this missense variant has a deleterious effect on protein structure/function and has not been previously published as pathogenic or benign to our knowledge. Franklin database classified this variant as a likely pathogenic variant using the following ACMG criteria (PS4, PM2, and PP5). Varosme also calls this variant a likely pathogenic variant using (PM2, and PP5) ACMG criteria.

ii. A heterozygous missense variant has been found in MEFV gene located at exon 10 out of 10 total exons that is associated with Familial Mediterranean Fever (FMF). This variant (c.2177T>C, p. Val726Ala) is classified as pathogenic/likely pathogenic variant in Clin Var by multiple submitters with no conflicts (2-stars).

How to cite this article: Hadi Fakih M, Abdallah Dbouk. A Comprehensive Case Report of OPHN1 X-Linked Intellectual Disability and a Hazardous Association with Familial Mediterranean Fever Heterozygote Mutation. Acad J Ped Neonatol 2024; 14(2): 555936. DOI: 10.19080/AJPN.2024.14.555936

Further investigations performed included an abdominal ultrasonography that showed a mild left hydronephrosis, a normal echocardiography and a normal hearing screen test performed at birth.

Discussion

OPHN1 syndrome or X-linked intellectual disability-cerebellar hypoplasia syndrome, is a rare disorder that was discovered in 1998 [5], it is characterized by intellectual disability and changes in the part of the brain and the cerebellum, The syndrome mainly affects males. Signs and symptoms may include intellectual disability, hypotonia, developmental and cognitive delay, early-onset seizures, abnormal behavior, small or underdeveloped genitals, characteristic facial features that comprises long face, prominent forehead, eye creases, deep set eyes, and protuberant ears, The facial dysmorphism seen in almost all affected patients could be explained by the expression of OPHN1 in the craniofacial bones [6].

Strabismus and ataxic gait and movement are explained by the cerebellum function that is involved in oculomotor coordination, which may contribute to nystagmus and strabismus [7]. The oculomotor problems which seem to appear due to hypoplasia of the cerebellum are many times remarked on brain imaging studies [8]. Additionally, OPHN1 mutations have also been reported in individuals with autism or childhood onset schizophrenia, so OPHN1-associated clinical phenotypes are variable [9]. The most common Magnetic resonance imaging (MRI) brain scan anomalies reported in different studies were cerebellar hypoplasia, especially of the lower vermis, enlarged cisterna magna, or retrocerebellar cysts, the anterior vermis may be disorganized and also hippocampal alteration [10].

The determination of a genetic diagnosis for the patient described in this report significantly altered his care. Prior to the diagnostic finding on WES, with presence of idiopathic short stature, failure to thrive and intellectual disability, his parents seek multiple medical and specialties advices and consultation with large number of tests and investigations performed and therapeutic recommendations. Subsequent to the diagnosis, with an improved understanding of the underlying cause of his clinical condition, the parents are convinced about his final diagnosis and prognosis and focused mainly on performing musculoskeletal, speech and behavioral therapy.

Conclusion

As in this case, a thorough diagnostic evaluation and the performance of appropriate diagnostic test such as Whole Exome Sequencing WES of individuals considered to have intellectual disability, dysmorphism and short stature may provide significant benefit to families and patients via improved understanding of prognosis, therapy, and recurrence risk and solicit the family to perform an early genetic screening for the coming pregnancy.

References

1. Nadif Kasri N, Van Aelst L (2008) Rho-linked genes and neurological disorders. Pflugers Arch 455(5): 787-797.
2. Mandel JL, Chelly J (2004) Monogenic X-linked mental retardation: is it as frequent as currently estimated? The paradox of the ARX (Aristaless X) mutations. Eur J Hum Genet 12(9): 689-693.
3. Zamboni V, Jones R, Umbach A, Alessandra A, Maria P, et al. (2018) Rho gtpases in intellectual disability: from genetics to therapeutic opportunities. Int J Mol Sci 19(6): E1821.
4. Santos-Reboucas CB, Belet S, Guedes de Almeida L, et al. (2014) A novel in-frame deletion affecting the BAR domain of OPHN1 in a family with intellectual disability and hippocampal alterations. Eur J Hum Genet 22(5): 644-651.
5. Billuart P, Bienvenu T, Ronce N, des Portes V, Vinet MC, et al. (1998) Oligophrenin-1 encodes a rhoGAP protein involved in X-linked mental retardation. Nature 392(6679): 923-926.
6. Zanni G, Saillour Y, Nagara M, Billuart P, Castelnau L, et al. (2005) Oligophrenin 1 mutations frequently cause X-linked mental retardation with cerebellar hypoplasia. Neurology 65(9): 1364-1369.
7. Menten B, Buysse K, Vermeulen S, Valerie M, Vandesompele J, et al. (2007) Report of a female patient with mental retardation and tall stature due to a chromosomal rearrangement disrupting the OPHN1 gene on Xq12. Eur J Med Genet 50(6): 446-454.
8. Ophn1-syndrome (2024) National Organization for Rara Disorders.
9. Piton A, Gauthier J, Hamdan FF, Lafrenière RG, Yang Y, et al. (2011) Systematic resequencing of X-chromosome synaptic genes in autism spectrum disorder and schizopherinia. Mol Psychiatry 16(8): 867-880.
10. Tzschach A, Grasshoff U, Beck-Woedl S, Claudia D, Claudia B, et al. (2015) Next-generation sequencing in X-linked intellectual disability. Eur J Hum Genet 23(11): 1513-1518.

DOI: 10.19080/AJPN.2024.14.555936

How to cite this article: Hadi Fakih M, Abdallah Dbouk. A Comprehensive Case Report of OPHN1 X-Linked Intellectual Disability and a Hazardous Association with Familial Mediterranean Fever Heterozygote Mutation. Acad J Ped Neonatol 2024; 14(2): 555936. DOI: 10.19080/AJPN.2024.14.555936