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Case Report

Novel USP9X Mutation in A Lebanese Patient with Delay and Microcephaly: Case Report and Review of Literature

Pierre Ghostine[1], Marie-Christine Seghaye[2], Bassam Romanos[3], Mohamad Fattah[4] and Hicham Mansour[5]*

[1] *Department of Pediatrics, Centre Hospitalier Régional de Huy, Huy, Belgium.*

[2] *Department of Pediatrics, University Hospital Liège, Belgium.*

[3] *ENT department, Eye and Ear Hospital, Beirut, Lebanon.*

[4] *Department of Pediatrics, Military Hospital, Beirut, Lebanon.*

[5] *Department of Pediatrics, Saint George Hospital University Medical Center, Beirut, Lebanon.*

***Corresponding Author:** Hicham Mansour, Department of Pediatrics, Saint George Hospital University Medical Center, Beirut, Lebanon.*

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Abstract

Introduction: USP9X gene is located on the X-chromosome and encodes for an enzyme that regulates important substrates involved in neuronal growth and development. Thus, rare USP9X mutations were identified as directly causative of neurodevelopmental disorders (NDDs) and Intellectual Disability (ID) in homozygous males and more rarely in heterozygous females. In males, USP9X variants have been linked to an X-linked mental retardation syndrome that includes; central nervous system (CNS) abnormalities (white matter disturbances, thin corpus callosum, widened ventricles, and cerebellar defects), global delay with significant alteration of speech, language and behavior, hypotonia, joint hypermobility, digital abnormalities, gastro-intestinal symptoms, visual system defects and dysmorphic facial features.

Patient Data: We report the rare case of a 3 years old and 8 months male patient presenting with NDD, ID, speech delay, progressive aggressive behavioral changes and CNS abnormalities (microcephaly, left periventricular lesion). He was found to have a USP9X variant carrying a missense mutation: USP9X, c.1870A>T p.(Met624Leu) on Whole-Exome Sequencing (WES).

Discussion: Our patient had most of the important features of the previously described X-linked mental retardation syndrome but some were absent such as dysmorphic features, digital or visual abnormalities and hypotonia. Microcephaly rather than macrocephaly was noted, which could be an additional potential CNS malformation, expanding the spectrum of phenotypic characteristics of the USP9X variants. No associated congenital anomalies were noted that are usually more common in female subjects.

Conclusion: This is to our knowledge the first reported case of a USP9X variant in Lebanon. The clinical characteristics matched most of the previously described features in the literature. Microcephaly was a new clinical feature not previously described and could be a new possible phenotypic characteristic of the disease.

Keywords: USP9X variants, Intellectual Disability, Neurodevelopmental Disorder

Introduction

The gene USP9X, located on the X-chromosome, encodes for deubiquitylating enzyme that prevents its substrates degradation by the proteasome, thus stabilizing their concentrations (1). These substrates play a crucial role in neuronal maturation, migration and development on the level of neurodevelopmetal signaling pathways such as Notch, Wnt and TGF-β (2-5). Therefore, USP9X mutation variants have been implicated in X-linked neurodevelopmental disorders (NDDs) and Intellectual Disability (ID) by disrupting normal neuronal development and growth (5-6).

There is little literature available on USP9X mutations to fully understand the global genotypic and phenotypic spectrum of the disease. The available data so far indicate that clinical presentations and inheritance patterns of the USP9X mutations differ between males and females (5). Homozygous male USP9X variants often have missense mutations causing partial loss of function of the USP9X gene which leads into a male-restricted X-linked mental retardation syndrome with particular clinical features (MIM 300919) (5-7).The mutation can be inherited from a carrier mother or de-novo. The clinical features include: central nervous system (CNS) abnormalities (white matter disturbances, thin corpus callosum, widened ventricles, and cerebellar defects), global delay with significant alteration of speech, language and behavior, hypotonia, joint hypermobility, digital abnormalities, gastro-intestinal symptoms, visual system defects and dysmorphic facial features (5). Congenital heart disease has recently been reported in a USP9X male variant (8) as well as periventricular heterotopia (9) potentially expanding the genotypic and phenotypic presentation of the syndrome.

In contrast, female USP9X variants have complete loss-of-function mutations leading to syndromes known as female-restricted X-linked syndromic mental retardation-99 (MIM 300968), and X-linked recessive mental retardation-99 (MIM 300919) consisting of NDD and ID, as well as a wide range of congenital anomalies (7,10-13). Even though CNS anomalies can be similar in both genders, the frequency of associated major congenital anomalies is much higher in female subjects (5,7).

We report the rare case of a male patient presenting with NDD, ID, microcephaly, hyperlaxity, speech delay, progressive aggressive behavioral changes and CNS abnormalities who was found to have a USP9X variant carrying a missense mutation : USP9X, c.1870A>T p.(Met624Leu).

Case Report

We report the case of 3 years and 8 months old boy who first presented in 2018 to the pediatric neurology consultation. He is born from nonconsanguineous healthy parents: Lebanese father and a Syrian mother (Figure 1). The child had only one healthy female sibling. The child had no significant perinatal history, born at term with no recorded perinatal complications and had a history of bilateral ear tympanostomy tube placement with adenoidectomy done at the age of 1 year and 2 months. He had normal developmental milestones up until 1 year of age when he first walked and started his first few words. After his first birthday, his language skills remained limited to monosyllabic words and had features of ID with evident below-average cognitive functioning. An Auditory Brainstem Response (ABR) test was done before presentation to assess for any hearing deficiency and was normal. On physical exam his head circumference was 46 cm ($<5^{th}$ percentile for age) and following the same head circumference growth curse since birth. A metabolic workup was done and revealed to be normal. A Brain MRI with spectroscopy was done and showed a small left periventricular lesion (Figure 2). Cardiac Doppler ultrasound showed no associated congenital heart disease. The patient started to show behavioral changes marked by mild aggressiveness starting the age of 5 years. Blood Karyotype and Whole-Exome Sequencing (WES) test was done showing a novel missense mutation in the USP9X gene (c.1870A>T p.(Met624Leu)), confirming the diagnosis of a USP9X homozygous variant. The mother was not tested genetically to identify if the mutation was transmitted genetically or de-novo.

This is to our knowledge the first reported Lebanese patient with this mutation. The patient has been followed for the past five years by a team of therapists in a specially adapted educational program at a specialized center. By the age of 8 years, he has acquired the capacity to speak clearly in Arabic and French, as well as writing the basic numbers and letters in both languages, while remaining behind his peers educationally.

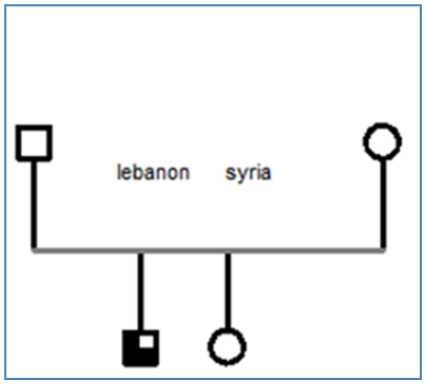

***Figure 1**: Patient Pedigree.*

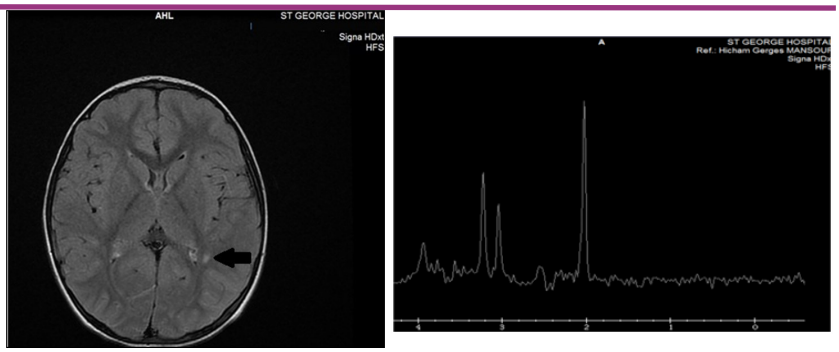

***Figure 2:** Brain MRI with spectroscopy showing a small left peri -ventricular lesion (arrow) and no anomalies on the spectroscopy Sequence.*

Discussion

Even though evolving into an urban society, the Lebanese population remains highly consanguineous (14) with a widely spread phenotypic spectrum for every mutation, leading to identification of multiple disorders by using the next generation genetic studies (15-16) like the case of this reported patient.

The full clinical spectrum of USP9X mutations is still not fully clear because of the rarity of these mutations and the lack or unavailability of WES to diagnose them. Johnson et al. (2020) tried to establish phenotypic characteristics of 12 USP9X missense mutations in male variants of the male-restricted X-linked mental retardation syndrome (5). The main features were CNS abnormalities (white matter disturbances, thin corpus callosum, widened ventricles, and cerebellar defects, macrocephaly), global delay with significant alteration of speech, language and behavior, hypotonia, joint hypermobility, dental abnormalities, asymmetric hypomastia, heart defects, urogenital abnormalities, scoliosis, postaxial polydactyly, seizures, hypotonia, recurrent respiratory tract infections, gastro-intestinal symptoms, visual system defects and dysmorphic facial features (12).

The perturbation of the cytoskeletal dynamics leading to the defective migration and axonal growth is regarded as a potential pathological responsible for the ID associated with USP9X mutations (6). In the previous reported cases the intellectual disability was described without detailing the outcomes, in our patient we have noticed an acceptable cognitive improvement with the patient learning the basics of reading and writing in two different languages, when following an adapted educational program in parallel with speech and psychomotor therapies, thus highlighting the importance of the educative integration of patients affected with USP9X mutation.

The cerebral radiological finding reported in our patient seems to be incidental and not associated with the mutation, and doesn't seem to be affecting the patient phenotypically.

In our patient, microcephaly rather than macrocephaly was noted, which can be an additional potential CNS malformation, expanding the spectrum of phenotypic characteristics of the USP9X variants. Even though microcephaly was never reported clinically in patients bearing USP9X mutations before, but Kodani et al. suggest that the USP9X gene plays a direct role in stabilizing the microcephaly STIL protein, and controlling the centriole duplication, the disruption of the centrosome biogenesis results in the abnormal neuronal development (17).

To note also that our patient did not show any marked dysmorphic features, digital or visual abnormalities or hypotonia. No serious associated congenital malformations were noted in our patient; although a recent case report showed a potential association with congenital heart disease (8). Associated congenital malformations are much more common in female heterozygous subjects (7).

Conclusion

In conclusion, this is to our knowledge the first reported case of a USP9X variant in Lebanon. The clinical characteristics matched some of the previously described features in the literature. Microcephaly was a new clinical feature not previously described and could be a new possible phenotypic characteristic of the disease. The patient showed limited cognitive and educational improvement when followed in a specialized center.

Conflict of Interest

The authors declare no conflict of interest.

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