

X-Linked Opitz Syndrome in a 19-Month-Old Male Patient

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Abstract

X-Linked Bohring Opitz Syndrome (XLOS) is a rare genetic syndrome caused by mutations in the MID1 gene and is inherited in a X-linked recessive manner. Clinical findings include facial dysmorphic features, malformations of midline structures mainly genitourinary and laryngotracheoesophageal anomalies, midline brain defects and congenital heart defects. Developmental delay and intellectual disability may also be present.

Herein, we present the case of a 19-month-old male patient diagnosed with XLOS manifesting almost all the clinical features of this condition. The patient initially presented with imperforate anus at birth and throughout the course of 19 months he was also diagnosed with hypertelorism, complete ptosis of his left palpebrae, congenital heart defects, hypospadias and vesicoureteral reflux (VUR). A clinical diagnosis of XLOS was made, which was then confirmed through molecular genetic testing. This case represents one of the very few reported cases of XLOS in Albania, with a conclusive diagnosis established by genetic testing. Its purpose is to draw attention to this seldom encountered, yet often contentious condition and emphasize the importance of adopting a multidisciplinary approach in the continuous management of the extensive clinical manifestations and complications of the condition and long-term care of these patients.

Keywords: X-Linked Opitz Syndrome; MID-1 Gene; Midline Defects; Facial Dysmorphia; Hypertelorism; Hypospadias; Imperforate Anus; Congenital Heart Defects

Introduction

Opitz G/BBB syndrome encompasses a number of phenotypically similar but genetically heterogeneous congenital malformation disorders, with two different modes of inheritance: one that is X-linked (XLOS or Opitz G/BBB syndrome type I) and one that is autosomal dominant (Opitz G/BBB syndrome type II) [1]. The first clinical reports made by Opitz et al. in 1969, classified the G syndrome and the BBB syndrome into two different entities [2]. The G and BBB represent the initials of the last names of the families where these clinical manifestations were firstly observed, while Opitz is the last name of the doctor who described the clinical manifestations for the first time [1]. Later reports of individuals of the same family, manifesting both the characteristics of the G and BBB syndromes, brought to the conclusion that they were part of the same disorder [1].

XLOS (OMIM 30000) is a rare, congenital malformation disorder affecting the embryological development of midline structures with an estimated prevalence of 1:50,000 to 1:100,000 males [3].

It is caused by loss-of-function mutations in the MID1 gene that encodes the Midline 1 protein, which seems to play an important role in the normal development of the midline structures affected in XLOS [4,5]. It has an X-linked recessive inheritance pattern, with males being predominantly affected. Heterozygous females are generally silent carriers with no clinical manifestations other than hypertelorism and have a 25% chance of having an affected son or a carrier daughter [3]. Wide phenotypic variability is encountered even within families [3].

Based on the frequency of their presentation, clinical manifestations of the syndrome are classified into two categories: major findings and minor ones. Major manifestations are present in more than 50% of patients and include facial dysmorphic anomalies [4,6,7] (hypertelorism, prominent forehead, widow's peak, broad nasal bridge, anteverted nares), genitourinary abnormalities [4,8] (hypospadias, cryptorchidism, and hypoplastic/bifid scrotum), and laryngotracheoesophageal defects [9].

Minor manifestations are present in less than 50% of the affected individuals and include: cleft lip and/or palate, impairment in normal neurological development, intellectual disability, ocular manifestations which can be congenital cataracts and optic nerve demyelination, and malformations affecting other organ systems such as congenital heart defects (ventricular septal defect, atrial septal defect, coarctation of the aorta, persistent left superior vena cava, patent ductus arteriosus, patent foramen ovale) [2,4] midline brain defects (Dandy-Walker malformation and agenesis or hypoplasia of the corpus callosum and/or cerebellar vermis), and imperforate or ectopic anus [4,6,9,10].

In clinical practice, diagnosis is suspected based on the clinical findings and is ultimately confirmed by molecular genetic testing, either gene-targeted testing or comprehensive genomic testing [3]. Differential diagnosis must exclude Optix G/BBB syndrome type II (with an autosomal dominant mode of inheritance and a mutation affecting the SPECC1L gene in chromosome 11), FG syndrome (with an X-linked mode of inheritance but affecting different sets of genes and including signs of congenital hypotonia and a characteristic personality; FG stands for the last name initials of the first family with this diagnosis), craniofrontonasal dysplasia and Moat Wilson syndrome [3].

The management of XLOS requires the efforts of a multidisciplinary team of physicians working in tandem to provide the appropriate care of the numerous congenital defects that may be present [3]. Frequent neurological assessment, early intervention and speech therapy are crucial to ensure patients achieve the developmental milestones and help with intellectual disabilities when present.

Case Presentation

We present the case of a 19-month-old male patient, the second child of non-consanguineous parents, born at term (39 weeks), via a vaginal delivery with no complications. The obstetric history was unremarkable and prenatal ultrasounds were normal, without evidence of any anomalies. At birth, the patient presented with hypertelorism, abdominal distention, hypospadias and an imperforate anus. An abdominal x-ray (Fig.1) showed multiple dilated intestinal loops, with absence of gas in the rectal region. An emergency colostomy was performed within a few hours after delivery and a subsequent posterior sagittal anorectoplasty (PSARP) three months later, providing a definitive treatment of the anal defect.

On physical examination initially a closed left palpebrae was present, with subsequent ptosis developing a few months later. A cardiac ultrasound performed shortly after birth, revealed a patent foramen ovale and a small peri membranous interventricular septal defect, with a left to right shunt and a pressure gradient between the two chambers of 70 - 80 mmHg. Aortic arch anatomy and left ventricular

function were normal, with no presence of a pericardial effusion. At 17 months he was brought to the Emergency Department with complaints of high fever (39.5°C) and crying/agitation during urination that had lasted four days. Physical examination was unremarkable and a comprehensive workup was ordered. Complete blood count (CBC) revealed leukocytosis, with white blood cells (WBC) levels of $11.7 \times 10^3 / \text{mm}^3$ ($4.0\text{-}10.0 \times 10^3 / \text{mm}^3$) and elevated levels of C-reactive protein (CRP) of 69.2 mg/L (0-5 mg/l). Urinalysis and urine culture confirmed the diagnosis of a urinary tract infection (UTI) (*E. coli* identified 10.000.000/ml). An abdominal ultrasound revealed bilateral proximal hydroureter and hydronephrosis (left pyelocaliectasis stage II, left dilated proximal ureter 9.6 mm and right pyelocaliectasis stage I, right dilated proximal ureter 7.5 mm).

Renal scintigraphy to evaluate renal function showed a normal size and position, normal perfusion and parenchymal transit of the right kidney. On time/complete excretion suggested mild obstruction, with relative function of 70.8%. Examination of the left kidney showed a normal position but smaller size, slightly decreased perfusion and parenchymal transit. Decreased excretion with delayed completion after 40 minutes suggested significant obstruction, with a relative function of 29.2%.

Cistography showed the presence of stage V vesicoureteral reflux. At first, the patient was treated with intravenous (IV) cefazolin for his UTI and then underwent a surgical correction and placement of a temporary ureterostomy bag for his vesicoureteral reflux. The post-operative abdominal ultrasound, performed after the surgical correction of the vesicoureteral reflux, showed a complete resolution of the obstruction along with the bilateral hydroureter and hydronephrosis (Figure 1-4).

Hitherto, the patient exhibits normal gross and fine motor development, normal muscle tone and reflexes. Cognitive function seems to be slightly impaired and some signs of delayed speech are evident as well. However, the patient can walk well since the age of 1 years old, he can say a few words (mom, dad), asks for food and toys, recognizes people, smiles and cries to the present situation and follows instructions accordingly.

The patient is closely cared for by a team of medical specialists including a pediatric surgeon, a neuropaediatrician, a pediatric nephrologist and cardiologist.

Abdominal X-ray



Figure 1: Multiple dilated intestinal loops, with absence of gas in the rectal region

Abdominal ultrasound post-surgery.



Figure 2: L. Right kidney is with normal parenchima, normal calyces and dimensions normal positions and dimensions .



Figure 3: Liver is with normal echostructure.



Figure 4: Left kidney and spleen are with normal echostructure normal positions and dimensions.



Figure 5: Urinary bladder presents with normal walls and clean contentence.

In the post-operative abdominal ultrasound, complete resolution of the previous obstruction is evident. Both liver and spleen have a normal echostructure and dimensions. Both kidneys present with normal parenchima, normal calyces, normal positions and normal dimensions. Urinary bladder presents with normal wall and clean contentence.

Diagnosis of X-linked Bohring Opitz Syndrome.

A peripheral blood sample was collected for DNA extraction. Whole genome microarray CGH analysis was performed in order to investigate the presence of copy number aberrations (genomic imbalances, deletions and/ or duplications) and to determine their possible association with pathological phenotypes.

Results

This male patient harbors a pathogenic hemizygous microdeletion in the X chromosome (Xp22.2) encompassing the entire MID-1 gene. Mutations and hemizygous deletions of the MID1 gene have been previously reported in literature and international databases in male patients, and have been associated with the genetic disorder Opitz GBBB syndrome type I inherited and expressed as an X-linked recessive disease. As the microdeletion in this male child was likely inherited from a carrier mother, genetic testing of the mother for the presence of the microdeletion is highly recommended prior to future pregnancies in order to determine the recurrence risk (50% for similarly affected males).

Discussion

XLOS is caused by mutations in the MID1 gene [2]. This gene is located in the short arm (p) of the X chromosome at position 22.2, Xp22.2. The MID1 gene is a part of the tripartite motif (TRIM) family, whose products are involved in many cellular activities, particularly in recycling unwanted proteins [9]. The MID1 gene codes for a protein known as the E3 ubiquitin-protein ligase or Midline 1 which is a part of a group of proteins called RING finger proteins [5,12,13]. Midline 1 is characterized by an N-terminal and a C-terminal where coincidentally most XLOS mutations are found [5,13,14].

Studies show that the MID1 gene is expressed in almost all embryonic tissue, with the highest levels found in undifferentiated cells of the central nervous system, developing branchial arches, and the gastrointestinal and urogenital system [11].

MID1 gene mutations in the interventricular septum correlate with congenital heart defects, and mutations in the cerebellar bud correlate with cerebellar hypoplasia or agenesis. This expression pattern corresponds with the organ involvement present in Opitz syndrome [9].

The Midline 1 protein is associated with microtubules [15] (structures that form the cytoskeleton of cells) through phosphorylation and dephosphorylation induced by MAP kinase and protein phosphatase PP2A, respectively. This role seems to be important in the normal development of the midline structures that are affected in XLOS [5,16]. The Midline 1 protein is thought to play another important role in the targeting and future degradation of certain proteins (PP2A, IGTA4 and STK36) [17-19]. The mechanism proposed involves the polyubiquitination of alpha4, a regulatory subunit of protein phosphatase 2A (PP2A), that ultimately results in the recycling of PP2A [17]. Studies suggest that mutations involving the MID1 gene are loss-of-function mutations [4,5] resulting in a compromised functionality of the Midline 1 protein with a reduced binding affinity to the microtubules and an inability to properly regulate the turnover of PP2Ac. This causes the accumulation of clumps of the catalytic units of PP2Ac that ultimately cause hypo-phosphorylation of MAPs, disrupting the normal dynamics of the microtubules and the cytoskeleton. It is postulated this may possibly interfere with key cellular functions during the normal embryological development of the structures commonly affected in XLOS [13]. Data from these studies suggests this pathological mechanism is consistent with the OS phenotype [17].

Conclusion

In conclusion, taking in consideration current literature and medical databases the pathogenic hemizygous microdeletion in the X chromosome (Xp22.2) encompassing the entire MID-1 gene found in our patient, was consistent with X-linked Opitz G/BBB Syndrome (type I). In routine clinical practice, clinical findings suggestive of XLOS warrant a comprehensive evaluation of routinely affected systems and molecular genetic testing to reach a conclusive diagnosis.

Through this case report, we aim to bring attention to this disorder that is sporadically encountered in clinical practice and highlight the importance of adopting a multidisciplinary approach in the long-term management of these patients. A team of surgeons, neuropediatricians, early intervention specialists and speech therapists is essential in treating serious, life-threatening congenital defects, preventing secondary complications, improving cognitive function, achieving speech and developmental milestones and in time improving the patient's quality of life.

Conflicts of Interest

We declare that there is no conflict of interest or financial interest linked to this article.

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