A Novel ASXL1 Variant in a Case with Bohring-Opitz Syndrome

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Abstract

We report a case of a child born with features consistent with Bohring-Opitz syndrome, an extremely rare genetic disorder, confirmed by genetic analysis. As with other previously documented cases, the patient ultimately required tracheostomy and percutaneous endoscopic gastrostomy for support. Whole exome sequencing was performed on himself and his parents; a novel de novo variant, NM_015338.6:c.1180dup (p.R394Pfs*16), in the Additional Sex Combs-Like (*ASXL1*) gene was identified in the patient.

Introduction

Bohring-Opitz syndrome (BOS) is an extremely rare and severe genetic disorder. Up until recently, only roughly 20 cases have been genetically confirmed worldwide.[1] Reported cases had several clinical features in common; these included a prominent metopic suture, hypertelorism, exophthalmos, cleft lip and palate, limb anomalies, difficulty feeding, and severe developmental delays. In almost 50% of cases meeting the clinical criteria of this syndrome, de novo pathogenic variants have been detected in the Additional Sex Combs-Like (*ASXL1*) gene.[2] The *ASXL1* gene encodes a protein belonging to the polycomb group and trithorax complexes family, suggesting that it plays a role in overall gene silencing and transcription regulation.[3] Whole Exome Sequencing (WES) has proven invaluable in identifying de novo germline pathogenic variants as the underlying cause of rare diseases.[4] We present a case of BOS, confirmed through the detection of a novel frameshift variant in the ASXL1 gene using WES. This discovery not only contributes to the understanding of BOS but also highlights the critical role of genetic analysis in diagnosing and managing this exceptionally rare genetic disorder.

Case

Proband is a seven-week-old boy, who was born via induced vaginal delivery at 37 weeks and 3 days of gestation due to severe fetal growth retardation. He was noted to have a low birth weight of 1.8 Kg with Apgar score of 3-7-9. He was the third child born to a 23-year-old Caucasian female; the other children were within normal limits. After delivery, the patient developed apneic events with persistent desaturations requiring continuous positive airway pressure (CPAP) placement. Chest X-ray and arterial blood gas were unremarkable. The patient was then admitted to the neonatal intensive care unit for close monitoring and further evaluation by otolaryngology with concern for obstructive sleep apnea.

On physical examination, the child was noted to have exophthalmos, nevus flammeus, posteriorly rotated ears, abundant hair on the body and forehead, prominent lips, retrognathia, elongated fingers, bilateral cryptorchidism (confirmed via scrotal ultrasound), bilateral overlapping third toes, a tuft of hair on sacral dimple, and was small for gestational age.

Figure 1: Photo depicting physical features of the patient that can coincide with BOS; exophthalmos, nevus flammeus, forehead hair, prominent lips, retrognathia.

Because of these phenotypical features, a genetics consultant recommended chromosomal microarray testing; results were within normal limits. WES of the patient and his parents showed that the patient had a de novo heterozygous frameshift variant, NM_015338.6:c.1180dup (p.R394Pfs*16), in *ASXL1*. According to the guideline for the interpretation of sequence variants,[5] this frameshift variant appeared to be classified as pathogenic due to a predicted null variant (PVS1), a variant absent in population databases (PM2), and a de novo variant (PM6), resulting in the diagnosis of BOS. Further questioning with the family revealed no obvious signs or evidence of other genetic disorders as well for at least 2 generations (Figure 2).

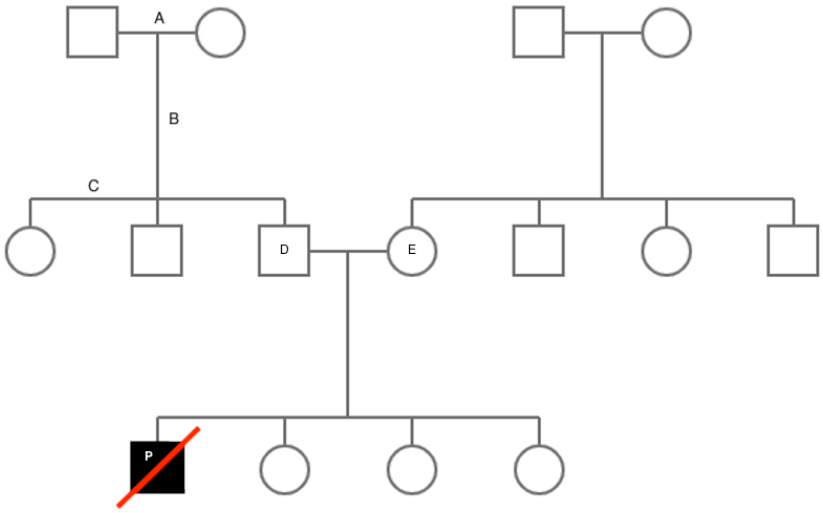

Figure 2: Figure depicting pedigree of deceased proband spanning two generations. Proband is indicated by the letter "P" (black box) with a red strike-through indicating that the patient is deceased. Line "A" indicates a relationship between 2 individuals. Line "B" indicates descent. Line "C" indicates siblingship. Male gender is represented as squares. Female gender is represented with circles. The letter "D" represents unaffected father. The letter "E" represents unaffected mother.

For further screening, an echocardiogram and renal ultrasound were performed, but the acute findings were negative. A brain MRI was unremarkable, and a spinal canal and spinal cord ultrasound was negative for spinal deformity. The patient continued to require mechanical ventilation ultimately requiring tracheostomy due to developing tracheomalacia. Because the patient had difficulty feeding, a percutaneous endoscopic gastrostomy (PEG) tube was placed to provide nutritional support (Figure 3). He was eventually discharged to a long-term care facility with a follow-up with genetics, urology, nephrology, and otolaryngology teams as well as surveillance renal imaging due to increased risk for Wilms tumor. Due to worsening oxygen requirements, he returned to the hospital shortly after. Imaging showed significant worsening of pneumonia. Tracheostomy suctioning and bag-valve oxygenation were initially attempted. Respiratory status continued to diminish and bradycardia worsened; cardiopulmonary resuscitation was initiated following an advanced cardiovascular life support protocol. Despite best efforts, the patient remained in pulseless electrical activity on the monitor and was pronounced dead approximately 25 minutes later.

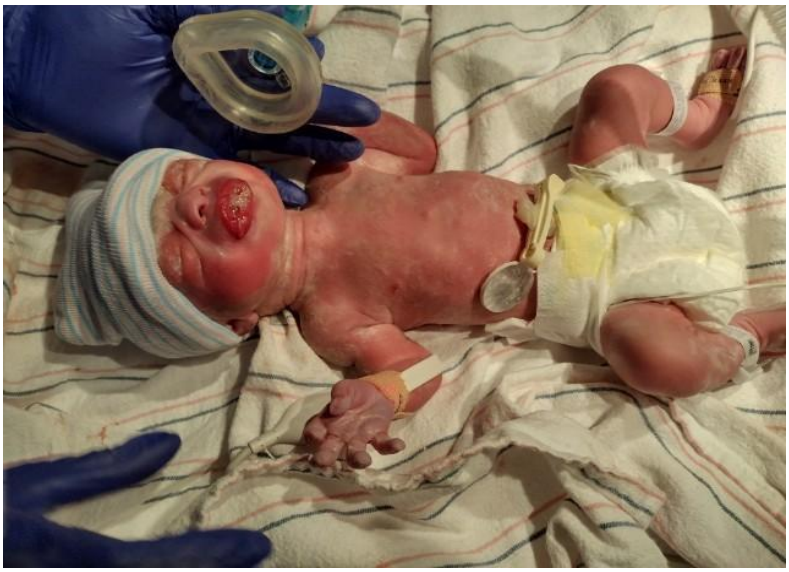

Figure 3: Figure depicting small for gestational age patient status post PEG tube placement for nutritional support.

Discussion

Clinical features of BOS are vast since the *ASXL1* gene provides instructions for proteins involved in regulating gene activity.[6] Craniofacial abnormalities can be one of the most prominent and obvious features present at birth.[7-8] They are associated with feeding difficulties; issues with latching causing poor oral intake can further exacerbate growth delays. Impedance in swallowing can also lead to complications such as gastroesophageal reflux disease and aspiration. Evaluation for possible interventions via fundoplication or gastric/gastro-duodenal tubes can also be made. These may help in decreasing reflux and aspiration risk as well as improve nutritional delivery. These interventions can help in the interim to provide the patient with adequate feeding until they are stable/strong enough for any kind of reconstructive surgery (if

warranted/indicated). As with our patient, difficulties in respiration and feeding can lead to the decision for placement of tracheostomy and PEG tube.

Intrauterine growth restriction is also an important complication affecting many of these infants and can be worsened by inadequate feeding and oxygenation. Respiratory issues can also arise secondary to the facial/pharyngeal deformities. Issues with oxygenation can lead to apneic events resulting in OSA. With this, interventions can be implicated to help temporize and circumvent specific problems. Sleep studies can be performed for further assessment for which appropriate supplemental oxygen can be indicated (i.e. CPAP).

Those with BOS often develop seizure-like activity varying from tonic-clonic to absence. Neurological work-up would be warranted pending the severity; this can include electroencephalogram monitoring and medical intervention. Brain imaging can be done to look for intracranial malformations as well. Hypoplasia or absence of the corpus callosum is one of the most common neurological defects; others, such as Dandy-Walker malformations, have also been noted.[1] Patients can be commonly started on anti-epileptic medications if there is concern for seizure-like activity. Intellectual disabilities are also associated for which there is no cure.[2] Close educational and language therapy can however help with development. Deformities to the jaw can also bring forth speech impediments and difficulties for which continued speech therapy can be of great benefit.[9]

In terms of cardiovascular complications, structural deformities such as defects and hypertrophy have been documented; these can include atrial septal defects, patent foramen ovale, dysplastic valves, etc.[10] These can lead to worsening of cardiac function. Roughly 1/3rd of reported cardiovascular deaths have been associated with apneic and bradycardic events.[1] An echocardiogram can be done following initial diagnosis to help better delineate the underlying structural pathology.[11] Ophthalmologic complications are common as well. These can range from exophthalmos, strabismus, and hypertelorism. Severe myopia has also been documented as well for which individuals would require corrective lenses at an early age.[1]

Musculoskeletal anomalies can result in the typical “BOS posture”. This presents as elbow flexion and ulnar deviation/flexion of the metacarpophalangeal joints and wrists.[12] Both hypo and hypertonia can both be observed in extremities with contractures of various joints (i.e. arms, fingers, knees, etc.). Physical deformities and muscle tone discrepancies can also be seen. These posturing complications would require routine exercises and stretching; continuous work with physical and occupational therapists would be ideal. For those who still find difficulty in ambulation and movement, support devices such as canes, special footwear, and wheelchairs may be required.

The associated genetic mutations can lead to a downstream effect of DNA methylation. The variations in hyper and hypomethylation at certain promoter sites of DNA show association with an acceleration of epigenetic age. In other words, an affected individual's genetic age may not correspond to their chronological age.[13] Hypermethylation of certain tumor suppressors is also of concern; the associated hypermethylation of the HOXA5 CpG site, for example, has been related to an increased risk of developing Wilm’s Tumor.[14] In one study, it was noted that there was roughly a 6.9% increased risk of Wilm’s Tumor with a median age of occurrence around 24 months.[15] Further imaging, such as renal ultrasounds, can be useful tools for evaluation.

Conclusion

BOS is devastating and current management is to address complications on an individual basis. As seen with our patient, pneumonia seems to be one of the most common causes of death in infants with a morbidity rate of up to 40%.[11] Other common causes include unexplained bradycardia and OSA.[16] With rapid advances in genetic sequencing, more definite etiologies for this disorder may surface which can lead to the development of better treatment options. At this time, a combination of surgical interventions, various therapy modalities, and adequate nutrition are the mainstay of treatment. Prenatal and genetic counseling are recommended to help inform families of the possible risks and outcomes of their newborns.

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