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CASE REPORT

Phenotypic expansion of Zimmermann-Laband syndrome associated with cardiac and hearing loss: a case report

Mohammed Omar Galal[1*], Mohamed Hesham Mashali[1], Ahmad Zaheer[1], Zuhair Rahbeeni[2]

ABSTRACT

Background: *ATP6V1B2* gene mutation is associated with Zimmermann-Laband syndrome 2 (ZLS2), which is a rare developmental disorder characterized by nail hypoplasia and hereditary deafness.

Case Presentation: We report a new phenotypic mutation of *ATP6V1B2* associated with ZLS 2. The patient has atresia of the left pulmonary artery (LPA) and features of hearing loss and nail hypoplasia. The other interesting part is that the child had two types of mutations inherited from father and mother. He is carrier for *GJB2* mutation (inherited from father) and diseased with *ATP6V1B2* mutation (inherited from mother).

Conclusion: The association of ZLS features with absent LPA was not reported previously in the literature. This finding will add new information to the database of previously reported *ATP6V1B2* rare mutations.

Keywords: Zimmermann-Laband syndrome, agenesis of left pulmonary artery, deafness, nail hypoplasia, inheritance.

Introduction

V-type proton Adenosinetriphosphatase subunit B, brain isoform, is an enzyme in humans encoded by the *ATP6V1B2* gene and mediates acidification of eukaryotic intracellular organelles. V-ATPase dependent organelle acidification is necessary for such intracellular processes as protein sorting, zymogen activation, receptor-mediated endocytosis, and synaptic vesicle proton gradient generation (1). Diseases associated with *ATP6V1B2* gene mutation include autosomal dominant deafness onychodystrophy (DDOD) syndrome (congenital deafness, onychodystrophy) and Zimmermann-Laband syndrome 2 (ZLS2) (2). ZLS2 [*OMIM:616455*]: is a rare developmental disorder characterized by facial dysmorphism with a bulbous nose and thick floppy ears, gingival enlargement, hypoplasia or aplasia of terminal phalanges and nails, hypertrichosis, joint hyperextensibility, and hepatosplenomegaly. Some patients manifest intellectual disability with or without epilepsy. ZLS2 inheritance is autosomal dominant (3). Three variants of ZLS have been identified based on the underlying genetic mutation. Mutations in *KCNH1* cause ZLS1, mutations in *ATP6V1B2* cause ZLS2, mutations in *KCNN3* cause ZLS3 (3). DDOD [*MIM:124480*]: is an autosomal dominant syndrome characterized mainly by congenital sensorineural hearing loss accompanied by dystrophic or absent nails. Coniform teeth, selective tooth agenesis, and hands and feet abnormalities are present in some patients (4).

Case Presentation

We are presenting a 3.5 years old male who initially was presented at the age of 4 months at the referral hospital with bronchiolitis and a family history of deafness. An initial echocardiogram raised the suspicion of atresia of the left pulmonary artery (LPA) with pulmonary hypertension. Further workup included computed tomography, which confirmed the diagnosis and the patient was referred to us for further workup and management. At the age of 3 years, his weight was 13.7 kg, and his height was 94 cm (25th centile for height and weight) (-1 STD). His respiratory

Correspondence to: Mohammed Omar Galal
*King Faisal Specialist Hospital and Research Centre, Jeddah, Saudi Arabia.
Email: ogalal@yahoo.com
Full list of author information is available at the end of the article.
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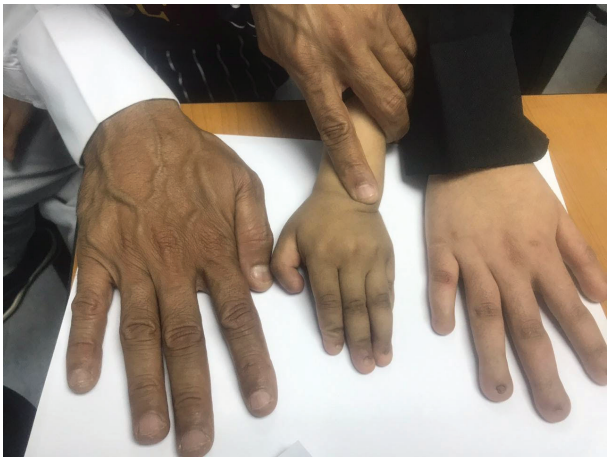

Figure 1. *Hand of father, patient, and mother in comparison. Father's hand looks normal, while the mother and patient have significant nail hypoplasia.*

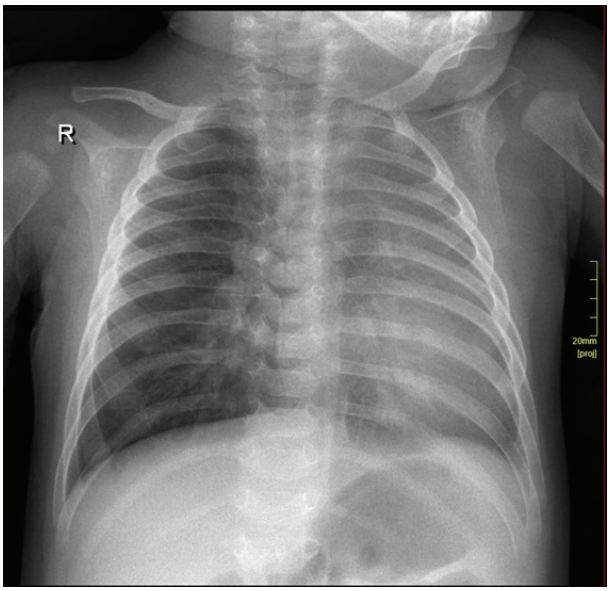

Figure 2. *Chest X-ray shows situs solitus, cardiac silhouette shifted to the left. Normal bone structure, no scoliosis, left lung not well aerated-decreased vascularity.*

rate was 22/minute with oxygen saturation of 97% on room air. On examination, he had no facial dysmorphic features. He had nail hypoplasia of all fingers (Figure 1). Chest auscultation revealed diminished air entry on the left side. He had normal first and second heart sounds with an ejection systolic murmur 2/6 over the left sternal border. Chest X-ray demonstrated cardiac silhouette to be shifted to the left with decreased vascularity. Normal bone structure, no scoliosis, left lung not well aerated (Figure 2). Initial echocardiography showed a 5 mm atrial septal defect (secundum) with the left to right shunt, mild tricuspid regurgitation with a peak systolic pressure gradient of 25 mmHg. No pulmonary valve stenosis, trivial pulmonary regurgitation. Absent versus atretic LPA, good-sized right pulmonary artery with preferential blood flow. Good biventricular systolic function. Normal arch, no coarctation. No patent ductus arteriosus. Possibly small collateral from the neck vessel and draining down

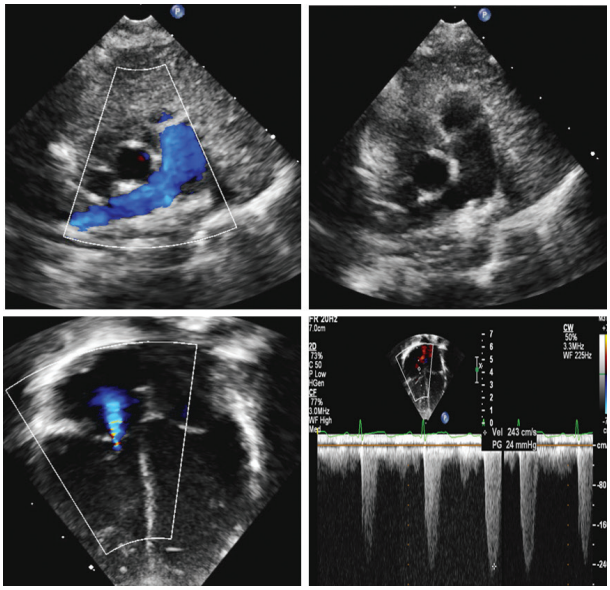

Figure 3. *Echocardiography showing mild Tricuspid regurge with Peak systolic pressure gradient (PSPG) of 25 mmHg. Absent versus atretic LPA, good size Right pulmonary artery (RPA) with preferential blood flow.*

to the left lung. Follow up echocardiogram done 1½ year later showed closed interatrial communication. Apart from that, no changes were seen compared to the first echo done (Figure 3). Cardiac catheterization done on presentation revealed right ventricle (RV) pressure equivalent to 60% of systemic pressure. Angiography in the RV in anteroposterior and lateral views showed a dilated right pulmonary artery, while the LPA was atretic (Figure 4). It was decided to treat him conservatively and consider starting him on sildenafil if the right ventricular pressure is getting higher. Hearing evaluation and tympanometry was done and showed bilateral flat type B tympanometry, flat tracing. Tone burst auditory brainstem response testing was done and showed profound hearing loss at the tested frequencies. Auditory steady-state response (ASSR) testing showed profound hearing loss bilaterally (Figure 5). Genetic consultation was done, and the patient was seen when he was 21-month-old with congenital deafness, nail hypoplasia, and congenital heart disease. Mother had the same clinical features without cardiac affection; however, the father has deafness only. No consanguinity. Family history revealed that the father had five brothers. Four were deaf and had four sisters, one of them was deaf. From the maternal side, due to communication problems, the only information available was that she was the only one affected in her family. The child has a sister who is 1 year older and has the same clinical features as him and his mother but without a cardiac problem. Whole examination sequencing (WES) found two mutations, a heterozygous *ATP6V1B2* gene variant causing Zimmermann-Laband syndrome, which fits the phenotype of the index case, and *GJB2* heterozygous mutation causing Autosomal recessive (AR) deafness which explains locus heterogeneity of deafness in the father. WES was done for the child, his daughter, in addition to father and mother. Result of child's analysis revealed double mutations: *ATP6V1B2*: NM_001693:

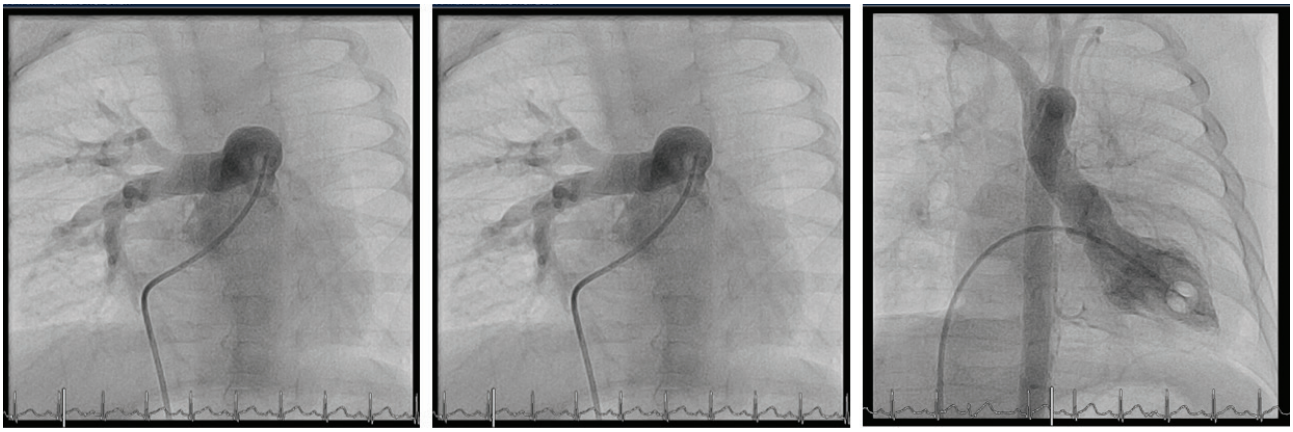

Figure 4. *Angiography in the RV in anteroposterior and lateral showed a dilated right pulmonary artery, while the LPA was atretic. Left ventricular angiography showed a normal functioning left ventricle: left aortic arch and no major aortopulmonary collaterals.*

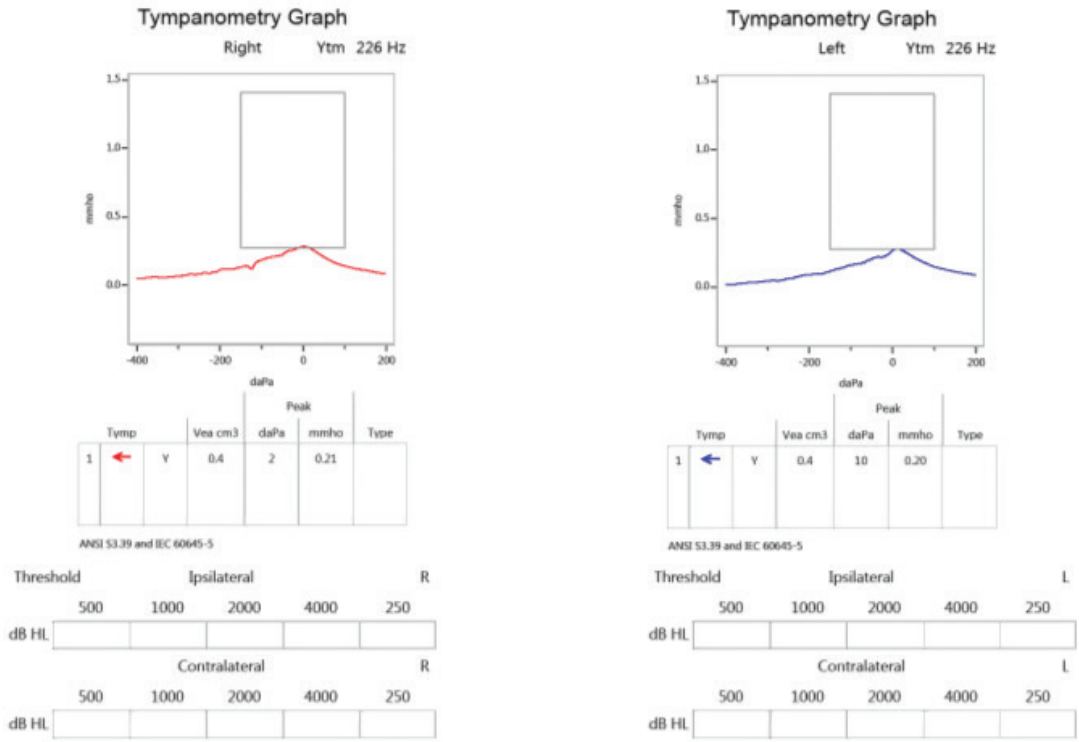

Figure 5. *Tympanometry was done and showed bilateral flat type B tympanometry, flat tracing. Tone burst auditory brain stem response testing was done and showed profound hearing loss at the tested frequencies. ASSR testing showed profound hearing loss bilaterally.*

Table 1. *Clinical characteristics of individuals with ATP6V1B2 mutations.*

	Our patient	Menendez et al. (5)	Yuan et al. (4)	Kortüm et al. (3)
No. of affected individuals	1	1	3	2
Diagnosis	ZLS	DDOD	DDOD	ZLS
Coarse facies	-	-	-	2/2
Thumbs	-	Triphalangeal		
Absent/hypoplastic fingernails	1/1	1/1	3/3	2/2
Deafness	1/1	1/1	3/3	1/2
Intellectual disability	-	-	-	2/2
Hypertrichosis	-	-	-	2/2
Pulmonary artery lesion	1/1	-	-	-

exon14:c.1516C>T:p.R506X(HETEROZYGOUS) and *GJB2*:NM_004004: exon2: c.35delG: p. G12fs (HETEROZYGOUS). The father's analysis revealed single mutation *GJB2:* NM_004004: exon2: c.35delG: p. G12fs -- (HOMOZYGOUS). The mother's and daughter's WES showed single mutation *ATP6V1B2*: NM_001693: exon14: c.1516C>T: p. R506X (HETEROZYGOUS). Therefore, the patient acquired the AD mutation from the mother and the AR mutation from the father.

Discussion

The *ATP6V1B2* gene plays a critical role in the auditory system. Mutations in this gene are a well-established cause of autosomal dominant ZSL2, as well as autosomal dominant congenital deafness with onychodystrophy (DDOD syndrome) (4). The typical symptoms of ZLS2 include significant gingival hyperplasia, hypoplasia of terminal phalanges and nails, whilst DDOD is associated with deafness, hypoplasia of nails, dystrophic nails, phalangeal hypoplasia, and other hand and feet malformations. In our case, the child presented with bronchiolitis, and by chance, he was discovered to have agenesis of the LPA. At that time, it was found that he was additionally deaf and had nail hypoplasia. Along with the genetic examination, the diagnosis of ZLS was also done, which was later confirmed by WES sequencing. Our case is peculiar as cardiac involvement in these has not been described before, and it could either be a phenotypic expansion or a mere coincidence. Our case shows hereditary deafness and nail hypoplasia. Hence our issue with two mutations, namely *ATP6V1B2* gene heterozygous causing AD disease including Zimmermann Laband syndrome, fitted to the phenotype and was inherited from the mother. It also showed *GJB2* heterozygous mutation causing AR deafness and local heterogeneity and was inherited from a father who only had deafness without nail affection. We reviewed the literature for the cases with *ATP6V1B2* mutation, and in Table 1, we compared the clinical features of these cases, including our case.

Conclusion

We describe a new phenotypic mutation of *ATP6V1B2* associated with ZLS 2. The patient has atresia of the LPA and features of hearing loss and nail hypoplasia. The cardiac evaluation may become an essential part of the assessment of ZLS. To the authors' knowledge, this association was not reported previously in the literature. The other interesting part is that the child had two types of mutations inherited from father and mother. He is a carrier for *GJB2* mutation (inherited from father) and *ATP6V1B2* mutation (inherited from mother). This novel finding will improve the diagnostic accuracy of disease, further benefiting patients with *ATP6V1B2* mutations.

List of Abbreviations

AD	Autosomal dominant
AR	Autosomal recessive
ASSR	Auditory steady state response
ATPase	Adenosinetriphosphatse
DDOD	Autosomal Dominant deafness onchodystrophy
LPA	Left pulmonary artery
PSPG	Peak systolic pressure gradient
RPA	Right pulmonary artery
RV	Right ventricle
TR	Tricuspid regurge
WES	Whole exome sequencing
ZLS	Zimmerman laband syndrome

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Declaration of conflicting interests

The authors of this report have no affiliations with or involvement in any organization or entity with any financial interest or nonfinancial interest in the subject matter or materials discussed in this manuscript.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

Consent for publication

Written informed consent was obtained from the parents .

Author details

Mohammed Omar Galal, Mohamed Hesham Mashali[1], Ahmad Zaheer[1], Zuhair Rahbeeni[2]

1. Department of Pediatrics, King Faisal Specialist Hospital and Research Centre, Jeddah, Saudi Arabia
2. Department of Medical Genetics, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia

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