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Case Report

Cochleovestibular Phenotype in a Rare Genetic MED13L Mutation

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The gene MED13 participates in transcription. The MED13L gene is a paralog of MED13 that is involved in developmental gene expression. Mutations in the gene have been shown to result in a heterogenous phenotype affecting several physiological systems. Hearing loss has been reported very rarely, and vestibular weakness has never been reported in the condition. In this report, we present a mutation of MED13L in c.1162A > T (p.Arg388Ter), where we detail and describe a cochleovestibular phenotype with objective vestibulometry for the first time. The child showed bilateral sloping sensorineural hearing loss, a bilateral vestibular weakness, and an inner ear vestibular structural abnormality on imaging. Early intervention with hearing aids and vestibular rehabilitation led to a favorable outcome in terms of speech, communication, and balance. We emphasize the importance of comprehensive audiovestibular assessment in children diagnosed with MED13L mutations for effective management of these children.

KEYWORDS: MED13L, hearing loss, vestibular function, video head impulse test, vestibular evoked myogenic potential test, pediatric audiology

INTRODUCTION

A mediator complex (MED) gene, including the MED13 complex, is involved in the majority of RNA polymerase II-mediated transcript expressions[1,2] regulating critical developmental gene expression programs.[1] A mutation results in a heterogeneous syndrome consisting of cardiovascular/developmental/metabolic/neurological/skeletal/higher center function/intellectual deficits.[3] The gene MED13L is a MED13 paralog (both genes sharing a common ancestry in the same genome as a result of duplication) with some different phenotype characteristics. This is a rare disorder affecting about 1.6 per 100 000 newborns.[4]

The MED13 gene has been associated with hearing loss/developmental coordination disorder (DCD).[2,5] However, audiovestibular involvement in its paralog MED13L is rare.[1] In this paper, we elaborate the cochleovestibular phenotype of a MED13L mutation with objective vestibular quantification for the first time.

CASE PRESENTATION

The child born of nonconsanguineous parents who failed hearing screening was diagnosed with a mild-to-moderate sensorineural hearing loss (SNHL) with normal middle ear (Figure 1). Audiovestibular management was performed by a tertiary pediatric audiovestibular medicine center in Liverpool, UK. Otoacoustic emissions were absent. They were aided early with digital amplification, with favorable outcome leading to reasonable speech development. The hearing loss did not progress on hearing monitoring.

They presented with delayed motor milestones/incoordination in motor skills/unsteadiness/postural instability with a diagnosis of DCD. Subsequent vestibular function tests indicated unsteadiness on the vestibulospinal test battery, and the video head impulse test (vHIT) showed the presence of saccades on the lateral/posterior semicircular canals with normal/reduced vestibulo-ocular reflex (VOR) gains on the lateral semicircular and posterior canals, respectively (Figure 2). Suppression Head Impulse test (SHIMP) demonstrated a 52% asymmetry (L < R, Figure 3). Cervical vestibular evoked myogenic potential (cVEMP) test revealed a 100% asymmetry

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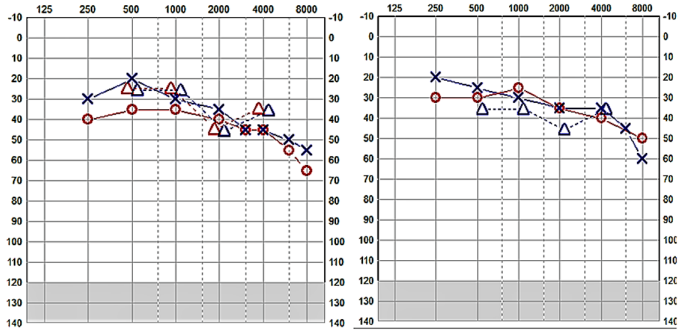

Figure 1. Pure tone audiometry at age 7 and age 16 with right sloping mild-to-moderate sensorineural hearing loss without any progression.

with an absent response on the left and a grossly reduced amplitude of 0.5 microvolts on the right (Figure 4). The vestibular tests agreed with a compensated bilateral vestibular weakness as suggested by the symptoms. Balance improved with vestibular rehabilitation.

The child underwent comprehensive etiological investigations for bilateral SNHL, including genetic testing for SNHL as recommended by the British Association of Audiovestibular Physicians (www.baap.org.uk). These were normal. A high-resolution computed tomography and magnetic resonance imaging (MRI) scan showed bilateral posterior semicircular canal dysplasia (Figure 5A-5D).

Ophtlamological/cardiological/metabolic/developmental/neurological/infective/autoimmune-inflammatory screen/CMV (cytomegalovirus) diagnostic markers/urine examination and a full family history were obtained. Their non-audiovestibular features included significant learning disability/swallowing problems/hypermetropia/astigmatism/thoracic kyphosis/spondylolisthesis/insulin resistance, which were addressed by an expert multidisciplinary team. Given the heterogeneous presentation, a genetic syndrome was actively sought. Genetic studies through the disability gene panel detected a mutation of the MED13L gene at a locus c.1162A>T (p.Arg388Ter) in chromosome 12 that unified the heterogeneous phenotype and was deemed responsible for the overall phenotype by the multidisciplinary expert team, including genetics.

Being a case report, this paper did not require formal ethical committee approval, and signed informed consents were obtained from both mother and the child.

DISCUSSION

MEDs that regulate gene expression in transcription[1] are large multiprotein complexes arising from combined 30+ subunits.[6] These genes are unique with greater flexibility and variable subunit configurations to function differently in gene/cell specific ways.[1]

MED13 is a critical component of a CDK8-kinase module reversibly binding to the mediator complex causing substantial structural shifts.[1,2] MED13L is a rare paralog of MED13. Animal models/human pedigree segregations reveal that MED13/paralogs regulate early developmental gene expression. Their mutations are associated with congenital heart defects/metabolic processing disorders/developmental delay/intellectual disability/skeletal dysmorphic features/facial dysmorphisms/muscular and neurological dysfunction including hypotonia/abnormal electroencephalogram/MRI findings, and interestingly, ataxia and coordination problems.[1-3,6-8] The child reported in this report showed most of these syndromic features.

High tone SNHL has been reported only once in 1 MED13L variant[8] and on 3 occasions in CDK8-kinase mutations.[9] The child presented with bilateral, symmetrical sloping SNHL with another MED13L variant. Available SNHL genetic tests were negative. Admittedly, these tests do not assess all known genes causing SNHL; however, the chances of 2 separate genetic mutations responsible for a hearing

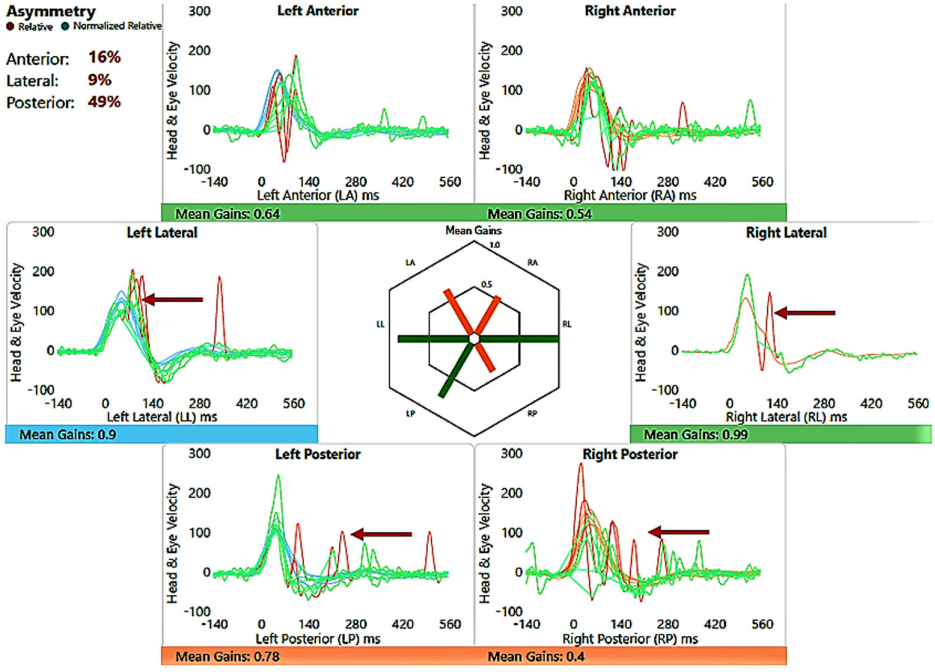

Figure 2. Video head impulse test at age 16 showing saccades in the lateral and posterior semicircular canals with normal VOR gain in the lateral but reduced VOR gain in the posterior semicircular canal (arrow). VOR -vestibulo-ocular reflex.

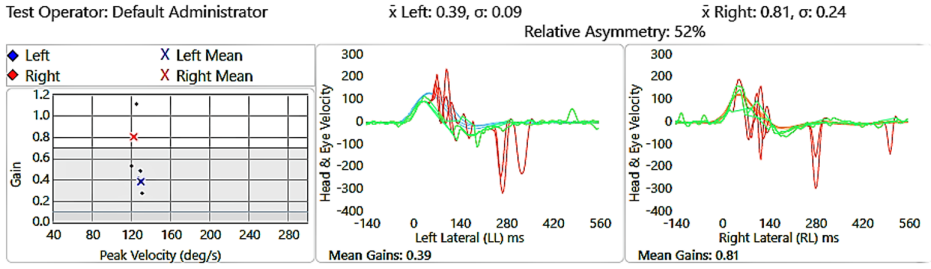

Figure 3. Suppression Head Impulse test at age 16 showing asymmetry between the right and the left side and normal peak saccadic velocities.

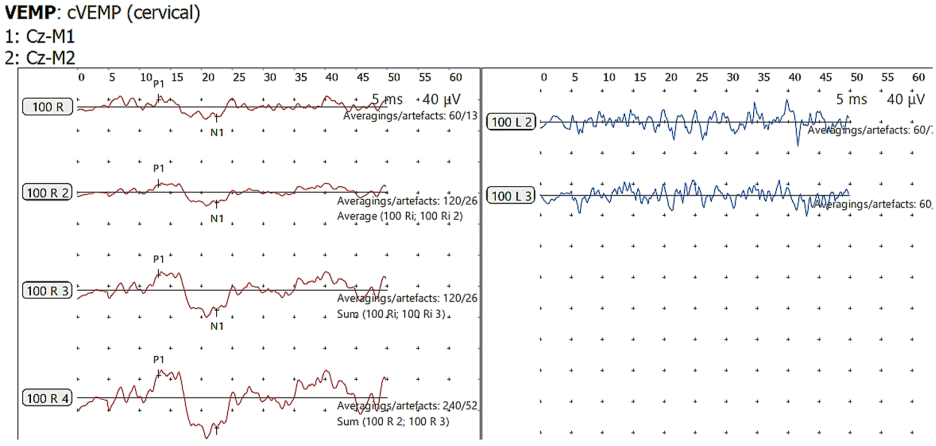

Figure 4. Cervical evoked myogenic potential test at age 16 showing absent responses on the left and a reduced amplitude on the right with 100% asymmetry when compared to the left. cVemp - cervical vestibular evoked myogenic potential.

loss is quite remote in nonconsanguineous families[10] as in this child. Furthermore, MED13 participates in neural crest development[11] that crucially participates in cochleovestibular development.[12] Thus, we believe that by eliminating other causes of SNHL (genetic/metabolic/infective/inflammatory causes), the observed association between the MED13L mutation and SNHL is highly probable.

Since the vestibular organs, just like the cochlea, have a common phylogenetic origin, it is likely that they will also be involved in the syndrome. Ataxia/coordination difficulties have been reported[7] and DCD labeled to explain this. The child reported in this paper presented with balance difficulties (incoordination/postural instability/delayed motor development/ataxia) that we believe are significantly contributed by a fundamentally weak vestibular system and not explained by a presumed DCD alone. This observation has not been reported before.

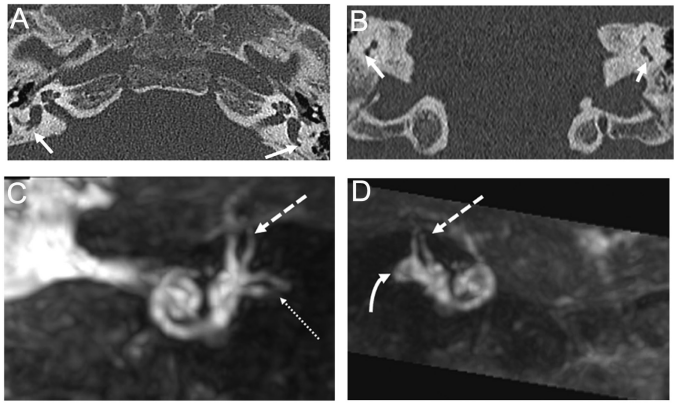

Figure 5. Axial (A) and coronal (B) computed tomography scan images of the petrous temporal bone demonstrate bilateral hypoplastic posterior semicircular canals (arrow). Selected maximum intensity projection reconstructions of the Magnetic Resonance Imaging(C and D) demonstrate a small and dysplastic left posterior semicircular canal (curved arrow). Similar appearances were noted on the right. Normal superior (dashed arrow) and lateral (dotted arrow) semicircular canals are shown.

Objective vestibular quantification should be performed in all children presenting with balance issues, especially when associated with hearing loss, being reliable indicators of vestibular function.[13] The child's high-frequency vestibular function quantified by the vHIT test was abnormal on both sides. The VOR gain was normal in the lateral semicircular canals that in the presence of saccades indicated compensation.[13] In addition, a recent test called the SHIMP in the child indicated good compensation,[13] explaining the child's good balance function.[14] The cVEMP test suggested bilateral otolith weakness, suggesting a globally weak vestibular system in both angular motion and gravitational sensor function.[13]

Bilateral semicircular canal dysplasia was observed once in MED13 mutation.[15] The child presented with bilateral posterior semicircular canal dysplasia. Causes for canal dysplasia include nonsyndromic autosomal genetic hearing losses/otic capsule dysgenesis syndr omes/trisomies/enlarged vestibular aqueduct/CHARGE (coloboma, heart defect, atresia choanae, retarded growth and development and/or central nervous system abnormalities, genital hypoplasia, and ear anomalies and/or deafness)/BOR branchiootorenal) syndromes. The child did not fit the phenotype of these syndromes and rigorous karyotyping/genetic testing/imaging did not reveal these either. These conditions were excluded in the child in question by

the responsible audiovestibular physician and by the expert multidisciplinary team. Thus, we feel given that vestibular dysplasia has been reported before in the condition, the probability of the association in this case between the genotype and the phenotype cannot be ignored.

This report is the first time that the rare MED13L genotype with a detailed cochleovestibular phenotype is presented. We emphasize that there must be a high level of suspicion to consider a unifying genetic syndrome like MED13L in a heterogeneous phenotype with hearing and balance issues. Children with such issues must undergo a full audiovestibular function test battery. Vestibular weakness accounting for balance issues in children with MED13L mutation must be factored in to avoid mislabeling them as DCD. Audiovestibular rehabilitation should be prompt, appropriate, and effective and should be part of a holistic multidisciplinary effort for a maximally favorable outcome. Genetic counseling for MED13L mutations regarding hearing/balance issues is recommended to be provided to carers and treating professionals.

CONCLUSION

MED13L is a rare genetic disorder that can affect several systems influencing development in a child. A hearing loss is rarely reported, and a vestibular dysfunction has never been reported. Our case provides a valuable insight/knowledge to the condition with an objectively quantified cochleovestibular weakness for the first time in MED13L mutation with a structural vestibular abnormality on imaging. We emphasize that MED13L syndromic presentations with hearing loss/balance issues in children are assessed for detailed cochleovestibular function for genetic counseling and early intervention for a favorable outcome in these children.

Informed Consent: Informed consents were obtained from both the mother and the child consenting for publication.

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