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BRIEF COMMUNICATION

Antenatal Presentation of *TMEM5* Gene-Associated Congenital Muscular Dystrophy Expanding the Phenotypic and Genotypic Spectrum

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Abstract We describe a clinicoautopsy phenotype of an occipital skull defect, ventriculomegaly, agenesis of corpus callosum and Dandy Walker Malformation (DWM) with a novel single base insertion in the *TMEM5* gene, known to cause Walker Warburg syndrome. The clinical features of DWM extends the phenotype, while the pathogenic variant observed expands the mutational spectrum of the syndrome. This case highlights the importance of detailed postnatal phenotyping after a pregnancy is discontinued for an antenatallly detected malformation. Fetal samples must also be preserved for genetic tests to allow an etiological diagnosis in these situations. It is important for the fetal medicine specialists to remember to test for single gene disorders, after a normal chromosomal microarray especially in case of recurrence of a disease in a family.

Keywords *TMEM5* · Walker Warburg · Dandy Walker malformation · Novel mutation

Introduction

Central nervous system (CNS) malformations are the most common cause for second trimester terminations. Congenital muscular dystrophies (CMD) are known for varied involvement of the CNS [1]. The Walker Warburg syndrome (WWS) lies at the severe end of the spectrum of the CMD. It is characterized by multiple anomalies in the eye, brain and muscle (dystrophy) and death early in infancy. Increasing number of genes causing this disorder have been identified with exome sequencing [5, 6]. Mutations and copy number variations in the *TMEM5* gene have been recently shown to cause WWS. We describe a case of WWS with a novel mutation in *TMEM5* gene.

Case report

An apparently healthy pregnant woman presented at 19 weeks with level II ultrasound showing fetal malformations. This was the second pregnancy of this non-consanguineous couple. Their first pregnancy was terminated in view of ultrasonographic evidence (at 19 weeks) of frontal bone scalloping, hypoplastic cerebellum with defective posterior fossa (lemon and banana sign present) and unilateral ventriculomegaly. In the current pregnancy, the ultrasound at 12 weeks revealed a nuchal translucency of 1.8 mm (< 90th centile), normal nasal bone at a crown lump length of 44 mm. The ultrasonographic studies at 15 weeks showed an abnormal shape of the foetal skull with frontal bone scalloping, normal sutural lines and absent cavum septum pellucidum. Both choroid plexus were anteriorly placed filling the frontal horns. Posterior fossa showed an effaced cerebellum with enlargement of the cisterna magna. Facial profile showed sloping forehead. The nasal bone was not visualised. A repeat ultrasound study done at 18 weeks revealed severe ventriculomegaly (right: 18 mm, left: 21 mm), Dandy Walker malformation (DWM) and vermian aplasia. The couple was counselled regarding the grave prognosis and the need for genetic testing. Following this, the couple opted for termination and postnatal evaluation. Fetal autopsy was performed, pictures were taken, and radiographic studies were done.

On gross examination of the fetus, facial dysmorphism was present which included large anterior fontanelle,

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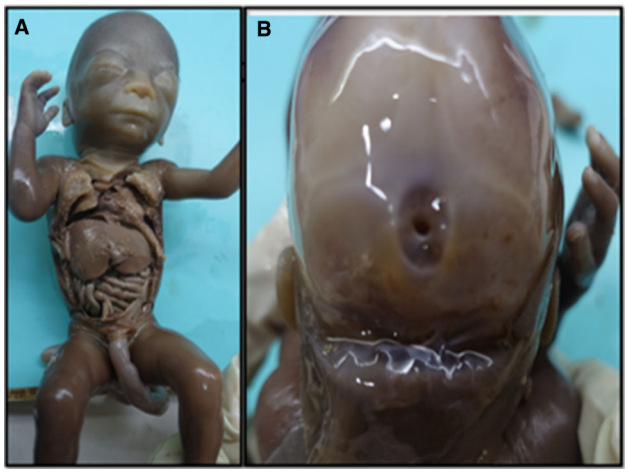

Fig. 1 **a** Autopsy image of the fetus showing facial dysmorphism (hypertelorism, long palpebral fissures, long smooth philtrum, thin upper lip and facial hirsutism) and normal position of the umbilical cord, liver, heart and the intestines. **b** Occipital bone after removal of the skin from the scalp showing a circular defect

hypertelorism, long palpebral fissures, long smooth philtrum, thin upper lip and facial hirsutism (Fig. 1a). Fetal weight was 180 g, head circumference 20 cm, CRL 18.5 cm, all corresponding to 19 weeks of gestation.

The cranial cavity was opened via an incision through the anterior fontanel extending across the sagittal suture and the bilateral lambdoid sutures. A circular skull defect was noted in the posterior occiput which was found after opening the skin (Fig. 1b). The two parietal lobes were normal in appearance. Agenesis of the posterior part of the corpus callosum was present, better appreciated on separating the two cerebral hemispheres (Fig. 2a). Axial section revealed severe ventricular dilatation bilaterally (Fig. 2b). The incision was extended posteriorly to include the cerebellum and cervical part of the spinal cord. Gross examination of the cerebellar hemispheres was normal. The evaluation of the posterior fossa revealed enlarged cisterna magna and DWM (Fig. 2c). Rest of the examination was unremarkable. Retrospective re-looking at the infantogram (skeletal survey) revelaed a defect which was visible in the occiput. Cardiac dissection revealed no abnormalities. No anomalies were noted in the eyes, viscera or gonads. A whole genomic microarray (AGILENT -180 K) was reported to be normal, no region of loss of heterozygosity was present. A TRIO whole exome sequencing was ordered in view of recurrence of fetal malformations and to establish a diagnosis.

The whole-exome analysis revealed a homozygous single base pair insertion in exon 1 of the *TMEM*5, c.116dupC (chr12:64173855_64173856insC; Depth: 127x) (p.Arg41AlafsTer24; ENST00000261234). The observed variant is not reported in the 1000 genomes; it has a minor allele frequency of 0.004% in the Exac (non-pass variant based on variant quality score recalibration). In silico prediction# of the variant is damaging by MutationTaster2. The reference codon is conserved across primates. The reference region is conserved across species.

It is likely pathogenic according to the modified ACMG criteria (PVS1 + PP3 + PP4), known to cause congenital muscular dystrophy–dystroglycanopathy with brain and eye anomalies (type A).

The variant was Sanger-validated and segregation analysis in the parents revealed the variant to be present in a heterozygous state in both, the mother and the father.

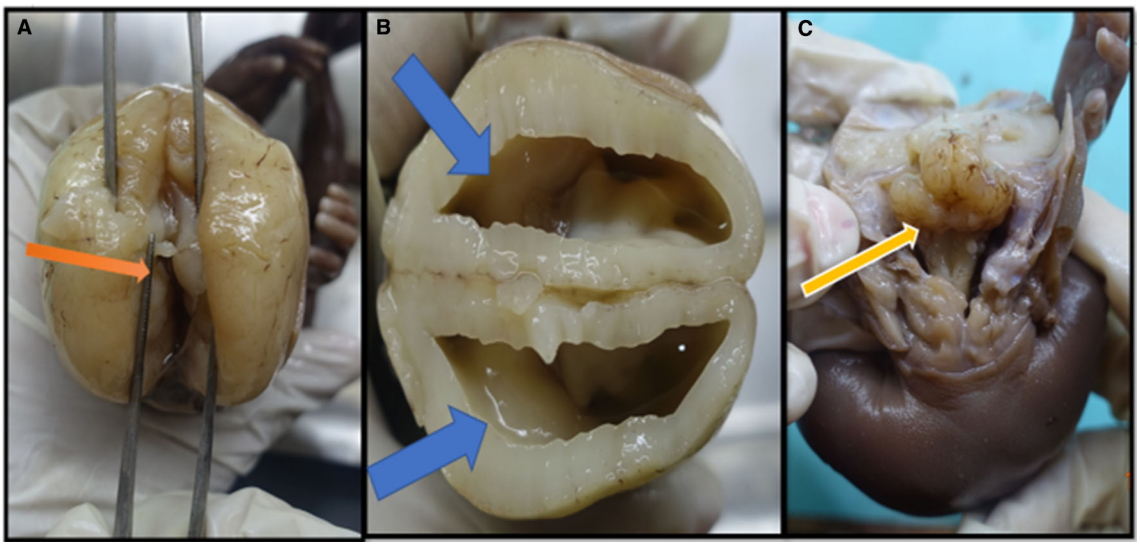

Fig. 2 **a** Brain specimen with the forceps separating the two cerebral hemispheres with agenesis of corpus callosum (dark orange arrow). **b** Axial section of the brain showing severe bilateral ventriculomegaly (blue arrows). **c** Posterior fossa of the brain with enlarged cisterna magna and Dandy Walker malformation (light orange arrow)

Discussion

CMD-α-dystroglycanopathy with brain and eye anomalies (type A) is a disorder with brain and eye malformations, profound intellectual disability, and death usually in the first years of life [1]. The affected go on to develop symptoms of muscular dystrophy, if they live long enough. The *TMEM5* gene, present on chromosome 12q, encodes a transmembrane protein believed to have glycosyltransferase function [2]. It is one of the 11 known genes to cause the Walker Warburg syndrome. This disorder represents the most severe end of the spectrum of a group of conditions resulting from defects in glycosylation of alpha-dystroglycan. Central nervous system involvement includes cobblestone lissencephaly, cortical dysplasias and occipital neural tube defects [3, 4]. Other features described are lissencephaly type I with cobblestone cortex, obstructive hydrocephalus, neuronal heterotopias, a fusion of the hemispheres, and pontocerebellar hypoplasia with fourth ventricle dilatation [5, 6].

To the best of our knowledge, only five families with foetuses affected with *TMEM5* associated CMD have been reported so far (Vuillaumier et al.).We report the sixth case worldwide and the first case from India with a fetus affected with occipital skull defect and severe ventriculomegaly, as seen in the series by Vuillaumier et al. DWM was present in the proband, which has not been described earlier, thus expanding the phenotypic spectrum of the disease.

The variant in the *TMEM5* gene, detected on WES, c.119dup (p.Arg41AlafsTer24) causes a frameshift, leading to premature truncation of the protein 24 amino acids downstream to codon 41. A duplication has not been reported in the TMEM5 gene earlier and should be considered a possible mechanism of protein disruption. This is a novel variant and thus extends the genotypic spectrum.

This disorder follows an autosomal recessive mode of inheritance, thus every offspring has a 25% risk of being affected. Options of prenatal and as well as pre-implantation genetic diagnosis should be explained to the patient.

Thus, we present a fetal presentation of *TMEM5*-associated muscle eye brain disease with an occipital neural defect and a novel finding of DWM. This case aims to alert obstetricians and foetal medicine specialists to keep in mind this disorder when dealing with a neural tube defect, especially in case of a recurrence. It is important to consider single gene disorders and to not stop testing at the more common copy number variations (chromosomal disorders).

References

1. Falsaperla R, Praticò AD, Ruggieri M, Parano E, Rizzo R, Corsello G, et al. Congenital muscular dystrophy: from muscle to brain. Ital J Pediatr. 2016;42(1):78. https://doi.org/10.1186/s13052-016-0289-9.
2. Yokoyama-Kobayashi M, Sugano S, Kato T, Kato S. A signal sequence detection system using secreted protease activity as an indicator. Gene. 1995;163(2):193–6.
3. Vuillaumier-Barrot S, Bouchet-Seraphin C, Chelbi M, Devisme L, Quentin S, Gazal S, et al. Identification of mutations in TMEM5 and ISPD as a cause of severe cobblestone lissencephaly. Am J Hum Genet. 2012;91:1135–43.
4. Jae LT, Raaben M, Riemersma M, van Beusekom E, Blomen VA, Velds A, et al. Deciphering the glycosylome of dystroglycanopathies using haploid screens for Lassa virus entry. Science. 2013;340(6131):479–83.
5. Taniguchi K, Kobayashi K, Saito K, Yamanouchi H, Ohnuma A, Hayashi YK, et al. Worldwide distribution and broader clinical spectrum of muscle–eye–brain disease. Hum Mol Genet. 2003;12:527–34.
6. Clement E, Mercuri E, Godfrey C, Smith J, Robb S, Kinali M, et al. Brain involvement in muscular dystrophies with Warburg syndrome. Am J Med Genet. 1989;32:195–210.