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CASE REPORT Open Access

Prenatal presentation of Walker–Warburg syndrome with a *POMT2* mutation: an extended fetal phenotype

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Abstract

Background: Walker–Warburg syndrome (WWS) is a rare, lethal, genetically, and clinically heterogeneous congenital muscular dystrophy resulting from defective glycosylation of *α*-dystroglycan (*α*-DG) and is associated with both cranial and ocular malformations. Prenatal detection of posterior fossa anomalies in association with hydrocephalus are nonspecific, however, an additional finding of eye anomalies are typical for WWS. The purpose of this report is to elucidate the pattern of associated malformations in a fetus with WWS born to 3rd degree consanguineously married couple. Additionally, the fetal ultrasonography revealed congenital heart disease, clenched hands, and talipes equinovarus; these findings have not been previously reported and represent an expansion of prenatal spectrum associated with WWS.

Case presentation: We report on a specific sonographic pattern of congenital anomalies including hydrocephalus, agenesis of corpus callosum, and Dandy–Walker malformation. Ocular abnormalities include microphthalmia, cataract, and an echoic structure suggestive of persistent primary vitreous. Other features include congenital heart disease, unilateral multicystic kidney, and previously unreported findings of bilateral clenched hands and talipes equinovarus. The molecular analysis detected a homozygous splicing mutation, c.924-2A>C, in the *POMT2* gene; this variant segregated with the phenotype.

Conclusion: WWS syndrome has characteristic prenatal ultrasound findings which can improve the prenatal identification of this condition and help in guiding the molecular diagnosis and counseling. The detection of bilateral clenched hands and talipes equinovarus is a novel finding that further expands the phenotypic spectrum of WWS.

Keywords: Walker–Warburg syndrome, Ocular abnormalities, Clenched hands and talipes, Cystic kidneys, *POMT2* gene

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Background

Walker–Warburg syndrome (WWS; OMIM 236 670) is considered to lie at the most severe end of the spectrum of the congenital muscular dystrophies group, with a life expectancy of less than 3 years [1, 2]. It has a worldwide distribution, the overall incidence is unknown, however, and an estimated incidence rate of 1.2 per 100,000 live births has been previously reported in northeastern Italy [3, 4]. A combination of congenital muscular dystrophy in association with ocular, cerebellar, and cerebral anomalies in addition to myopathy is considered to be pathognomonic of a spectrum of clinically and genetically heterogeneous disorders including Walker–Warburg syndrome (WWS), Fukuyama muscular dystrophy, and muscle–eye–brain disease [3, 5]. All these autosomal recessive disorders, grouped under the term "α-dystroglycanopathies," result from defective glycosylation of an α-dystroglycan (*α*-DG) that is important for the structural integrity of the muscular and neural tissue and neuronal migration [6–8].

A clinical delineation of WWS has been described by Dobyns et al. [2]; aside the severe congenital muscular dystrophy with postnatal marked hypotonia and elevated levels of creatinine kinase (CK), the brain malformation is constantly present and represented by cobblestone lissencephaly, obstructive hydrocephalus, corpus callosum agenesis, and pontocerebellar hypoplasia with fourth ventricle dilatation, moreover, kinking of the brainstem and, less commonly, Dandy–Walker malformation and occipital cephalocele [5, 9, 10]. The ocular abnormalities affect the anterior and posterior chambers with resultant retinal detachment and blindness; additionally, optic nerve hypoplasia, iris malformation, cataract, microphthalmia, and megalocornea may be found [11–13]. Less frequent clinical manifestations include facial dysmorphic features with micrognathia, and cleft lip or palate [14, 15]. The renal affection in WWS has not been described comprehensively in the literature. Recently, pathology reports identified multicystic dysplastic kidneys, renal cysts, unilateral kidney agenesis, or cystic kidneys as possible associations [16–19]. From several studies including large numbers of affected cases, it is estimated that *POMT1*, *POMT2*, *POMGNT1*, *FKTN*, *LARGE*, and *FKRP* account for approximately 42% of WWS cases. Additionally, there is no evident genotype-phenotype correlation, as most cases; the defective gene cannot be predicted from the clinical phenotype [1, 20–22].

Until recently, the prenatal diagnosis of WWS was described only during late pregnancy [23]. The technical evolution in ultrasound and molecular genetic diagnosis allowed possible early detection of this syndrome with the subsequent elucidation of its natural history [24]. Our report highlights the prenatal ultrasound findings of a fetus with WWS linked to homozygous *POMT2* gene mutations.

Case presentation

A 26-year-old G3P1A1L0 female patient was referred in her 3rd pregnancy for a prenatal genetic consultation at 20 weeks' gestation following the detection of polyhydramnios and suspected abnormal posterior fossa in a female fetus. Paternal age was 36 years, and the parents were 1st degree paternal cousins of Egyptian descent. The couple is completely healthy, their medical and family histories were unremarkable, and their chromosomal analysis was normal. The pregnancy history was unremarkable, and the patient denied any maternal illnesses or exposure to teratogens.

Obstetric history included a previous male neonatal death at the age of 10 months with hydrocephalus, eye abnormalities, hypotonia, and persistent elevated CK. This was followed by an induced termination of a female fetus at 26 weeks' gestation due to ultrasound findings of hydrocephalus and a suspected Dandy–Walker malformation, and cephalocele amniocentesis was performed, and chromosomal analysis revealed normal female karyotyping but no further genetic tests or autopsies were performed.

During the current pregnancy, the patient was examined by Voluson E8 (GE Medical Systems, Zipf, Austria) ultrasound machines with 4–8 MHz curvilinear abdominal probes and 5–9 MHz curvilinear vaginal probe. Apart from markedly increased fetal head circumference 190 mm at the 95th centile for the corresponding gestational age, fetal biometric parameters were within limits. Moreover, throughout the examination there was a reduced fetal movement with clenched hands and bilateral talipes equinovarus. Fetal neurosonogram confirmed the presence of abnormal posterior fossa consisted of cerebellar vermis aplasia with communication between the fourth ventricle and a CSF-containing space in the midline, suggestive of Dandy–Walker malformation. There was also cerebellar hypoplasia with the transcerebellar diameter measuring 15 mm just below the 5th centile for the corresponding gestational age. In addition to agenesis of corpus callosum, both lateral ventricles were grossly dilated and the third ventricle was also dilated in consistence with aqueduct stenosis or communicating hydrocephalus.

Assessment of the fetal face revealed macrocephaly, low-set ears, and micrognathia. The fetal eyes' examination revealed microphthalmia, hyperechoic, and opaque lenses suggestive of cataracts and unilateral abnormal echogenic mass with irregular borders expanding from the posterior lens surface to the posterior wall of the right eye suggestive of persistent primary vitreous. The detailed evaluation of fetal cardiac structure by fetal echocardiography demonstrated atrioventricular septal defect; additionally, the fetus had enlarged multicystic dysplastic left kidney measuring 45 mm (range; 16–30); the right kidney had a normal shape and size (Fig. 1).

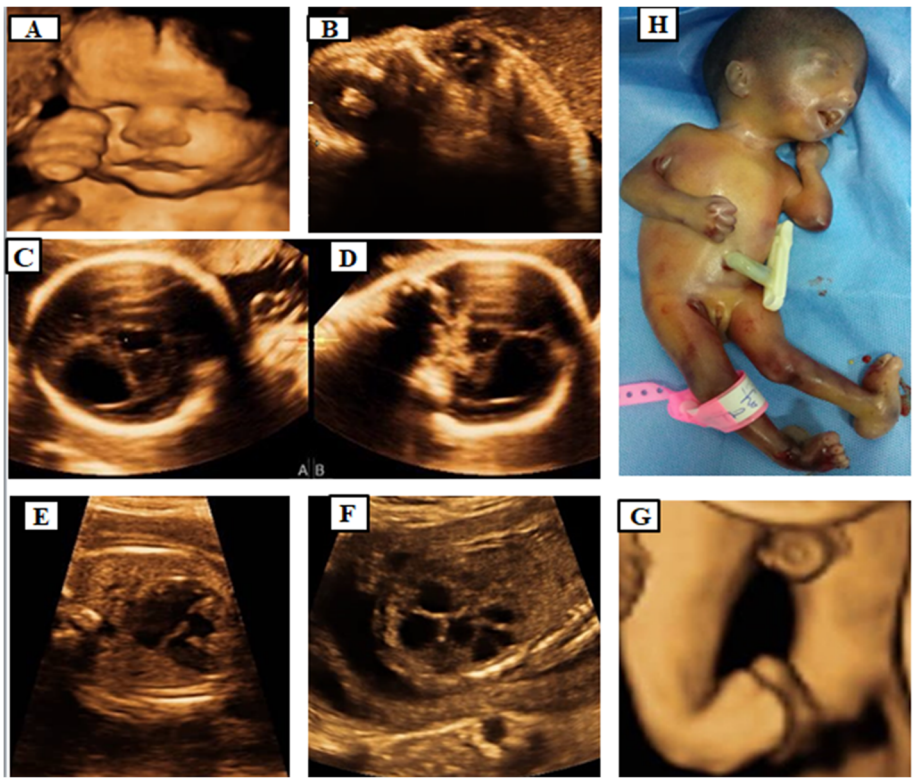

Fig. 1 Fetus at 20 weeks' gestational age with ultrasound findings of Walker Warburg syndrome. **a** Three-dimensional surface rendering of the fetal face showing bilateral microphthalmia and a clenched hand. **b** Axial US through the orbits showing asymmetric affection with the left eye demonstrating homogeneous opacity of the lens in the left eye consistent with cataract, and the right eye showing echogenic band consistent with hyperplasia of the vitreous chamber. **c** Axial trans-ventricular plane of the fetal head demonstrating agenesis of corpus callosum, dilatation of the third ventricle, and the anterior and posterior horns of the lateral ventricles. **d** Axial transcerebellar plane of the fetal head showing cerebellar hypoplasia and vermian agenesis with open fourth ventricle communicating with the cisterna magna and non-expanded posterior fossa. **e** Fetal echocardiogram demonstrating AVSD (atrial ventricular septal defect). **f** Coronal US image of multicystic dysplastic kidney (MCDK) showing enlarged kidney with several subcortical small cysts. **g** Three-dimensional surface rendering mode of lower extremities showing hyperextended knees and bilateral talipus with deformed lower limbs. **h** Postmortem image confirms the presence of the above findings

Due to the current pregnancy ultrasonographic findings, the diagnosis of WWS was suspected. The couple was advised to perform genetic testing. Amniocentesis was performed for whole exome sequencing (WES) analysis to confirm the underlying genetic cause. WES detected a homozygous pathogenic variant, c.924-2A>C, in the *POMT2* gene; that was validated by Sanger sequencing (Fig. 2). The couple was informed with the poor prognosis of the condition that was confirmed by molecular testing; subsequently, they opted to terminate the pregnancy at 24 weeks' gestation and autopsy was declined.

The fetal weight was 645 g; head circumference and CRL were 25 cm and 21.5 cm, respectively. All these measurements were corresponding to 24–25 weeks of gestation. Physical examination showed a dysmorphic infant with macrocephaly, bilateral microphthalmia, bilateral cataracts, low-set ears, and micrognathia.

Discussion

The prenatal phenotype of WWS has not been fully delineated, and a small number of cases of prenatal diagnosis have been reported. Challenges in the prenatal detection of this syndrome have been recently highlighted in the literature [16, 23, 25–30]. The characteristic sonographic features, including hydrocephalus, ocular, cerebellar, and in some cases, meningocele, are considered non-specific, and therefore, a more definitive diagnosis could have been achieved only in the presence of family history [16, 23, 25–30]. This was demonstrated in a recent cohort of 65 cases including both fetuses and neonates, in which the diagnosis of index cases was achieved only after neuropathological evaluation [31, 32]. Another major difficulty is that pathognomonic signs of WWS including cobblestone lissencephaly and the double kink of the mesencephalic-pontine junction cannot be confirmed until the 3rd trimester, even with MRI or transvaginal ultrasonography [23, 30, 32]. A previous case report in 2005 detected lateral ventricles dilatation at 14 weeks of gestation, while hydrocephalus and the cobblestone lissencephaly were only evident at 30 weeks [25].

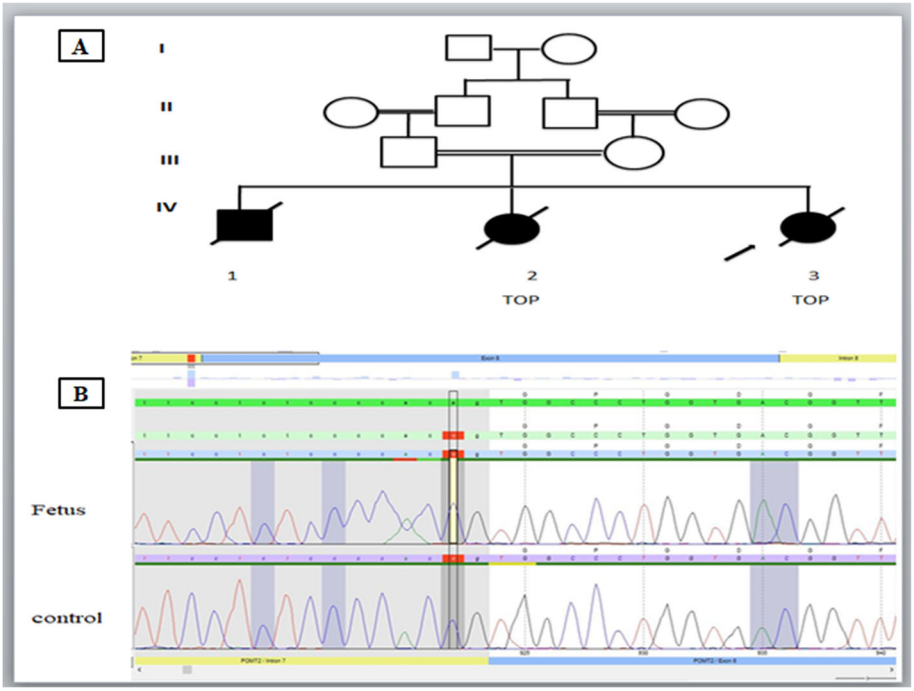

Fig. 2 POMT2 mutations and the pedigree in the fetus with Walker–Warburg syndrome. **a** Pedigree of the family showing the previous 2 affected siblings with arrow indicative of our index case. **b** Portion of the sequencing chromatogram showing the *POMT2* pathogenic variant identified in our fetus; the *POMT2* variant c.924-2A>C is predicted to disrupt the highly conserved acceptor splice site

The fetus we are reporting here presented with a diverse spectrum of manifestations with a suspected diagnosis of WWS. We managed to genetically confirm the diagnosis where WES identified a highly conserved splice site mutation in the *POMT2* gene.

The triad of hydrocephalus, posterior fossa, and ocular abnormalities is considered a common feature for three closely related disorders: WWS, muscle–eye–brain (MEB) disease, and Fukuyama-type congenital muscular dystrophy (FCMD) [26, 32, 33]. As a result of the severe fetal phenotype in this report and the lethal course of the disease in this family, we present our fetus to have WWS rather than the less severe forms, which has a longer survival [32, 33]. The characteristic cerebral and cerebellar malformations in WWS enabled its differentiation from other differential diagnoses including syndromes with lissencephaly as Miller–Dieker syndrome, Lowe Syndrome which is associated with bilateral cataract and cerebral anomalies and seen almost exclusively in male fetuses, X-linked lissencephaly with agenesis of the corpus callosum, and Norman–Roberts syndrome [26, 34, 35].

Congenital syndromic hydrocephalus is a common feature in various genetic disorders with different etiopathological mechanisms [36]. It has been shown that the defective glycosylation of α-dystroglycan in WWS results in defective neuronal migration with subsequent severe cortical malformations and neuronal ectopia causing thickening in the leptomeninges. Secondary hydrocephalus results from the obliteration of the subarachnoid space caused by the irregular meningeal thickening [8, 29]. In the present report, we demonstrated that anomalies of the posterior fossa appear before lateral ventricular dilation progressing to hydrocephalus which is considered a secondary process. The association between *POMT2* mutations and cerebral anomalies not considered as constant features of WWS such as Dandy–Walker malformation, hypoplastic cerebellar vermis, and corpus callosum abnormalities has received little attention in prior prenatal studies [16, 23, 25–30]. Therefore, our findings expand the prenatal phenotypic spectrum of the disease.

The fetal orbits can be extensively evaluated during the 2nd trimester [37, 38]. A heterogeneous group of ocular abnormalities has been reported prenatally in WWS cases including orbital asymmetry, microphthalmia, persistent fetal vasculature, and cataract [39]. These ocular ultrasound findings have been detected at a relatively advanced stage of gestation preventing early intervention and counseling [23]. The ocular anomalies in the current case present at a relatively earlier gestational age of 20 weeks' gestation with a smaller orbit, cataract; additionally, we observed a hyperechogenic cord between the lens and the retina suggesting a hyperplastic primary vitreous. The prenatal diagnosis of persistent

hyperplastic primary vitreous (PHPV), an abnormality resulting from incomplete embryonic primary vitreous regression, is extremely rare [40]. Similarly, as in our case, approximately 90% of cases of WWS, their ocular affections are asymmetrical [28].

Another striking finding in the fetus presented was the detection of a unilateral enlarged multicystic dysplastic kidney. This finding can be explained by the defective glycosylation occurring in the renal parenchyma, as the *POMT2* gene is also expressed in the kidneys. The prenatal presentation of cystic kidneys has been described earlier in the literature in association with glycosylation defects [16, 41, 42]. Interestingly, although cystic renal involvement has been reported in the context of many other well-defined syndromes, it has been described in association with *POMT2* mutation only in one case [16]. Other reports did not include cystic dysplastic kidneys in the renal phenotype of *POMT2*-associated disorders [21, 22]. We here add the association of renal cystic disease to expand the spectrum of *POMT2*-associated WWS associated manifestations. Additionally, the uniqueness of the present case also lies in unilateral renal involvement.

Interestingly, in the current report, we detected both congenital heart disease and congenital contractures in the form of bilateral clenched hands and talipes. These features were not previously detected prenatally in fetuses with WWS and expand the phenotypic spectrum of this disorder.

The *POMT2* variant c.924-2A>C identified in the present case is predicted to disrupt the highly conserved acceptor splice site. This variant has previously been described as disease-causing for Walker–Warburg syndrome by vanReeuwijk et al. [3], Bouchet et al. [43], Manzini et al. [44], and Abumansour et al. [29]. Although no clear-cut genotype-phenotype correlations were observed, however, it has been shown that homozygosity for the c.924-2A>C mutation resulting in severe disruption of the gene is associated with a consistently severe WWS phenotype [29].

Conclusion

In conclusion, this report expands the current prenatal phenotypic spectrum of *POMT2* associated with WWS. Moreover, our case is unique as it delineates relatively early changes in the eyes, the brain, and kidneys, therefore shedding some light on the time sequence of the emergence of the malformations and adding previously described features of clenched hands and talipes equinovarus to this lethal fetal syndrome. Finally, we highlight the evolving power of prenatal imaging by high-resolution ultrasound that improved the early characterization of fetal structural malformations. This in combination with systematic genomic studies might provide new insight into the distinguishing function of several genes acting during fetal life. Further, it permits obtaining a molecular diagnosis prenatally that can be used to confirm uncertain diagnoses and inform reproductive choices.

Abbreviations

WWS: Walker–Warburg syndrome; α-DG: α-Dystroglycan; CK: Creatinine kinase; WES: Whole exome sequencing; MEB: Muscle–eye–brain disease; FCMD: Fukuyama-type congenital muscular dystrophy; PHPV: Persistent hyperplastic primary vitreous

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Authors' contributions

SH designed the study; collected, assembled, and interpreted the data; and wrote the manuscript. HH helped with the laboratory work and the genetic counseling. AE provided key information and helped revise the manuscript. MYI revised the manuscript and consulted the patient. All authors have read and approved the manuscript and ensure that this is the case.

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Availability of data and materials

The data supporting the findings of this study are available with the corresponding author upon request.

Ethics approval and consent to participate

This research was reviewed and approved by the Medical Research Ethics Committee of the National Research Centre according to "World Medical Association Declaration of Helsinki," and written informed consent was obtained from the parents.

An informed consent to participate in the study was obtained from the parents of the patient, and a statement for this is included in the manuscript.

Consent for publication

Written informed consent was obtained from the parents of the patient for the publication of this case report and accompanying images.

Competing interests

The authors declare no conflict of interest.

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