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Case Report

Walker-Warburg syndrome: A case report of congenital muscular dystrophy with hydrocephalus ☆

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ABSTRACT

Walker-Warburg Syndrome is a genetically heterogeneous disease with autosomal recessive inheritance characterized by brain and eye deformities, profound mental retardation, congenital muscular dystrophy, and early death. This case study demonstrates a mutation on chromosome 12q14 in the TMEM5 gene (RXYLT1; 605862), which encodes a transmembrane protein with glycosyltransferase function. We present a case of a full-term male baby delivered by Cesarean section due to macrocephaly. At birth, the newborn had hypotonia and respiratory distress, requiring mechanical ventilation. On examination the patient was found to have macrocephaly, generalized hypotonia, hyporeflexia, and retinal degeneration. Genetic testing revealed a homozygous variant in the RXYLT1 gene, consistent with the diagnosis of autosomal recessive muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies) type A10. The patient underwent a ventriculoperitoneal shunt and received supportive management. WWS is a fatal disease, and most affected children do not survive beyond the age of 3. Prenatal screening, ultrasonography and magnetic resonance imaging can aid in the detection and confirmation of abnormal brain development in WWS cases.

☆ Competing Interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Introduction

Congenital muscular dystrophy-dystroglycanopathy with brain and ocular anomalies (type A) is an autosomal recessive disorder characterized by a range of clinical features. Infants affected by this syndrome typically exhibit brain and eye deformities, developmental delays, intellectual disabilities, and congenital muscular dystrophy. Tragically, the disease often progresses rapidly, and the majority of affected individuals do not survive beyond the first few years of life [1]. The brains of individuals with this disorder display a condition called cobblestone lissencephaly. This distinct pattern is attributed to cortical malformation. Clinically, this condition is referred to as both Walker-Warburg syndrome (WWS) and muscle-eye-brain disease (MEB), representing the most severe end of a phenotypic spectrum of related disorders [1]. The underlying cause of these conditions can be attributed to defective glycosylation of a protein called alpha-dystroglycan (encoded by the DAG1 gene; 128239). This defective glycosylation process is responsible for a group of disorders known as 'dystroglycanopathies' [1].

Case presentation

We report a case of a 5-month-old boy full-term baby who was delivered by cesarean section due to macrocephaly at a Ministry of Health Hospital. After birth, the infant showed symptoms of respiratory distress and hypotonia. Initially, the infant required respiratory support through mechanical ventilation. The patient was then transferred to Al-Jadaani Hospital for further evaluation and management. On the seventh day of life, the baby was referred to Saudi German Hospital for pediatric neurology and a neurosurgeon for V-P shunt. He is the second and only living child of a first-degree couple, his elder sister died at the age of 3 months with a diagnosis of muscular dystrophy- dystoglycanopathy. The parents were consanguineous first-degree cousins. The mother is a known case of sickle cell trait. Pregnancy passed uneventfully, the mother received folic acid for 2 months of preconception and was on regular antenatal care.

Clinical examination at birth revealed a birth weight of 4 kg, macrocephaly with a head circumference of 48 cm, wide sutures, and a large anterior fontanel. The patient had moving limbs, but generalized hypotonia and hyporeflexia were present (Fig. 1). Facial examination revealed sunken eyes otherwise no abnormalities, while an ophthalmological examination revealed retinal degeneration.

The laboratory tests including biochemical studies and CBC were within the normal range. However, there was a significant elevation in the level of creatine kinase, reaching up to 8139 U/L. Echocardiography showed severe dilated cardiomyopathy with LVEF 25% and mild mitral regurgitation. Abdominal and pelvic ultrasounds did not reveal any abnormalities. Magnetic resonance imaging (MRI) demonstrated thinning of the supratentorial ventricular system, significant ventricular dilation without an underlying obstructing mass lesion (Fig. 2).

Fig. 1 – General appearance and examination: Generalized hypotonia and hyporeflexia.

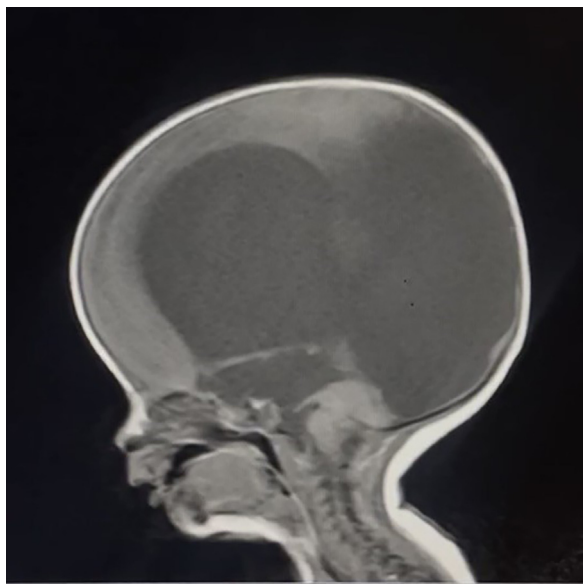

Fig. 2 – MRI brain: MRI brain showing significant ventricular dilation without an underlying obstructing mass lesion and thinning of the supratentorial ventricular system.

Genetic testing revealed a homozygous variant in the RXYLT1 gene. This finding is consistent with the genetic diagnosis of autosomal recessive muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies)

type A10. To manage the patient condition, a ventriculoperitoneal shunt was performed, and supportive measures were implemented. Unfortunately, at age of 8 months patient died after developing desaturation and bradycardia.

Discussion

Walker-Warburg Syndrome (WWS) is an autosomal recessive rare genetic disorder that is caused by mutations in different genes involved in the glycosylation processes of α-dystroglycan, resulting in abnormal neuronal migration and muscle development [2]. The incidence is estimated to be 1-2 per 100,000 live births [3]. The identified genetic mutations associated with WWS include POMT1, POMT2, FKRP, FKTN, LARGE, and POMGNT1 [3]. Genetic testing conducted on our patient revealed the presence of the recently discovered RXYLT1/TMEM5 gene, which has been associated with the development of a severe form of cobblestone lissencephaly and a clinical presentation which consistent with Walker-Warburg syndrome (WWS) [4]. The syndrome is characterized by a wide range of clinical manifestations, including structural brain abnormalities (such as lissencephaly and hydrocephalus), Other common findings are ventricular dilatation, corpus callosum hypoplasia or agenesis, occipital encephalocele, cerebellar hypoplasia, and Dandy-Walker malformation may be present [2,5]. Ocular defects (such as retinal detachment and cataracts, microphthalmia, cataracts, microcornea) and muscular dystrophy [2,5]. Muscle involvement in WWS can manifest as hypotonia as seen in this case and, generalized muscle weakness [2]. Diagnosing WWS relies on clinical criteria including (lissencephaly type II, ocular and cerebellar malformation, and CMD) [2,6].

Creatine kinase (CK) can initially reach very high levels in patients with congenital muscular dystrophy indicating widespread muscle necrosis during the prenatal period. However, as the disease progresses and muscle mass decreases, CK levels tend to become low or normal. Laboratory findings usually reveal elevated levels of creatine kinase (CK), dystrophic muscle disease/myopathy, and abnormal alpha-dystroglycan [2].

The management of WWS primarily focuses on providing supportive treatment and taking preventive measures [2,5,6]. Monitoring of feeding is important, and in certain cases, supplemental nasogastric or gastric tube feeding may be necessary. In some cases, shunting of hydrocephalus may be required, as was the case with the patient mentioned. Treatment with anticonvulsant medications may be necessary if the patient develops seizures. Although there are reports suggesting that physical therapy could potentially prevent the worsening of contractures, its effectiveness has not been definitively established [2].

During pregnancy, Walker-Warburg syndrome can be identified through specific ultrasound findings including ventriculomegaly, abnormalities in the posterior fossa, ocular abnormalities and encephalocele. However, prenatal ultrasound has limitations in detecting milder forms of lissencephaly, as it is more inclined to identify severe forms such as complete agyria. This is due to the fact that the extent of cerebral involvement can vary. In such cases, MRI can be a valuable tool for detecting and confirming abnormal cortical development, as well as less severe forms of lissencephaly. However, MRI is typically only performed if ultrasound findings yield abnormal results [2].

Conclusion

In summary, we presented a case of a 5-month-old boy with Walker-Warburg syndrome (WWS). The syndrome is characterized by a wide range of clinical manifestations, including structural brain abnormalities, ocular defects, and muscular dystrophy. Our patient exhibited clinical features of the disorder, including macrocephaly, respiratory distress, hypotonia, and retinal degeneration. Genetic testing revealed a homozygous variant in the RXYLT1 gene, consistent with the diagnosis of autosomal recessive muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies) type A10. Management done for this baby is a ventriculoperitoneal shunt and supportive management. In conclusion, Further research is needed to better understand the underlying genetic and molecular mechanisms of WWS and develop potential targeted therapies.

Patient consent

Informed consent was obtained from the patient legal guardian for the publication of this case report.

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