

## Case Report

## Walker-Warburg Syndrome: A Case Report

Magdy H Shafik<sup>1</sup>, Mohamed Taha Mohamed<sup>1</sup>, Talaat M Yousef<sup>2</sup><sup>1</sup>Department of Pediatrics, Farwaniya Hospital, Kuwait<sup>2</sup>Department of Radiology, Farwaniya hospital, Kuwait

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## ABSTRACT

Congenital muscle dystrophy (CMD) is a group of disorders characterized by significant muscle weakness early in life. Two broad groups of CMD are recognized; those with major brain anomalies and those without.

Walker-Warburg syndrome (WWS) belongs to the first group. It is a rare autosomal recessive, genetically heterogeneous disorder characterized by a triad of CMD, brain and eye anomalies. Clinical features and brain magnetic resonance imaging (MRI) findings previously

used to diagnose the syndrome remain valid.

In the presence of an affected sibling, prenatal diagnosis is possible by fetal brain MRI and/or vaginal sonography. Mapping of the WWS gene is still not possible.

We report a Kuwaiti girl with WWS. The diagnosis was based on clinical, neurophysiological and MRI findings. To the best of our knowledge, this is the first case of WWS to be reported, with some details, in the Arab population.

KEYWORDS: cobblestone cortex, congenital muscle dystrophy, type II lissencephaly

## INTRODUCTION

The muscular dysfunction in children with congenital muscle dystrophy (CMD) results from deficiency or dysplasia of a group of proteins that are vital for skeletal muscle action. Many of these proteins play an important role during brain development. That is why brain anomalies occur in some groups of congenital muscle dystrophy.

Merosin (laminin 2) is an example of the skeletal muscle proteins. This, with other proteins, is likely to have a regulatory role in neuronal migration and organization of the cortex during brain development.

Deficiency or dysfunction of some of these proteins may explain the neuronal migration defects (overmigration) in the group of CMD that is associated with brain malformation<sup>[1]</sup>.

Walker-Warburg Syndrome (WWS) is the most severe form of CMD that is associated with brain and eye anomalies. The diagnostic criteria for WWS have been established by Dobyns *et al*<sup>[2]</sup> in 1989. They suggested CMD, type II lissencephaly, cerebellar malformation and ocular anomalies (mainly retinal and anterior chamber malformation) to be the principal diagnostic features of WWS.

Other brain anomalies, such as occipital encephalocele, absent corpus callosum and fusion of the hemispheres were reported in some patients with WWS. Though not constant in all patients,

these anomalies were considered in favor of the diagnosis of this syndrome and, in association with the severity of the brain malformation, are helpful in distinguishing WWS from another clinically similar disorder, that is muscle - eye - brain disease (MEB)<sup>[3]</sup>.

## CASE HISTORY

The patient was a fifteen-month-old girl, who was born at term by an elective cesarean section. She was the second child to a first cousin parents with one healthy male sibling.

Routine antenatal ultrasonographic examination at 24 weeks of gestation revealed cerebral ventriculomegaly. At birth, her weight (2.2 kg) and height (44 cm) were just below the 5<sup>th</sup> percentile for age, while the head circumference (36cm) was on the 95<sup>th</sup> percentile.

Examination revealed some dysmorphic features in the form of brachycephalic skull, depressed nasal bridge, widely spaced eyes with bilateral corneal opacities, epicanthic folds and rocker bottom feet deformity.

System review revealed a hypotonic baby with absent deep tendons reflexes, poor muscle power and weak sucking reflex. No other abnormal findings could be detected.

Bilateral glaucoma with irido-corneal adhesions (Peter's anomaly) was diagnosed upon ophthalmological evaluation.

Address correspondence to:

Dr. Magdy H. Shafik, Department of Pediatrics, Farwaniya hospital, P.O. box 43375, Hawally 32048, Kuwait. Tel: 00965-2626769, Mob: 00965-9535979, E-mail: magdyhshafik@hotmail.com



Fig. 1: Sagittal SE 440/22 image shows agyria, ventriculomegaly, thin corpus callosum, collicular fusion, pontine and cerebellar hypoplasia, and a distinctive dorsal kinking at the mesencephalic-pontine junction (a forme fruste occipital encephalocele).

- ⇨ Mesencephalic - pontine kinking
- ⇩ Thin corpus callosum
- ⇩ Collicular fusion

Routine biochemical investigations, screening for congenital infections, inborn error of metabolism and chromosomal anomalies were normal.

Cerebral computerized tomography (CT) at age of one week confirmed the antenatal ultrasonographic findings of ventriculomegaly.

Serum creatinine phosphokinase (CK) enzyme level was high (1400 U/l) at age of 10 days.

Nasogastric tube feeding was commenced in the second week of life due to poor sucking and frequent choking episodes. This is continued till date.

Brain MRI at age of three weeks showed gross ventriculomegaly, thin corpus callosum, pontine and cerebellar hypoplasia, collicular fusion, dorsal kinking of the brain stem, nearly complete agyria and irregular gray-white matter junction, a pattern characteristic of cobblestone lissencephaly.

A ventriculo-peritoneal shunt was inserted at age of one month due to progressive head enlargement.

A repeated serum CK enzyme level at five and twelve months of age revealed high levels (540 and 490 U/l respectively).

Electromyography (EMG) at age of 13 months showed a myopathic pattern

Follow up examination of the child at age of 15 months showed that she is markedly hypotonic with absent deep tendons reflexes and severely failing to thrive {Weight (5kg), Height (63 cm) and head circumference (40 cm) were all far below the 5<sup>th</sup> percentile for age}. Developmentally, she was globally delayed with very poor visual and hearing abilities.



Fig. 2a



Fig. 2b

Fig. 2 a & b: Axial (a) and coronal (b) SE 440/22 images shows vermian hypoplasia, marked ventriculomegaly and smooth brain with periventricular irregular low signal intensities representing irregular cortical projections into the underlying white matter giving an irregular gray - white matter junction

- ⇨ irregular gray - white matter junction

## DISCUSSION

WWS is a rare form of congenital muscle dystrophy (CMD) which is associated with brain malformation and eye anomalies. The first case was reported by Walker<sup>[4]</sup> in 1942 who described a case of lissencephaly (Greek, smooth brain) and eye anomalies.

Familial occurrence was first reported by Chemke *et al*<sup>[5]</sup> as he noted three out of seven siblings of 3<sup>rd</sup> cousin parents were affected.

Warburg<sup>[6]</sup> reported several patients with hydrocephalus and retinal detachment. She suggested an autosomal recessive inheritance noting the occurrence of the syndrome in a sibling of related parents<sup>[7]</sup>. Myopathy was first reported by Williams *et al*<sup>[8]</sup> as part of the syndrome.

In the past WWS was known as HARD ± E syndrome (Hydrocephalus, Agyria, Retinal Dysplasia ± Encephalocele). The condition is usually lethal

within the first few months of life. Survival beyond three years is unusual<sup>[3]</sup>.

WWS shows some similarities with two other syndromes, namely Muscle-Eye-Brain disease (MEB) and Fukuyama muscle dystrophy (FMD). In all these three syndromes there are muscle dystrophies, eye anomalies and brain malformation. WWS is the most severe form of the three syndromes in terms of brain malformation<sup>[9]</sup>.

Brain anomalies in WWS were given the term "cobblestone complex" by Cormand *et al*<sup>[3]</sup>. These anomalies include the neuropathological findings of "cobblestone cortex" with multiple coarse gyri and agyric regions<sup>[10]</sup>.

Radiologically, MRI brain shows markedly dilated lateral ventricles, irregular grey - white matter junction, absent or hypoplastic corpus callosum, flat brain stem and cerebellar hypoplasia with minimal brain convolutions resembling lissencephaly<sup>[3]</sup>. These features are typically reported in the MRI study of our patient (Fig. 1 & Fig. 2 a & b).

The term "type II lissencephaly" (with disorganized cortical layers) describes the minimal brain convolutions in WWS, and is used to characterize it from the classic 4-layered lissencephaly<sup>[2]</sup>.

Occipital encephalocele is in favour of the diagnosis of WWS<sup>[3]</sup>. This is seen in our case as a forme fruste (aborted form) with dorsal kinking of the brain stem (Fig. 1).

Ocular anomalies in WWS include microphthalmia, congenital cataract, retinal dysplasia, buphthalmus, chamber dysgenesis, corneal clouding, Peter's anomaly and congenital glaucoma (the last three findings were reported in our case).

Congenital muscle dystrophy (CMD) as part of the syndrome, has been shown in our case both clinically (hypotonia with absent deep tendon reflex) and by elevated CK on many occasions after the age of six months, with myopathic pattern of EMG.

CK level normally can be as high as 700 U/l immediately after delivery, but falls to normal range (5-130U/l) by 6-10 weeks<sup>[11]</sup>.

In patients with CMD, CK may reach thousands, early in life, reflecting wide spread muscle necrosis in the perinatal period. Later on, these patients have low or normal CK because of lack of muscle mass and limited mobility<sup>[9]</sup>.

While the molecular genetic basis of FMD and MEB disease are clearly identified, the molecular and genetic basis of WWS is still unclear<sup>[3]</sup>. Mutation in O-mannosyltransferase gene (POMT1) was found in 20% of patients with WWS phenotype studied by Beltran *et al*<sup>[12]</sup>. They explained the severe neuronal migration defect in WWS by mutation in this gene. This gene encodes synthesis of an

enzyme that catalyze the first step in synthesis of a specific glycosylated protein called  $\alpha$ -dystroglycan, which is found in brain, muscles and peripheral nerves of mammals<sup>[13]</sup>.

However, POMT1 gene mutation was not found in cases studied by Jiemenz *et al*<sup>[14]</sup> though they found almost complete absence of  $\alpha$ -dystroglycan with mild reduction in laminin- $\alpha$ 2 (merosin) in muscles of patients with WWS. They assumed that muscle degeneration in WWS is due to defective  $\alpha$ -dystroglycan / laminin  $\alpha$ 2 axis in the muscle fiber's basal lamina.

Moreover, mutation in fukutin gene (responsible for Fukuyama muscle dystrophy) has been reported by others<sup>[15,16]</sup> in patients with phenotypic features of WWS. Their results confirm that WWS is a genetically heterogenous condition.

Although the phenotypic features of the three syndromes (WWS, FCMD, and MEB) might overlap, lack of consistent ocular abnormalities in FCMD allowed a clear clinical demarcation of this syndrome. Moreover, identification of the gene responsible for FCMD on chromosome 9 (q31-q33)<sup>[17]</sup> allows this syndrome to be defined at molecular and genetic level.

The presence of severe neurological changes both clinically and in the cerebral MRI studies, as reported in our patient, plus evidence of CMD are considered enough for WWS to be clearly differentiated from MEB<sup>[3]</sup>. Moreover, the MEB gene was recently localized to chromosome 1(p32-p34)<sup>[18]</sup>, and this allows MEB and WWS to be classified as distinct disorders on both clinical and genetic grounds.

Although molecular genetic study was not possible in our case, the diagnosis was confirmed by the typical clinical picture and the MRI findings in association with evidence of CMD. This is in keeping with the diagnostic criteria of WWS in other literature<sup>[3,19]</sup>.

Lack of consistent chromosomal abnormalities in WWS makes prenatal diagnosis a difficult task. However, prenatal diagnosis can be suspected by fetal brain MRI<sup>[20]</sup> and/or transvaginal fetal neurosonography<sup>[21]</sup>. Both methods allow lissencephaly to be detected prenatally. This in association with ventriculomegaly allows easy identification of an affected fetus especially with positive family history of a similar case. Proper counseling can thus be provided for parents, taking in consideration the poor prognosis of such condition.

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