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Walker Warburg Syndrome in a 03 Days Old Male Neonate– A Case Report.

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Abstract:
*Congenital muscular dystrophies are a complex group of disorders consisting of two broad divisions, namely, laminin alpha2 chain deficient type and with hypoglycosylated alpha-dystroglycan type. Magnetic resonance imaging of the brain reveals white matter abnormalities in the former, whereas both grey and white matter abnormalities in the latter group. There can be overlap of MRI findings. Imaging (**CT** and **MRI**) along with clinical-genetic correlation are extremely useful in disease detection and differentiation from other entities in the spectrum.*

Keywords:
- *Walker-Warburg Syndrome (MeSH unique ID: D058494).*
- *Lissencephaly (MeSH unique ID: D054082).*
- *Cobblestone Lissencephaly(MeSH unique ID: D054222).*
- *Magnetic Resonance Imaging (MeSH unique ID: D008279).*
- *Dystroglycans(MeSH unique ID: D049030).*
- *Muscle Hypotonia(MeSH unique ID: D009123).*

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I. Introduction

Congenital muscular dystrophies are hereditary disorders, most of which are autosomal recessive. These disorders manifest as hypotonia since birth with delayed motor development. In decreasing order of severity, this spectrum consists of Walker Warburg syndrome, muscle eye brain disease, Fukuyama muscular dystrophy, and congenital muscular dystrophy type 1D and 1C.[1]

CASE REPORT:

A03 days old full term male neonate product of nonconsanguineous marriage presented with history of fever, weakness in upper limbs and lower limbs. There was history of delayed cry after birth. There was no history of neonatal seizures, blood transfusion or family history of epilepsy. On examination, grasp and Moro reflexes were intact. Poor rooting, weak cry and generalized hypotonia were noted in all four limbs. No signs of meningeal irritation were noted. Serum electrolytes and calciumwere within normal limits. Magnetic resonance imaging of the brain was performed which revealeddiffusely thickened smooth cerebral cortex suggestive of lissencephaly(**Figure 1**). Flattened appearance of anterior portion of pons was noted with characteristic mesencephalic pontine junction kink (**Figure 2**).Eye globe size asymmetry and cerebellar vermis hypoplasia were noted (**Figure 3**). Gross dilatation of the ventricular system suggestive of hydrocephalus was also noted (**Figure 4**). Based on the imaging findings and clinical profile of the patient, a diagnosis of Walker Warburg syndrome was given.

Figure 1

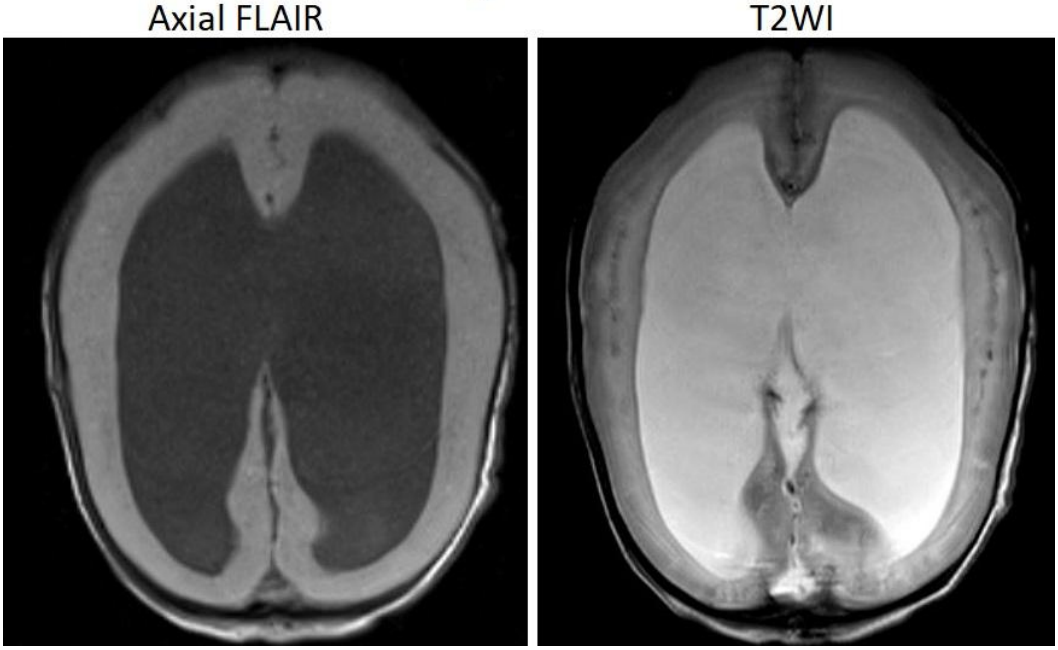

Figure 1: Axial FLAIRand T2WI showing bilateral cerebral hemispheres with diffusely thickened smooth cerebral cortex suggestive of lissencephaly.

Figure 2: Sagittal T1WI

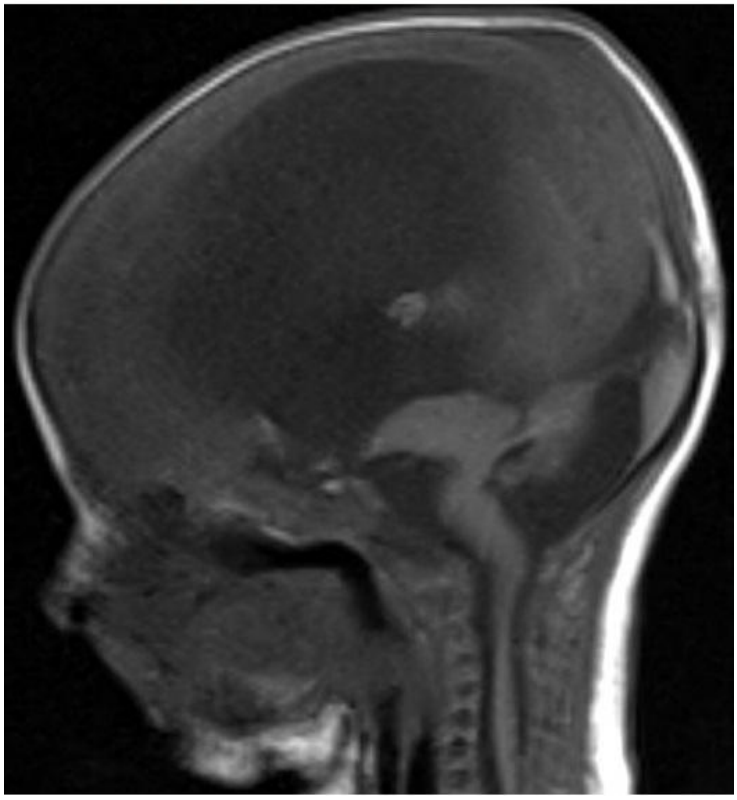

Figure 2: Sagittal T1WI showing flattened appearance of anterior portion of pons with mesencephalic pontine junction kink.

Figure 3: Axial T1WI

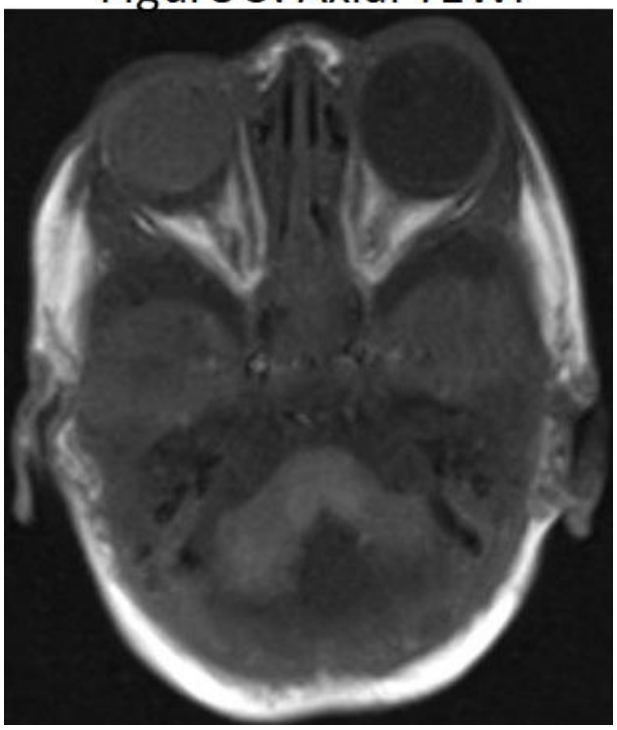

Figure 3: Axial T1WIshowing eye globe size asymmetry and cerebellar vermis hypoplasia.

Figure 4: Coronal FLAIR

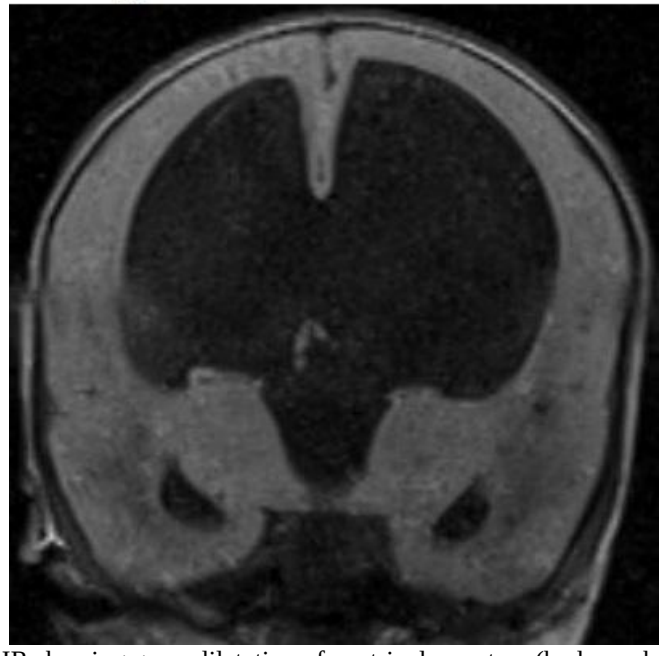

Figure 4: Coronal FLAIR showing gross dilatation of ventricular system (hydrocephalus) with lissencephaly.

II. Discussion

Walker Warburg syndrome is an autosomal recessive disorder which was first described by Walker in 1942. It affects eye, brain and muscles.[2]

Walker Warburg syndrome was earlier known as HARD±E (hydrocephalus, agyria, retinal dysplasia, ± encephalocoele) syndrome. It is an autosomal recessive disorder affecting brain and ocular development.[3]It has been demonstrated that this autosomal recessive entity is due to defective O-glycosylation of alpha-dextroglycan, which plays an important role in neuronal migration. This defect is caused by mutation of FKRP,

POMT1, POMT2 and Fukutin genes.[4] Walker Warburg syndrome is due to abnormality of chromosome 9q34.[5]

Although congenital muscular dystrophy with central nervous system abnormality was first described by Fukuyama et al.[2] Fukuyama type congenital muscular dystrophy shares multiple features with Walker Warburg syndrome and is an autosomal recessive disorder consisting of brain anomalies (like polymicrogyria) and congenital muscular dystrophy. It is the second most common childhood muscular dystrophy in Japan.[6]

In a study (63 patients) conducted by Dobyns et al, it was stated that type II lissencephaly, retinal malformations, cerebellar malformations and congenital muscular dystrophy are sufficient components to establish diagnosis of Walker Warburg syndrome. Type II lissencephaly consists of diffuse agyria, associated with ocular abnormalities, hydrocephalus and cerebellar vermian hypoplasia. However, there is absence of characteristic facial dysmorphism and microcephaly, which are seen in type I and type III.[3]

Hydrocephalus is commonly associated feature of Walker Warburg syndrome. Less commonly noted anomalies consist of congenital macrocephaly or microcephaly, cleft lip and cleft palate, posterior encephalocoele and genital abnormalities.[7]

Cerebellar malformations in Walker Warburg syndrome consist of vermian hypoplasia, afolia and hemispheric hypoplasia. Dandy Walker malformation is noted in half of the affected patients.Ocular abnormalities in Walker Warburg syndrome consist of mircophthalmia, congenital glaucoma, cataract, iridial anomalies, persistent hyperplastic primary vitreous, retinal dysplasia, coloboma, optic nerve hypoplasia and retinal detachment. Congenital muscular dystrophy is noted in all cases of Walker Warburg syndrome.[3]

Patients with Walker Warburg syndrome have hypotonia/ weakness and sometimes contractures at birth and in infancy period.Additionally, these patients have mental retardation and seizures.[1]

Computed tomography, magnetic resonance imaging and ocular ultrasonography accurately detect the associated ocular abnormalities like optic nerve hypoplasia, retinal detachment, persistent hyaloid artery and globe size asymmetry secondary to unilateral buphthalmos due to microphthalmos or congenital glaucoma.[2]

In Walker Warburg syndrome, simplified gyral pattern with thin cerebral mantle, mesencephalic-pontine junction kink and absent extra-axial spacesare detected on magnetic resonance imaging. Various associated ophthalmic abnormalities reported in Walker Warburg syndrome include Peter anomaly, retinal dysplasia, microphthalmia, persistent fetal vasculature and optic nerve coloboma.[4] Other neuroimaging findings are band heterotopia, corpus callosum dysgenesis, hypoplastic cerebral peduncles, collicular fusion, fusion of occipital poles and intra-ventricular haemorrhage.[7]

Laboratory investigation shows elevated serum creatine kinase levels and altered alpha-dextroglycan.[7]

Other dystroglycanopathies like Fukuyama congenital muscular dystrophy or muscle eye brain disease are differentiated from Walker Warburg syndrome on the basis of involvement of central nervous system, eye, motor function and intellectual disability. Walker Warburg syndrome is considered in the severe end of dystroglycanopathy spectrum with death reported in the patients before the age of 3 years.[7]

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III. Conclusion

In patients presenting with hypotonia, seizures and mental retardation in infancy and childhood period, imaging plays an essential role in narrowing down the differential possibilities from a broad spectrum to a limited number of conditions. Cases presenting with hypotonia, seizures and delayed motor development coupled with imaging features like hydrocephalus, lissencephaly, cerebellar vermis hypoplasia, microphthalmia and the characteristic mesencephalic pontine junction kink, imaging plays a crucial role in establishing the diagnosis of Walker Warburg syndrome and follow up of these patients.

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