

Walker-Warburg Syndrome

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Summary: The Walker-Warburg syndrome (WWS) is a rare autosomal recessive disorder characterized by lissencephaly, cerebellar and retinal malformations, and congenital muscular dystrophy. We report a new case of WWS identified with the aid of cranial MR and briefly review the radiologic findings of this lethal syndrome.

Index terms: Migration anomalies; Magnetic resonance, in infants and children; Brain, abnormalities and anomalies

Case Report

This full-term male infant was the product of a noncon-sanguineous union born to a 29-year-old mother. Prenatal history was positive only for the maternal use of topical minoxidil during the first trimester for focal alopecia. After vaginal delivery, Apgar scores of 7 and 9 at 1 and 5 min, respectively, were obtained.

Physical examination revealed a focal midline protuberance covered by a tuft of hair in the region of the posterior fontanelle. While grasp and Moro reflexes were intact, poor rooting and arousability, generalized hypotonia, and a weak cry were noted. Ophthalmologic examination revealed bilateral rubeosis suggesting retinal detachments and a left ocular cataract. No other abnormalities were found.

One hour postpartum, seizure activity ensued. Serum electrolytes, glucose, and ionized calcium were normal. Following resuscitation, parenteral antibiotic therapy was instituted. Blood, urine, and cerebrospinal fluid cultures yielded no bacterial growth. Toxoplasma and cytomegalovirus titers subsequently proved negative.

Cranial magnetic resonance (MR) performed on a 1.5 T unit revealed both brain and ocular abnormalities suggesting Walker-Warburg syndrome (WWS) (Figs. 1 and 2A–2C). Because of the infant's poor prognosis, further resuscitative efforts were aborted. The infant died at 5 days of age.

At autopsy, bronchopneumonia was found. Examination of the right eye revealed macrophthalmia, retinal dysplasia, and a retinal fold. Peripheral pseudorosette formation and focal alternating areas of ganglion cell and nerve fiber layer atrophy were present constituting the "leopard spot" retinopathy described in WWS. A persistent

hyaloid artery was present. Retinal dysplasia and a total retinal detachment accompanied by vitreous hemorrhage was found in the left oculus.

Gross and microscopic examination of the brain revealed agyria and cerebral cortical dysplasia (Figs. 3 and 4), periventricular heterotopias, a hypoplastic neocerebellum with cortical dysplasia, an aplastic cerebellar vermis and large posterior fossa cyst, dysgenesis of the corpus callosum, and a posterior midline craniomeningocele. The occipital cortices were fused in the midline. The colliculi were fused and enlarged. The thalami, basal ganglia, and limbic structures were poorly developed. The optic nerves, chiasm, and tracts were markedly hypoplastic. The leptomeninges appeared thickened and granular and displayed vascular proliferation (Fig. 3).

Skeletal muscle analysis demonstrated atrophy of both fiber types. No karyotypic abnormalities were identified.

Discussion

Known earlier as the HARD±E (hydrocephalus, agyria, retinal dysplasia, ±encephalocele) syndrome, the WWS is a lethal autosomal recessive disorder primarily affecting brain and ocular development (1). Because of its 25% recurrence risk, it is important to distinguish WWS from nonheritable entities such as intrauterine toxoplasma and cytomegalovirus infections, causing hydrocephalus and ocular abnormalities, and exposure to certain teratogens, such as retinoic acid derivatives, which can give rise to lissencephaly, hydrocephalus and vermian hypoplasia.

In a recent review of 63 cases, Dobyns et al (2) state that type II lissencephaly, cerebellar and retinal malformations, and congenital muscular dystrophy constitute "necessary and sufficient criteria" for the diagnosis of WWS. Type II lissencephaly is characterized by global agyria associated with hydrocephalus, ocular abnormalities, and cerebellar vermian hypoplasia, but lacks

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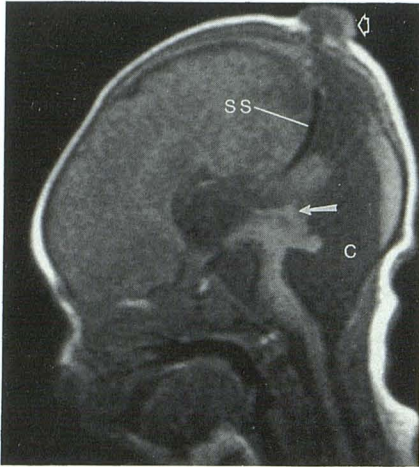


Fig. 1. Sagittal 500/20/1 (TR/TE/excitations) SE image near the midline reveals vermian aplasia and a large posterior fossa cyst (C) consistent with a Dandy-Walker malformation. Note the fused, enlarged colliculi (arrow). A posterior craniomeningocele (open arrow), upwardly displaced straight sinus (SS), and findings of callosal dysgenesis are also present. Hemorrhage layering posteriorly in the Dandy-Walker cyst is incidentally noted.

characteristic facial dysmorphisms and microcephaly seen in types I and III (3). All necessary diagnostic criteria for WWS were met by our patient.

Ventricular dilatation (secondary to faulty neuronal migration, fibroglial plugging of arachnoid granulations, or an associated Dandy Walker mal-

formation) was also present. Ventriculomegaly and anterior ocular chamber abnormalities were deemed "helpful but not necessary" by Dobyns et al (2) in making the diagnosis of WWS. Posterior encephaloceles or craniomeningoceles, seen in 25%–50% of infants with WWS, and neuronal heterotopias are associated anomalies well depicted by MR in our patient. The white matter is poorly myelinated, edematous, and sometimes cystic.

Cerebellar malformations present in WWS include variable vermian hypoplasia, as well as hemispheric hypoplasia and afolia. An associated Dandy-Walker malformation, present in our patient, is seen in 50% of affected individuals (2).

Both anterior and posterior ocular abnormalities are seen in WWS, but retinal malformations are universally present. Microphthalmia, cataracts, congenital glaucoma, iridial abnormalities, persistent hyperplastic primary vitreous, colobomas, retinal dysplasia, folds and detachment, and optic nerve hypoplasia have been demonstrated (4). Our patient demonstrated a persistent hyaloid artery and macrophthalmia in addition to a cataract, retinal dysplasia and detachment, and bilateral optic nerve hypoplasia.

Congenital muscular dystrophy (CMD) is seen in all patients with WWS (2). The "cerebro-oculo-muscular syndrome" as well as the "muscle-eye-

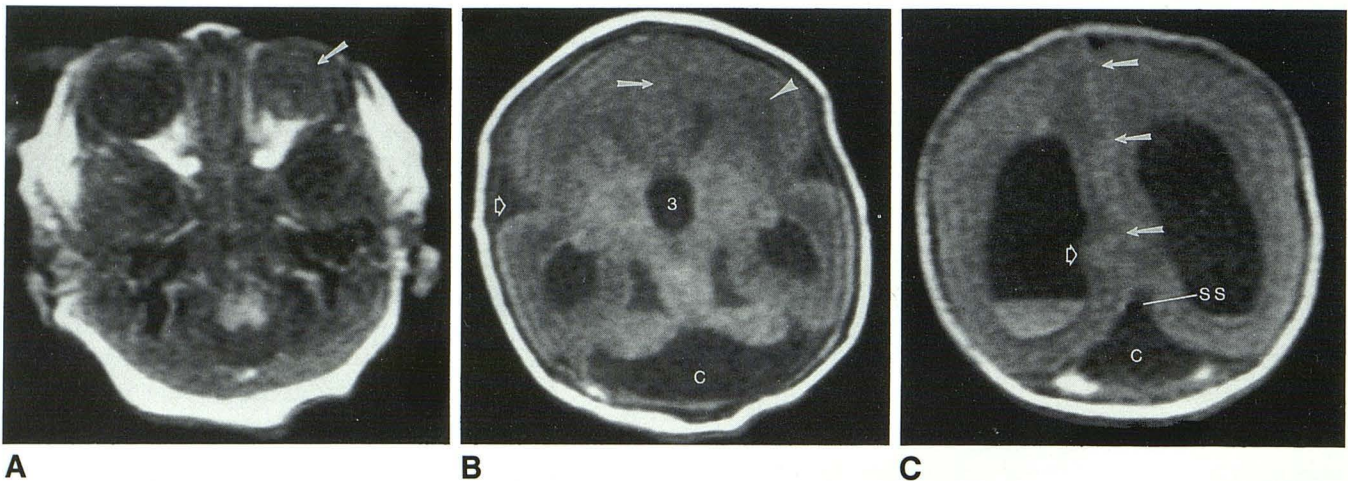


Fig. 2. Transverse 500/20 SE images.

A, At the level of the orbits, asymmetric eye size and increased signal from the left oculus (arrow), a result of retinal detachment with vitreous hemorrhage, is seen.

B, At the level of the third ventricle, a smooth cortical surface, open and shallow sylvian fissures (open arrow), a Dandy-Walker cyst (C), and enlargement of the lateral and third ventricles are demonstrated. A lack of cerebral gray-white matter interdigitation is seen (arrowhead) adjacent to a thickened cortical mantle. The anterior interhemispheric fissure is obliterated secondary to leptomeningeal thickening and proliferation (arrow).

C, Ventriculomegaly, agyria, and a heterotopia indenting the medial aspect of the right lateral ventricle (open arrow) are seen at a higher level. The interhemispheric fissure is obliterated in both its posterior and anterior extent (arrows). The straight sinus (SS) and posterior fossa cyst (C) are interposed between the posterior aspect of the occipital lobes as a result of torcular elevation. Hemorrhage layers dependently in both lateral ventricles.



Fig. 3. Specimen photograph; agyria and opercular underdevelopment are demonstrated. Thickened, granular leptomeninges contain a dense plexus of arborizing blood vessels (arrows).

brain syndrome" of Santavuori are previously described entities characterized by CMD and co-existing central nervous system (CNS) and ocular abnormalities that are probably identical to WWS (2). Fukuyama CMD is a related, but distinct, syndrome manifested by CMD and CNS anomalies. In this autosomal recessive disorder, less constant cerebellar and retinal dysplasias, and less severe gyral malformations, are present when compared with those seen in WWS (2). Genital anomalies, cleft lip, and cleft palate are anomalies

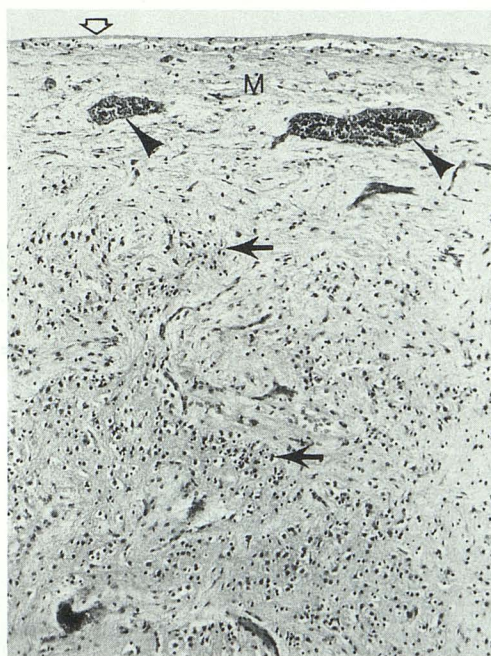


Fig. 4. Photomicrograph of the cerebral cortex illustrates confluent glial-neuronal heterotopias (arrows). Note the relatively acellular molecular zone (M) subjacent to the pial surface (open arrow) containing several blood vessels (arrowheads). The four-layered cortex of classical (type I) lissencephaly is not seen. (hematoxylin and eosin, 100X).

associated with WWS not manifested in our patient.

The computed tomography (CT) and MR imaging characteristics of the lissencephaly syndromes have been described (3, 5, 6). A smooth cerebral surface and incomplete opercular development creating a "figure-of-eight" appearance, a thickened cortex with a lack of gray-white matter interdigitation, colpocephaly, and dysgenesis of the corpus callosum can be seen in all types of lissencephaly. Progressive hydrocephalus, low-density white matter on CT, posterior cephaloceles, cerebellar hypoplasia, and Dandy-Walker malformations have been demonstrated in the type II but not type I lissencephaly syndromes (5). Hypoplastic cerebral peduncles, asymmetric eye size, and increased radiodensity in the region of the anterior interhemispheric fissure have also been demonstrated in WWS by CT (5).

Obliteration of the anterior interhemispheric fissure, secondary to leptomeningeal thickening and proliferation (1), was well demonstrated by MR in our patient. Midline fusion of the occipital lobes and collicular fusion, previously not described in WWS, were also evident. MR not only demonstrated asymmetric eye size, but displayed increased signal from the left oculus on both T1- and T2-weighted images, reflecting vitreous hemorrhage secondary to retinal detachment. Associated posterior cephaloceles have been demonstrated by CT in WWS patients (2) but not in those reports illustrating MR findings (3, 6). Our case demonstrates the utility of sagittal MR imaging in the detection and characterization of even small cephaloceles, as well as the callosal and posterior fossa abnormalities associated with this syndrome. In the majority of patients with WWS, who have both lissencephaly and hydrocephalus, characterization of the cerebral surface can be obscured by CT because of close contact with the calvarium (5). MR alleviates this problem. It may be difficult, however, to evaluate the gray-white matter interface in very young infants, and especially those with WWS, because of the sparse amount of myelinated white matter present (3).

Children with WWS have median survivals of 9 months, most dying as a result of severe CNS anomalies (2). Those surviving past the neonatal period display profound mental retardation, intractable seizures, hypotonia, and failure to thrive. Prenatal diagnosis is now possible utilizing fetal ultrasound (7), and should be attempted in women previously giving birth to a child with

WWS or those taking part in a consanguineous union.

Because WWS has a genetic basis, prenatal or early postnatal diagnosis is important for parental counseling, regarding both prognosis for the affected child and risk for recurrence in future pregnancies. MR best displays the intracranial and associated ocular abnormalities of WWS and is the postnatal imaging modality of choice in confirming a clinically suspected case of WWS.

Addendum

Since the original writing, the mother of the infant described in this report underwent a therapeutic abortion of a subsequent pregnancy at 15 weeks of gestational age, after fetal ultrasonography displayed ventriculomegaly, a posterior cephalocele, and a cleft between the cerebellar

hemispheres likely representing a posterior fossa cyst.

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