Syndrome of the month

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Walker-Warburg syndrome (Warburg syndrome, HARD + E syndrome)

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Walker-Warburg syndrome is a lethal autosomal recessive disorder of brain development and organisation leading to hydrocephalus, ocular abnormalities, and in some cases occipital encephalocele. The first detailed description of this syndrome was by Walker.1 Warburg2 reviewed published reports on hydrocephalus and retinal non-attachment and Chemke et al.3 reported recurrence in a consanguineous family. Pagon et al.4 introduced the mnemonic HARD + E for hydrocephalus, agyria, and retinal dysplasia with or without encephalocele, but later5 proposed the name Warburg syndrome. Recently, Dobyns et al.6 have reviewed 15 published cases and reported three others. This review is based on these reports, five personally observed cases, and two others reported by Levine et al.7 and later by Williams et al.8 who reported one further case and proposed that the condition be named Walker-Warburg syndrome.

Clinical features

HYDROCEPHALUS
The large head (13/26 cases) may cause obstructed labour but OFC can be normal at birth. Ventriculomegaly is always present.

ENCEPHALOCELE
Approximately half of the reported cases have had an occipital encephalocele. This may be small and only detected at necropsy (fig 1). There may be an occipital skin haemangioma (personal observation).

EYE ABNORMALITIES
Present in most cases are microphthalmia and/or anterior and posterior chamber abnormalities including corneal opacity, cataract, and persistent primary vitreous. Retinal dysplasia is always present (fig 2).

FACIAL APPEARANCE
There is no characteristic facial appearance (fig 3).

OTHER ABNORMALITIES
These include small penis and genital abnormalities (six cases) including undescended testes, hydrenephrosis secondary to pelviureteric junction obstruction (two cases), anoperineal fistula (one case), and talipes (one case).

Clinical course

The clinical course includes hypo- or hypertonia, progressive hydrocephalus, and unresponsiveness with minimal developmental progress. Early death is the rule with longest survival being one year (mean survival 3 months). Shunt therapy may prolong life but does not improve development.

Investigations

Investigations should include ultrasound scan and computerised tomography of the brain (fig 4) and detailed ophthalmological assessment. Brain biopsy may be considered.

Pathological features

BRAIN
The macroscopic appearance consists of agyria (type II lissencephaly9) (fig 5), thin cerebral mantle, absent corpus callosum or septum pellucidum or both, absent or hypoplastic optic nerves and olfactory bulbs, ventriculomegaly, cerebellar hypoplasia, Dandy-Walker malformation, and encephalocele. Under the microscope the cerebral cortex lacks...
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**FIG 1** Second affected child of second cousin parents: occipital encephalocele detected at necropsy, not visible externally.

**FIG 2** Second affected child of non-consanguineous parents: sagittal section of eye showing anterior and posterior chamber abnormalities.

**FIG 3** Facies of child in fig 1.
normal demarcation into the six cortical layers. Cellular disorganisation is also seen in the cerebellum.

**EYE**

Macroscopically, the features are as above under Clinical features. Microscopically, there is severe cellular disorganisation of the retina and non-attached retina.

**Aetiology**

There is probably a defect in migration of neuroblasts between 40 and 60 days after conception.

**Genetics**

Autosomal recessive inheritance is likely. Twenty-six cases (11 male, 15 female) from 18 families have been reported. Affected sibs of both sexes have been observed in seven families with parental consanguinity in two of these (Chemke et al and personally observed sib pair) and in a single case observed by us. Insufficient family data are reported for segregation analysis.

**Differential diagnosis**

Cerebro-oculo-muscular syndrome (COMS) is very similar and probably also an autosomal recessive disorder. Affected children have type II lissencephaly and similar ocular problems. They seem to differ only in that they have a congenital muscular dystrophy as evidenced by a raised creatine kinase level, a myopathic pattern on electromyography, and abnormal muscle histology. Further muscle studies
on Walker-Warburg cases are needed to determine whether COMS is a distinct disorder. Intrauterine infections, including toxoplasmosis and cytomegalovirus, may cause hydrocephalus and ocular problems and can be excluded by appropriate investigations.

References


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