Walker-Warburg Syndrome

Alternative Names
Hydrocephalus, Agyria, and Retinal Dysplasia
HARD Syndrome
HARD +/- E Syndrome
Warburg Syndrome
Chemke Syndrome
Pagon Syndrome
Cerebroocular Dysgenesis
COD
Cerebroocular Dysplasia-Muscular Dystrophy Syndrome
COD-MD Syndrome
Muscular Dystrophy, Congenital, plus Mental Retardation
Muscular Dystrophy, Congenital, Associated with Calf Hypertrophy, Microcephaly, and Severe Mental Retardation

WHO International Classification of Diseases
Congenital malformations, deformations and chromosomal abnormalities

OMIM Number
236670

Mode of Inheritance
Autosomal recessive

Gene Map Locus
19q13.3, 14q24.3, 9q34.1, 9q31

Description
Walker-Warburg syndrome is a recessive autosomal disorder characterized by congenital muscular dystrophy, severe brain malformation, and structural eye abnormalities. It is also known by the acronym HARD +/- E syndrome (hydrocephalus, agyri, retinal dysplasia, plus or minus "e" for encephalocele). Clinical features include a malformed head, small eyes, cataracts, retinal abnormalities, and muscle weakness. The brain manifests cobblestone lissencephaly with agenesis of the corpus callosum, cerebellar hypoplasia, hydrocephaly, and sometimes encephalocele. Seizures may occur. Encephalocele may be present as well. Microscopic examination reveals that the cells and tissues of the brain develop in a highly disorganized fashion. Life expectancy of patients with Walker-Warburg syndrome is usually less than 1 year.

Molecular Genetics
Walker-Warburg syndrome is caused by mutation in the POMT1 gene encoding protein O-mannosyltransferase. It is genetically heterogeneous, and approximately 20% of the patients show POMT1 mutations. The family of mammalian O-mannosyltransferases includes two enzymes, POMT1 and POMT2, which are thought to be essential for muscle and neural development. O-mannosylation is an important modification of proteins in various fundamental physiological processes. During embryogenesis, the murine POMT1 gene is prominently expressed in the neural tube, the developing eye, and the mesenchyme. These sites of expression correlate with those in which the main tissue alterations are observed in Walker-Warburg syndrome patients. The POMT1 gene contains 20 exons, spans about 20 kb, and is mapped to chromosome 9q34.1.

Epidemiology in the Arab World

Palestine
In 1997, Zlotogora analyzed 2000 Palestinian Arabic families and found that in 98 families at least one individual had congenital hydrocephalus and/or open neural tube defect. Among these families, 42 had congenital hydrocephalus without open neural tube defects; it was non-syndromal in 34 families and syndromal in the other eight (Meckel in 4, Warburg in 2, and an undiagnosed syndrome in each of the other 2 families). In the two families with Warburg syndrome there were three affected children who had hydrocephalus and one cephalocele, and in the last two families...
one child had hydrocephalus the other occipital cephalocele. Zlotogora (1997) indicated that Warburg syndrome was encountered in five Muslim families. The parents were first cousins in four of the families. In these families, 13 individuals were affected: ten with hydrocephalus and three with occipital cephalocele.

References

Contributors
Ghazi O. Tadmouri: 9.11.2005