Warburg Micro Syndrome

Alternative Names
- WARBM
- Micro Syndrome
- Warburg Sjo Fledelius Syndrome

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

OMIM Number
600118

Mode of Inheritance
Autosomal recessive

Gene Map Locus
2q21.3

Description
Warburg first described this extremely rare autosomal recessive genetic disorder in 1993. The disease is characterized by severe mental retardation, microcephaly, hypoplasia of the corpus callosum, microgenitalia and characteristic ocular findings, like microphthalmia, microcornea, congenital cataract, and optic atrophy. The patients also present with dysmorphic features, such as beaked nose with a prominent nasal root, large anteverted ears, hypertrichosis, micrognathia, and highly arched palate. Seizures and/or limb contractures may develop in some patients. Delayed puberty is commonly observed.

Up until now, only 24 definite cases of this disease have been reported. Diagnosis of the disease involves a thorough ocular examination, and brain scans. Although the RAB3GAP gene has been implicated in micro syndrome, to date no genetic test is available for its diagnosis. Treatment is symptomatic. Since congenital cataract is the most common symptom of the disease, most treatment strategies would target it. Physiotherapy is also an important component of the treatment plan, since most patients develop limb contractures and hypotonia.

Molecular Genetics
Micro syndrome has been found to be linked to the RAB3GAP gene, located on chromosome 2. This gene encodes a protein, which is implicated in regulated neurodevelopmental processes, such as proliferation, migration and differentiation before synapse formation, non-synaptic vesicular release of neurotransmitters, and regulated exocytosis of hormones. Mutations in the gene coding for the catalytic region of this protein have been found in patients of micro syndrome. It is presumed that the mutations lead to defects in the vesicular transport and exocytosis of neurotransmitters and hormones.

Epidemiology in the Arab World

Lebanon
Megarbane et al. (1999) described four children (one male and three females) from a highly inbred Shiite Muslim family from southern Lebanon with hypotonia, microcephaly, microphthalmia, congenital cataract, ptosis, short stature, severe mental retardation, and cerebral malformations. The first case was a girl, born to normal consanguineous parents. She presented with bilateral microphthalmia and cataract at birth. At 9 years of age, her length, weight and occipitofrontal circumference (OFC) were below the third centile. She had a long philtrum, a high arched palate, a pointed chin, kyphoscoliosis, contracture at the knees, and flexion contraction of all the fingers. Neurological findings included central hypotonia, spastic diplegia, increased osteotendinous reflexes with crossed adductors, scissoring, poor fixation and following with each eye, with wandering eye movements and horizontal nystagmus. Radiological
examination of the skeleton showed a left curved scoliosis, convex vertebral bodies, diffuse osseous demineralization, thin diaphyses of the long bones, bilateral subluxation of the femoral head, and fixed flexion of the knees. Her sister, five years younger, presented with the same set of features, except for the absence of contractures of the extremities, and presence of only a mild kyphoscoliosis to the right. She was found to have dense mature cataracts in both eyes and bilateral optic atrophy. Gyral anomalies, plagiocephaly, subcortical atrophy, and hypertrophy of the white matter were observed in MRI scans. Another male sibling of theirs, who had presented with the same features, had died at the age of 5 years. The third case was a distant cousin of these patients. She too presented with similar clinical features. The fourth case in the kindred was a boy, with similar clinical presentations as his cousins. His testes were undescended, and MRI scans showed diffuse cortical and subcortical atrophy, hypoplasia of the corpus callosum, predominantly posteriorly, and diffusely abnormal signal of the subcortical white matter with reduced myelination, bilateral hippocampic malformation, and small orbits. Five other children in this extended family, who had earlier died, were reported to have had microphthalmia and cataract. Megarbane et al. (1999) considered several differential diagnosis considering the overlapping symptoms, including Lenz microphthalmia, COFS, CAMAK/CAMFAK, Cockayne, and Matrsal syndromes. However, they found that the features most closely resembled the Warburg micro syndrome.

References

Contributors
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