Multiple Epiphyseal Dysplasia with Early-Onset Diabetes Mellitus

Alternative Names
MED-IDDM Syndrome
IDDM-MED Syndrome
Wolcott-Rallison Syndrome

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

OMIM Number
226980

Mode of Inheritance
Autosomal recessive

Gene Map Locus
2p12

Description
Multiple epiphyseal dysplasia with early-onset diabetes mellitus (also known as Wolcott-Rallison syndrome) is a rare autosomal recessive disorder that manifests itself in early infancy with symptoms of diabetes mellitus. Short stature and walking difficulties become evident in the second year of life when the child starts to walk. These skeletal changes are progressive with age. There is usually a short trunk, excessive lordosis, a short and broad chest and genu valgum. There might be limited movement of some joints, particularly the shoulders, hips, elbows, and wrists.

Skeletal survey shows findings suggestive of spondyloepiphyseal dysplasia. These include platyspondyly with irregular upper and lower end-plates of vertebrate. The epiphyses in general appear small and flattened with fragmentation. There is usually generalized osteoporosis, narrow iliac wings, coxa valga with hip dislocation and lateral displacement of the femoral epiphyses. The carpal centers of the hands are usually small and irregular and the middle phalanges can be short. Some epiphyses appear dense or ivory-like.

In Wolcott-Rallison syndrome, insulin-replacement therapy is required from the onset of diabetes, and autopsy explorations reveal a reduction in pancreatic beta-cells.

Molecular Genetics
Multiple epiphyseal dysplasia with early-onset diabetes mellitus results from mutations in the gene encoding the eukaryotic translation initiation factor 2-a kinase 3 (EIF2AK3, also called PERK or PEK). This enzyme phosphorylates EIF2A at Ser51 to regulate the synthesis of unfolded proteins in the endoplasmic reticulum. Targeted disruption of the Eif2ak3 gene in mice also causes diabetes because of the accumulation of unfolded proteins triggering B-cell apoptosis. Although these murine models have provided significant insight into the pathogenesis of Wolcott-Rallison syndrome, only few human cases have been characterized genetically.

Epidemiology in the Arab World

Kuwait
Marafie et al. (2004) described a male patient with Wolcott-Rallison syndrome born to healthy parents who were first cousins. Both were Kuwaitis from a large Bedouin tribe, the lineage of which extended back to the eastern coast of Saudi Arabia. Pedigree analysis revealed the presence of adult onset diabetes mellitus on both sides of the family, and early infant deaths, the cause of which could not be clarified. The child developed insulin dependant diabetes mellitus at the age of 2 months. At the ages of 10 months, 14 months and 2 1/2 years he developed gastroenteritis/upper respiratory tract infection with sever episodes of hepatitis with
altered consciousness, jaundice and extremely high hepatic enzymes with hypoglycaemia (a Reyes-like syndrome). The liver biopsy showed severe post-necrotic type bridging fibrosis with early nodular parenchymal hyperplasia, pale staining hepatocytes, and minimal inflammation, suggesting a metabolic disorder. At the age of 3 1/2 years he was diagnosed with hypothyroidism because of his short stature and dry skin. Clinical examination at the age of 7 years revealed a microbrachycephaly, a depressed nasal bridge, hypertelorism, a high arched palate, protruding ears with abnormal auricles, discolored and decayed teeth, a short neck with hyperpigmented dry skin. A skeletal survey revealed a generalized osteopenic texture, delayed bone age, multiple spondyloepiphyseal dysplasia. Marafie et al. (2004) expected that because of an increasing number of reports of Wolcott-Rallison syndrome in Arab children from the Arabian Peninsula there could be a quite large number of potential gene carriers in members of some highly inbred families from tribal origin in countries of the Gulf area.

Oman
Al-Gazali et al. (1995) described two male sibs with early onset diabetes and epiphyseal dysplasia (Wolcott-Rallison syndrome). The patients were born to a consanguineous couple of Omani origin. The fathers of the parents were half sibs. The couple had a female child, who at the age of two months developed weight loss, irritability, diarrhea, and died a few days later. The paternal grandfather had adult-onset diabetes. Both patients developed diabetes in the first few weeks of life. The first patient was microcephalic and mentally retarded with quadriplegia. The second patient had epiphyseal changes that were radiologically apparent at 6 months of age. The report of Al-Gazali et al. (1995) was the first to describe the syndrome in a consanguineous family confirming the autosomal recessive mode of inheritance. They also noted that the syndrome may be under-diagnosed because infants with neonatal onset diabetes often die early and are not X-rayed.

Saudi Arabia
In 1998, Bonthron et al. (1998) described the second family with Wolcott-Rallison syndrome in which parental consanguinity was present. The proband was born to first cousin Saudi parents and died at 2 years from the sequelae of poorly controlled diabetes. To test the hypothesis that mutation of PAX4, required in the mouse for pancreatic islet beta cell development, might cause Wolcott-Rallison syndrome, the structure of the human PAX4 gene was deduced and DNA from two unrelated Wolcott-Rallison syndrome patients sequenced. No PAX4 mutation was present, though the entire coding region was sequenced in both patients.

Abdelrahman et al. (2000) reported a 3.5-year-old Saudi boy with Wolcott-Rallison syndrome. Bin-Abbas et al. (2001) extensively revised the case of Abdelrahman et al. (2000). They reported that the infant was healthy until the age of 45 days, when he presented with poor feeding and severe dehydration. At 7 months of age, he was admitted with jaundice. Clinical examination was remarkable for hepatomegaly. At 21 months of age, the patient was re-admitted with fever and jaundice. The skeletal survey showed epiphyseal dysplasia. At 2.5 years of age, the child presented with a recurrent episode of acute hepatitis, associated hyperglycemia, fever, severe dehydration and anuria. Developmentally, the child had mild cognitive and motor delay with an estimated neurological age of one year. One year later, Bin-Abbas et al. (2002) reported two sibs with an infantile onset of hyperglycemia, recurrent hepatitis, renal insufficiency, developmental delay, and skeletal epiphyseal dysplasia are described. Clinical presentation and radiological features were suggestive of Wolcott-Rallison syndrome. In both cases, there was evidence of central hypothyroidism. In 2004, Senee et al. conducted genetic analysis on the boy reported by Abdelrahman et al. (2000) and Bin-Abbas et al. (2001). They also analyzed his brother who was much recently diagnosed with the disease. Senee et al. (2004) also conducted genetic analysis on the patients described by Bin-Abbas et al. (2002). At the time of analysis, a third sib was born to the family and was diagnosed with diabetes at 2 weeks of age.

[See also: Kuwait > Marafie et al., 2004].

Tunisia
Nicolino et al. (1998) described a consanguineous family from Tunisia with Wolcott-Rallison syndrome. The family included three affected and one unaffected sibs with unaffected parents who were related as first cousins. In 2004, Senes et al. revised the three affected sibs described by Nicolino et al. (1998). They noted that all patients showed signs of exocrine pancreas dysfunction with fibrosis infiltrations in the pancreas biopsy of one of the patients. Neutropenia was also noted with frequent infections (bacterial, viral, and fungic).
United Arab Emirates
[See also: Oman > Al-Gazali et al., 1995].

References


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