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Association of hyperprolinaemia type I and heparin cofactor II deficiency with CATCH 22 syndrome: evidence for a contiguous gene syndrome locating the proline oxidase gene

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Summary: Increased proline levels were found in plasma of a girl with slight psychomotor retardation, epilepsy, obesity, scoliosis, hypocalcaemia, variable lymphocytopenia and facial dysmorphy suggestive of CATCH 22 syndrome. Fluorescence *in situ* hybridization indicated the presence of a submicroscopic 22q11 deletion, confirming this diagnosis. Further investigation showed evidence that the patient was heterozygous for heparin cofactor II deficiency and for hyperprolinaemia type I, a proline catabolic disorder due to proline oxidase deficiency. This association extends the CATCH 22 syndrome and suggests that expression of the proline oxidase gene depends on the chromosome 22q11 region.

Two autosomally recessive disorders are known in the catabolic pathway of proline: type I hyperprolinaemia, due to a deficiency of proline oxidase (no EC number assigned), and type II hyperprolinaemia due to a deficiency of Δ^1-pyrroline-5-carboxylate dehydrogenase (EC 1.5.1.12) (Phang et al 1995). Type I is considered as a benign disorder, while type II is causally associated with neurological manifestations. The loci for these enzymes have not been mapped. We report on a girl with CATCH 22 syndrome (Demczuk and Aurias 1995) and partial heparin cofactor II deficiency who is also heterozygous for type I hyperprolinaemia, providing evidence that expression of the proline oxidase gene is closely linked to the chromosome 22q11.2 region.

PATIENT AND METHODS

The patient, a Belgian girl, was born in 1979 after a term pregnancy and normal delivery. Her birth weight was 3090 g. She had an older healthy sister. The parents are not related. Her father's mother had epilepsy from the age of 12 years, and an uncle of her mother reportedly died from epilepsy. She could sit without support at 8 months. At the age of 1 year she had generalized convulsions without fever, associated with hypocalcaemia

(1.9 mmol/L) and treated with calcium supplements and sodium valproate. Clonic convulsions reappeared at 7 years with normocalcaemia together with a 1-h period of stupor. Subsequently she also presented absences and temporal epilepsy, partially controlled by adding carbamazepine. She always had major schooling difficulties owing to hyperactive behaviour as well as poor concentration and limited fine motor abilities. Developmental quotient determined at 5 years (Terman method) was 94. At the age of 11 years, a thoracolumbar dextroconvex scoliosis with hyperlordosis was noted, for which a surgical correction was performed at 14 years. Menarche occurred at 15.7 years. At the age of 16.7 years, height was 159.2 cm (−0.5 SD score), weight 60 kg (+0.6 SD score), body mass index 23.7 (+1.2 SD score) and head circumference 56 cm (+1.3 SD score). The diagnosis of CATCH 22 syndrome was suspected at the age of 15 years on the basis of the characteristic dysmorphology with a broad and prominent nasal bridge, a gothic palate and long, thin fingers associated with intermittent hypocalcaemia (range 1.9–2.6 mmol/L), concomitantly low levels of serum parathormone and variable lympocytopenia.

At 14 years serum IgA (12 mg/dl; normal 81–232), IgG (657 mg/dl; normal 680–1493) and IgM (13 mg/dl; normal 45–237) were decreased; repeat analysis at 17 years showed only a slightly decreased IgA (56 mg/dl) and IgG_3 (26 mg/dl; normal 41–129). Urinary organic acids were normal. Δ^1-Pyrroline-5-carboxylate could not be detected in urine. Radiological examination of the skeleton showed, besides the scoliosis, mild osteoporosis. Echocardiography, renal echography, intravenous pyelography, cystography, ophthalmological examination, electromyography, nerve conduction velocity, brain magnetic resonance imaging and evoked potentials evidenced no abnormalities. Electroencephalography initially showed generalized epileptic activity only during sleep, but from 7 years on also when awake.

Plasma and urine amino acid levels were measured by cation-exchange chromatography. Heparin cofactor II antigen was determined by Laurell-Electrophoresis with an antibody from Behringwerke (Marburg, Germany). Chromosome studies were performed on a peripheral blood lymphocyte culture with G-banding and fluorescent *in situ* hybridization (FISH) using probe DO832.

RESULTS

Plasma proline levels were persistently increased in the patient at about twice the upper control value (814–1017 μmol/L; normal 100–433), while urinary proline levels were normal. Heparin cofactor II was decreased (46%; normal range 60–170). Prometaphase chromosome studies showed an apparent XX normal G-banded karyotype, but FISH revealed the presence of a submicroscopic 22q11 deletion in one chromosome 22 of all 10 examined cells. In the patient's parents and sister, plasma proline levels, heparin cofactor levels and FISH of 22q11 were normal.

DISCUSSION

The girl described presents three different disorders. She has the typical features of hyperprolinaemia type I in the heterozygous state, i.e. moderately elevated plasma proline levels in the absence of an increased excretion of proline and pyrroline-5-carboxylate. Heterozygotes for type II do not have hyperprolinaemia. Hyperprolinaemia type I is a very

rare and benign disorder. It is due to a deficiency of proline oxidase, the gene for which has not yet been mapped to a particular chromosome. As this enzyme is not present in skin fibroblasts or leukocytes, diagnosis by direct enzyme assay is currently not possible (Phang et al 1995). The presence of normal plasma proline levels in the parents indicates that the defect originated in the patient.

Furthermore, this girl has a documented CATCH 22 syndrome, a cardiac–abnormal face–thymus–cleft palate–hypocalcaemia syndrome due to a deletion of chromosome 22q11 and comprising the DiGeorge, Shprintzen and Opitz GBBB syndromes as well as isolated conotruncal cardiac defects (Scambler et al 1992; Demczuk and Aurias 1995; McDonald-McGinn et al 1995). Like most patients, this girl has a mild and partial expression. Her epilepsy is probably unrelated to this syndrome. We found a previously unreported association with an asymptomatic partial deficiency of heparin cofactor II which can be explained by the fact that the gene for this anticoagulation factor is located in the 22q11 chromosome region (Herzog et al 1991). Moreover, up to the age of about 17 years our patient had decreased serum immunoglobulin levels, which to our knowledge has not been described as part of the CATCH 22 syndrome, which usually affects only cellular immunity. This might be linked to a defect of the immunoglobulin lambda light chain gene cluster, which is also located in the 22q11 region (Frippiat et al 1995).

Taken together, these data extend the CATCH 22 syndrome to partial heparin cofactor II deficiency and suggest that the proline oxidase gene is closely associated with the chromosome 22q11 region.

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