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# Normal pubertal development in a female with carbohydrate deficient glycoprotein syndrome

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## Abstract

**A girl is reported who presented with many of the clinical and biochemical characteristics of type I carbohydrate deficient glycoprotein syndrome. Unusually, however, she experienced a normal pubertal development.**

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Carbohydrate deficient glycoprotein (CDG) syndromes are genetic multisystemic diseases characterised by a deficiency in the carbohydrate moiety of glycoproteins.[1 2] CDG syndrome type I is the most common of the three described variants. All reported females with CDG syndrome type I have hypergonadotropic hypogonadism with absent or delayed pubertal development.[3 4] We report the first Spanish patient with a CDG syndrome.

## Case report

This girl was the first child of unrelated, healthy parents. She was born after a normal pregnancy, at 36 weeks' gestation, with a birth weight of 2000 g.

At the age of 8 months she presented with severe psychomotor retardation and hypotonia with normal reflexes. A computed tomogram showed dilated ventricles and hypoplastic cerebellum. At 10 months she achieved head control.

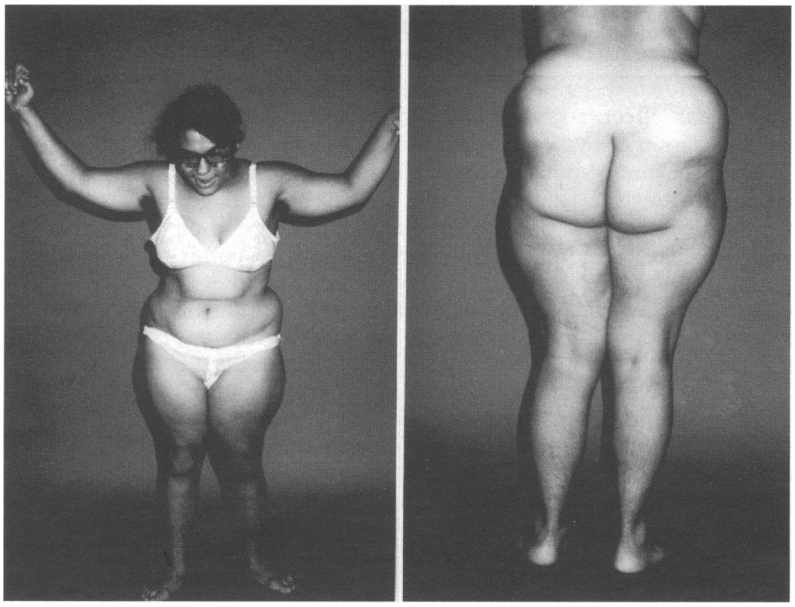
At 4 years she started walking with support but was ataxic; her tendon reflexes were still normal. At the age of 5 years she started to understand simple orders and to use single words.

At 7 years she had right tonic-clonic seizures controlled with phenobarbitone. Cerebrospinal fluid protein was raised (0·78 g/l), peroneal motor nerve conduction decreased (37 m/s; normal mean 50 m/s) and sensory conduction was absent. Her fundi showed myopic choroidosis.

Pubertal development was normal with menarche at 13 years of age. Height and bone maturity were within the normal range.

At the age of 15 years she returned to our hospital. Clinical examination showed a coarse face, pigeon barrel chest, lipodystrophy and significant fat accumulations on forearms and buttocks, with thin and hypotrophic legs (figure); she had alternating convergent strabismus with severe myopia and hypertrophy of the gums. She was very sociable, but her IQ was only 50. Abdominal ultrasound examination showed the absence of the right gonad with a normal uterus and kidneys.

Laboratory investigations excluded primary lysosomal and peroxisomal diseases. Serum cholesterol, transferrin, $\alpha_1$-antitrypsin, ceruloplasmin, complement C3, and complement C4 were normal. The following glycoprotein concentrations were abnormal: apolipoprotein B (0·44 g/l; normal range 0·59–1·58), haptoglobin 4·1 μmol/l (5·9–17·6), factor XI 25% (70–100), antithrombin 48% (80–120).



*Patient at the age of 17 years old showing a coarse face, hypotrophic legs, and fat accumulations on forearms and buttocks.*

## Methods

Carbohydrate deficient transferrin in serum was determined by radioimmunoassay (Kabi Pharmacia Diagnostics AB, Uppsala, Sweden). Analysis of transferrin isoforms were performed in serum and dried blood spots by isoelectric focusing with western blotting of transferrin.[5 6] Lysosomal enzymes were assayed in serum and cultured skin fibroblasts by standard methods. Endocrinological studies were carried out after stimulation with hypothalamic releasing hormones.

## Results

Abnormally raised carbohydrate deficient transferrin values were detected in dried blood spots (7·6 mg/l; normal range: 0·2–1·8) and in serum (112 mg/l; normal <20). Parents' serum carbohydrate deficient transferrin was normal.

Isoelectric focusing of serum sialotransferrins showed a cathodal shift similar to the pattern of CDG syndrome type I: increased asialotransferrin (4%; normal value <2%, type I: 2–32%) and disialotransferrin (27%; normal value <9%; type I: 23–36%), and decreased tetrasialotransferrin (49%; normal value 50–65%; type I: 12–48%). Trisialotransferrin and pentasialotransferrin fractions were normal. Activities of lysosomal enzymes in serum were within the normal range except for β-hexosaminidase, β-glucuronidase, and β-mannosidase which showed moderate hyperactivity (×1·8). Among the enzymatic activities studied in cultured skin fibroblasts, β-glucuronidase, arylsulphatase-A, β-glucocerebrosidase, and β-mannosidase were slightly but significantly increased.

Results of combined stimulation with thyrotrophin releasing hormone, gonadotrophin releasing hormone, and growth hormone releasing hormone showed a normal pubertal pattern: maximum value of 10·8 IU/l for luteinising hormone, 8·6 IU/l for follicle stimulating hormone, prolactin 2674 mU/l, oestradiol 162 pmol/l, growth hormone 100 mU/l, and thyroid stimulating hormone 14·2 mU/l. Serum concentrations of free thyroxine and triiodothyronine were 16·6 pmol/l (normal range 9·5–25·0 pmol/l) and 1·4 nmol/l (normal range 1·3–3·9 nmol/l), respectively. Antithyroglobulin and antiperoxidase antibodies were negative. Plasma concentrations of insulin like growth factor-I, growth hormone binding protein, and binding protein of insulin like growth factor were normal.

## Discussion

This patient, the first one reported from Spain, presents a number of features of CDG syndrome type I: severe psychomotor retardation, alternating convergent strabismus, myopia, axial hypotonia, ataxia, seizures, abnormal subcutaneous fat distribution, pectus carinatum, hypotrophy of the legs, olivopontocerebellar hypoplasia, peripheral neuropathy, and retinitis pigmentosa. Serum glycoprotein abnormalities, decreased serum albumin and low density lipoprotein cholesterol, increased cerebrospinal fluid protein, and the serum sialotransferrin isoform pattern, are consistent with this diagnosis.[1 2] However, there are also differences the most important being normal pubertal development. All reported girls with CDG syndrome type I have had hypogonadism with absent or delayed pubertal development. Whether this is due to a defect at the level of the ovaries or to a combined hypophyseal ovarian dysfunction remains to be determined.[1–4]

In our patient clinical, biochemical, and imaging data pointed towards normal ovarian function and development, except for the fact that the right ovary could not be seen on ultrasonography. Other endocrinological differences were the normal growth hormone and insulin concentrations, both in basal conditions and after stimulation. This is contrary to intermittent increases reported in other patients with CDG syndrome type I. Also at variance with type I was the persistence of pronounced abnormal subcutaneous fat distribution into adolescence, normal blood protein C concentration, and normal activity of arylsulphatase-A in serum associated with increased activity of some lyosomal enzymes in fibroblasts. CDG syndrome type I has recently been localised to chromosome 16p13·1–13·12.[7] However, so long as its basic defect remains unknown we cannot be certain whether our patient represents a variant of type I (for example a mosaic defect sparing the hypophyseal-gonadal axis) or a 'new' type. Studies of glycoprotein glycan structures and enzymatic studies are planned.

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