Journal of Neurology, Neurosurgery, and Psychiatry 1994;57:552–556

Carbohydrate-deficient glycoprotein syndrome: clinical expression in adults with a new metabolic disease

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Abstract

A new group of recessively inherited metabolic disorders affecting glycoprotein metabolism has been identified—the carbohydrate-deficient-glycoprotein (CDG) syndromes. Here the course and clinical expression of CDG syndrome type I in 13 patients who have passed the age of 15 years are described. All presented with early onset psychomotor retardation, in most cases combined with slight facial dysmorphic features, some degree of hepatic dysfunction, and in one case, pericardial effusion. About half of the patients had subcutaneous lipodystrophy and comatose or stroke-like episodes during childhood. After the age of 15 the disease was mainly characterised by neurological symptoms consisting of non-progressive ataxia associated with cerebellar hypoplasia, stable mental retardation, variable peripheral neuropathy, and strabismus. One third of the patients had generalised seizures, usually sporadic, and all had retinal pigmentary degeneration. In all cases there was more or less pronounced thoracic deformity and no female had passed puberty. Also, the oldest female showed premature aging. Severe internal organ symptoms, which are common in pediatric patients, were absent. All patients had highly raised serum concentrations of the biochemical marker carbohydrate-deficient transferrin, which can be used to verify the diagnosis. It is concluded that after childhood, CDG syndrome type I is a largely non-progressive disease compatible with a socially functioning but dependent lifestyle.

(*J Neurol Neurosurg Psychiatry* 1994;57:552–556)

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Received 14 May 1993
and in revised form
23 August 1993.
Accepted 10 September 1993

In recent years a new group of inborn errors of glycoprotein metabolism has been recognised.[1] Due to unique carbohydrate defects in secretory glycoproteins they have been termed carbohydrate-deficient glycoprotein (CDG) syndromes, of which three clinical and biochemical types have now been identified. The first described and best known, type I, seems to affect early neuronal development, whereas types II and III may be associated with dysmyelination or hypomyelination. All three types have variable manifestations outside the nervous system.[1–3]

The paediatric symptomatology in CDG syndrome type I is now well documented. In summary, in infancy and childhood the disease is primarily manifested by neurological symptoms consisting of psychomotor retardation, cerebellar and oculomotor dysfunction, peripheral neuropathy, comatose and stroke-like episodes, epilepsy, and retinal pigmentary degeneration. Other early manifestations are common including nutritional problems, hepatic dysfunction, pericardial effusions, infections, coagulation defects, nephropathy, osteopenia with skeletal deformities, and dystrophic alterations of adipose tissue and skin.[1–9]

The biochemical changes are dominated by a unique carbohydrate deficiency in a number of serum glycoproteins, which is most readily seen in transferrin.[4–6 8–13] Some of this glycoprotein lacks two or all of its four terminal trisaccharides,[10 12] and this aberration can be used as a diagnostic biochemical marker of CDG syndrome type I.[12] The ultrastructural changes described in liver and sural nerve biopsies are also characteristic, and particularly consist of various kinds of intracellular inclusion bodies and of attenuated myelin sheaths.[15 16] In a few necropsy examinations on children, olivopontocerebellar atrophy has been found, with nerve cell depletion and gliosis.[8 17]

The clinical expression of CDG syndrome type I in adult patients is incompletely known. We therefore describe here the course and manifestations of CDG syndrome type I in 13 patients who are now past the age of 15 years.

Materials and methods

Thirteen patients with CDG syndrome from nine unrelated Swedish families were examined within the age range of 15 to 50 (median 23) years. Six of them were females and seven were males. There were four affected sibling pairs: one pair were brothers, one pair were sisters, and in two families there was one sister and one brother each. One female patient had a deceased paternal cousin with the same disease, and one of the males has a younger brother with CDG syndrome. In these nine families there were five healthy full siblings and three half siblings, none of them born after the youngest affected patient. In none of the families was there any known consanguinity. All of them came from the southern third of Sweden. Information on the patients was obtained by assessment of clinical records and personal examinations by us. The diagnosis of CDG syndrome had been made on the basis

of clinical and biochemical findings[1] after the age of 15 years in 10 of the patients. The brains of nine patients had been examined by CT, one by pneumoencephalography, and one by MRI between the ages of 3 to 47, five of them after the age of 15. Nerve conduction velocity had been measured in nine cases, in five instances after the age of 15 years and in two patients repeatedly.

In 11 cases serum levels of aspartate- and alanine amino-transferase (ASAT, ALAT) and γ-glutamyl transferase (GT) were determined after the age of 15 years, as were concentrations of total transferrin (TT), thyroxine binding globulin (TBG), a_1-antitrypsin (AT), and apolipoprotein B (single radial immunodiffusion). Determination of carbohydrate-deficient transferrin (CDT) by anion exchange chromatography,[12] and immune isoelectric focusing of transferrin[12] were carried out in all patients after that age.

Results

CLINICAL SYMPTOMS

In all cases symptoms had been present during the first year of life. Presenting symptoms were failure to thrive or developmental delay in 12 instances, and in one patient a pericardial exudate. At first examination a slightly dysmorphic appearance[6 18] was seen in at least 10 patients, subcutaneous lipodystrophy[4 5 18] was specifically mentioned in six cases, and all had convergent strabismus (table 1). In eight patients there had been feeding difficulties, and hepatopathy of varying degree was present in those eight cases who had been examined for liver function. One patient had developed a Reye-like syndrome in connection with varicella.

From the second half of the first year, psychomotor retardation was evident with a combined cerebellar ataxia and peripheral neuropathy. None were able to walk, even with support, before the third year (table 2). During early childhood, generalised seizures had occurred in eight patients, and five had comatose or stroke-like episodes usually in connection with infections or trauma (table 1). The stroke-like episodes consisted of sudden focal cerebral symptoms lasting from a few hours up to three months. Within the first few years retinal pigmentary degeneration was found in all patients, as well as some thoracic deformity—for example, pigeon chest, scoliosis, or kyphosis (table 1).

During childhood and adolescence the neurological symptoms remained stable except for a slow gradual deterioration of the peripheral neuropathy, at least in those patients who had been followed up regularly. After the age of 14 years, stroke-like episodes had ceased to appear. Liver enzyme activities improved and feeding difficulties and lipodystrophy disappeared. Two patients had had signs of increased bleeding tendency, and one had a subclinical, verified deficiency of factors IX and XI.

At the age when this examination was carried out, moderate to severe but stable cerebellar ataxia and dyscoordination were present in all cases. Speech was primitive and "telegrammatic", with pronounced dysarthria, and three patients showed facial, truncal, and hand hyperkinesias when excited (table 1). All patients had some, but variable, muscular atrophy and weakness of the distal lower limbs (figs 1A, C, and D). Weak tendon reflexes could be elicited in five patients but were absent in eight. Only three male patients (aged 34–44 years) with mild neuropathy were able to walk atactically without support. Sporadic seizures continued to occur in four cases. All 13 patients had permanent, alternating, convergent strabismus (figs 1B, 2A, and 2B) and retinal pigmentary degeneration, but none were blind. Mental retardation was severe to moderate but non-progressive and combined with a most social, extrovert, and affectionate behaviour (table 1). Two patients had a remarkable memory for music. Five patients were able to read simple texts and to write short sentences (table 2). Understanding was generally better than expressive intellectual and motor capability. All patients had graduated from or were still attending special school, and seven of them had sheltered employment.

The seven males had apparently passed puberty and developed secondary sexual characteristics, whereas no female had shown any signs of puberty (table 1). The oldest female, now 50 years old, showed signs of premature aging (fig 2A). Eleven patients were short; two brothers were within normal height but were shorter than their healthy brother (table 1, fig 1). In six cases the thoracic and spinal deformity had become pro-

Table 1 Symptoms present in 13 adult patients with CDG syndrome

Major neurological symptoms	Mental retardation	13/13
	Cerebellar ataxia	13/13
	Cerebellar dysarthria	13/13
	Oculomotor disturbance	13/13
	Peripheral neuropathy	13/13
	Retinitis pigmentosa	13/13
Additional neurological symptoms	Epilepsy	4/13
	Hyperkinesias	3/13
Non-neurological symptoms	Short stature	11/13
	Thoracic deformity	13/13
	Female hypogonadism	6/6
	Facial dysmorphy	10/13
	Mild hepatopathy	3/11†
Reversible childhood symptoms*	Lipodystrophy	6/13
	Hepatopathy	5/8†
	Comatose/stroke-like episodes	5/13
	Epilepsy	4/13
	Bleeding tendency	3/13
	Pericardial exudate	1/13

* Number of patients in whom the symptom was observed during childhood but disappeared with age.
† The denominator indicates the number of patients who had been examined for liver function after the age of 15 years and in childhood respectively.

Table 2 Developmental hallmarks and functional ability in 13 adult patients with CDG syndrome

Developmental hallmarks	*Present functional ability*
Sitting: 15 months–4 years	Walking without support (n = 3)
Standing with support: 1–5 years	Reading simple texts (n = 5)
Walking with support: 3–5 years	Writing simple sentences (n = 5)
	Special school (n = 6)
	Sheltered employment (n = 7)

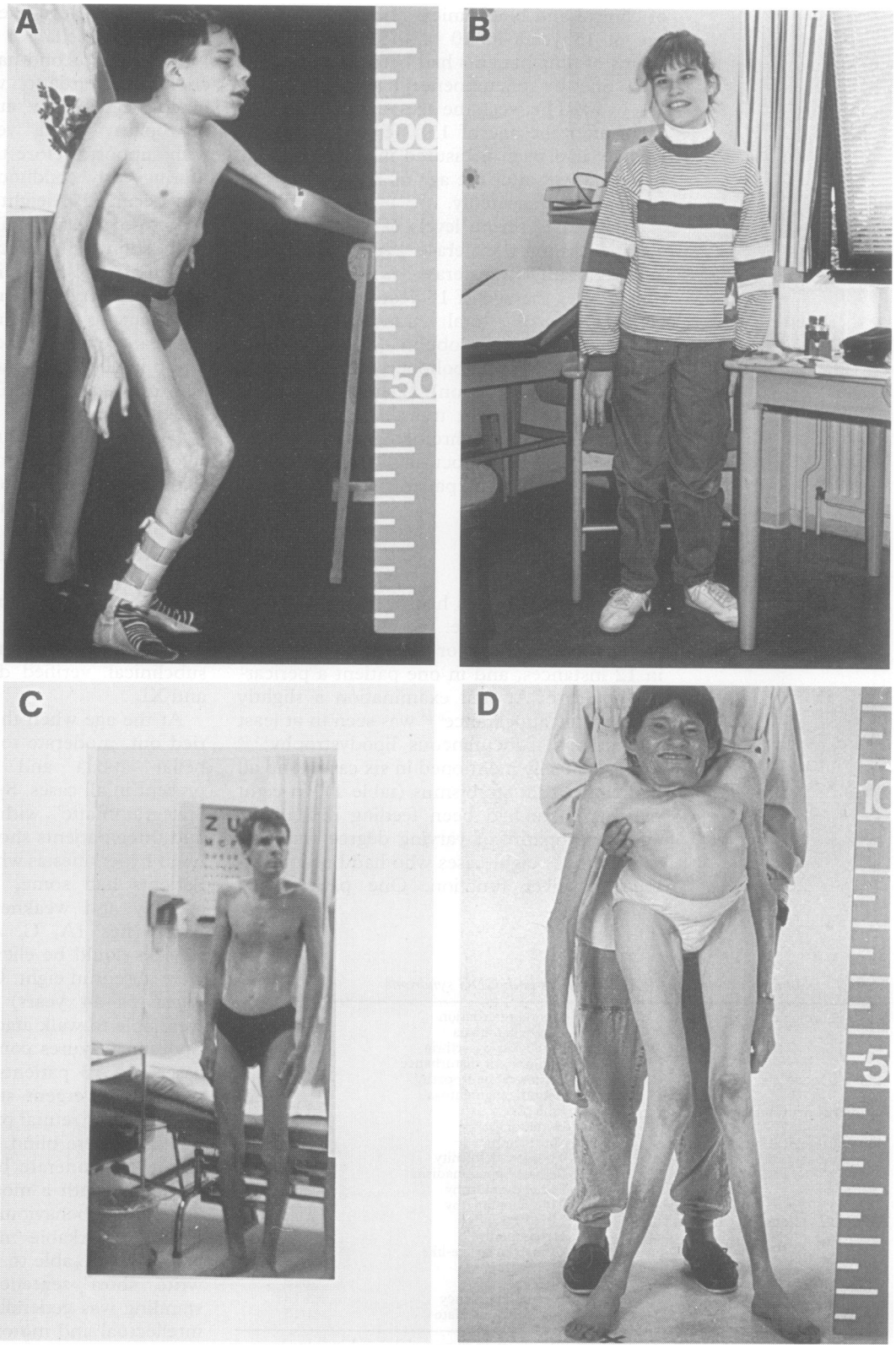

Figure 1 Four patients with CDG syndrome. (A) A boy aged 16. Note the short stature, prominent jaws, thoracic deformity, and atrophy of the lower limbs. (B) A women aged 22. Note the short stature, infantile habitus, and strabismus. (C) A man aged 35. Note the slight thoracic deformity and mild atrophy of the lower limbs. (D) A woman aged 47. Note the short stature, pronounced thoracic deformity, and atrophy of the lower limbs. There are no secondary sex characteristics. (With permission, Scandinavian University Press). Permission to publish these figures was obtained from the closest relatives.

nounced (table 1, fig 1D). The facial features were characteristic with prominent jaws, large ears, and a broad nose base (fig 1A, 2A). Many of them were alike.

NEURORADIOLOGY

All 11 examined patients showed generalised hypoplasia of the cerebellum, irrespective of the age at examination. Slight supratentorial atrophy was noted in two patients, one at the age of 8 and one at 47 years. There were no indications of hypomyelination or dysmyelination. One patient was examined with CT twice, at 8 and 13 years of age, without signs of progression of the cerebellar pathology.

NEUROPHYSIOLOGY

Eight of the nine studied patients had variable reduction of the peroneal motor nerve conduction velocities. In one 44-year-old male, peroneal nerve conduction velocities showed borderline values despite clinical signs of

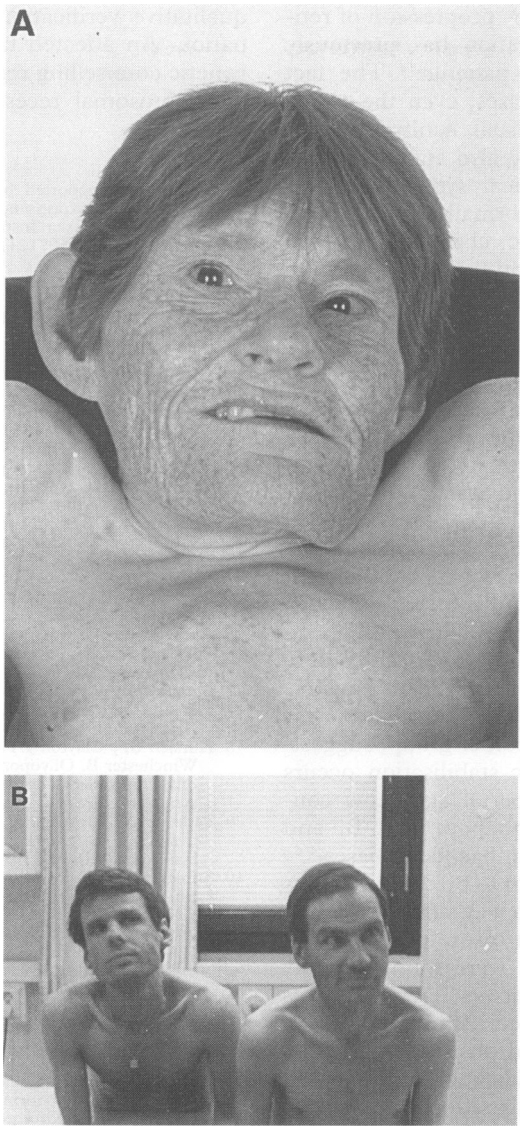

Figure 2 Three patients with CDG syndrome. (A) The woman in fig 1D, aged 47. Note the strabismus, premature facial aging, prominent jaws, and large ears. (B) Two brothers aged 35 and 42. Note the strabismus, somewhat prominent jaws, and kyphotic posture. There are no signs of premature aging in these men. Permission to publish these figures was obtained from the closest relatives.

distal neuropathy. In the oldest female patient, no responses were recorded from the peroneal nerves at the age of 47. The two patients who were examined repeatedly showed a gradual slowing of the peroneal nerve conduction velocities, at least until the age of 14.

BIOCHEMICAL ANALYSES

After the age of 15 years, ASAT or ALAT levels, or both, were slightly raised in three of 11 patients, ranging between 0·9 and 3·8 μcat/l. Serum concentrations of TBG were reduced in six of 11 patients (mean 8·85 (SD 2·37)) mg/l, reference range 10–40 mg/l), and apolipoprotein B was reduced in five of 11 cases (mean 0·50 (0·27) g/l, reference range 0·48–1·58 g/l). The serum concentration of AT was below normal in nine of 11 patients (mean 1·98 (1·25) g/l, reference range 2·0–3·28 g/l). Concentration of TT was normal in all but one patient (mean 2·82 (0·84) g/l, reference range 2·02–3·99 g/l). Determination of CDT in serum showed greatly increased values in all instances with a mean of 146 (36) mg/l (reference level in men ⩽17 mg/l and in women ⩽22 mg/l) (table 3). There were no significant correlations between the values of any of the analysed proteins except between TBG and apolipoprotein B ($r = 0·613$, $p < 0·025$). Only apolipoprotein B was correlated with age ($r = 0·836$, $p < 0·0005$).

Table 3 Values of carbohydrate-deficient transferrin (CDG) in serum in patients with CDG syndrome and in controls

Group	CDT (mg/l) mean (SD)
CDG syndrome (n = 55):	
<15 years old (n = 42)	246 (63)
>15 years old (n = 13)	146 (36)
Other PMR (n = 142)[21]	18 (6)
Healthy adults (n = 94)[12]:	
Females	17 (3)
Males	13 (2)

PMR = psychomotor retardation.

Immune isoelectric focusing of serum transferrin showed pronounced concentrations of abnormal isotransferrins corresponding to isoforms with two and four deficient carbohydrate chains, which is typical for CDG syndrome type I.[4-6 11 12]

Discussion

These 13 patients, with a median age of 23 years, represent the oldest group with CDG syndrome known to us. Altogether, we have diagnosed 60 cases with type I as of April 1993, and data from another eight patients have been reported,[1 9 13 14] representing 11 nationalities on three continents. The present patients show certain differences compared with many of the described paediatric cases. This report may therefore cast new light on the course and prognosis of CDG syndrome after the childhood stage with an estimated mortality of 15%–20%.[18]

Except for transient pericardial exudate in one patient and a Reye-like syndrome in another, none of them had had life threatening complications during infancy and childhood, such as severe infections, haemorrhages, or systemic organ failure, which have been reported repeatedly in paediatric cases.[5 6 8 9 17 18] The low frequency of those types of dramatic manifestations is probably responsible for the good prognosis for long term survival, and may have provided more favourable conditions for psychomotor development. It is possible that these patients represent a more benign phenotype than those with early severe multisystemic manifestations.

The course of the disease from adolescence was dominated by the neurological symptoms, which seemed to be stable with the possible exception of a slow deterioration of the peripheral neuropathy. The degree of neuropathy in the oldest patients was, however, variable, from very mild to severe. Walking ability seemed to be limited by the severity of the neuropathy. Cerebellar and mental symptoms remained stable and all patients achieved a socially functioning but dependent lifestyle. The frequency of epilepsy decreased, necessitating treatment in only one third of the patients, and stroke-like episodes disap-

peared completely. A slow progression of retinal pigmentary degeneration has previously been noted in younger patients.[19] The fact that all of the present cases, even the oldest ones, had functional visual acuity suggests that the retinopathy may also stabilise. With regard to non-neurological symptoms, liver enzyme levels had normalised in most instances, lipodystrophic changes were no longer seen, the spinal and thoracic deformity was highly variable, and hypogonadism was evident in all females. The type of hypogonadism has not yet been definitely determined, and it is not known whether some hypogonadism may be present in males as well, despite development of secondary sex characteristics. It should be noted that testicular atrophy has been found at necropsy examination in one male child.[17]

Biochemically, the concentrations of the characteristic marker, carbohydrate-deficient transferrin, were profoundly increased in all patients, but tended to be lower than in patients younger than 15 (table 3). Before that age, values showed a significant negative correlation with age.[12] This correlation was not found in the present older group, suggesting that some metabolic stabilisation occurs before the expected pubertal age. Low concentrations of TBG, apolipoprotein B, and AT have been reported in paediatric cases,[4-6 8 11] and AT has been shown to be deficient in its carbohydrate portion in a way similar to transferrin.[5 12 14] In the present cases, low TBG and apolipoprotein B values were found in only about half of the patients, whereas AT was more consistently reduced. Apolipoprotein B concentrations correlated positively with age, which may be another indication of a slow but continuous metabolic adaptation.

Both the ultrastructural abnormalities and studies of glycoprotein metabolism carried out to date indicate a basic defect in glycoprotein turnover, possibly affecting glycoprotein degradation or transport.[12 15 16] The underlying genetic deficiency has not yet been identified, but further biochemical and genetic investigations are under way.

In summary, in the adult patient the combination of early, non-progressive mental retardation and cerebellar hypoplasia, variable peripheral neuropathy, strabismus, retinal pigmentary degeneration, thoracic deformities, and female hypogonadism is strongly suggestive of CDG syndrome type I. The diagnosis can be verified by analysis of the transferrin isoforms in serum. For screening purposes the CDT assay is a rapid, simple method (available as CDTect at Kabi-Pharmacia, Uppsala, Sweden). A laboratory familiar with isoelectric focusing is needed for qualitative verification and subtype determination. An affected family should be offered genetic counselling regarding the highly probable autosomal recessive inheritance of this disease.[9 20]

This work was supported by grants from the Bergendahl, Carlsson, Cornell, Expressen, and Jerring foundations, as well as from the Karolinska Institute and the Swedish Medical Research Council (No 07121).

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