

## Carbohydrate-deficient glycoprotein syndromes

Neil Gordon

### Summary

**Four types of carbohydrate-deficient glycoprotein syndrome have been described, and the cause of two of them has been found. The symptoms and signs of these syndromes are described, with variations that occur at different ages. The commonest is type Ia with an autosomal recessive form of inheritance, and the gene responsible has been mapped to 16p. The typical pathology is atrophy of the cerebellum and brainstem, sometimes also involving the cortex, although both the pathology and the biochemical deficiencies vary between different types of syndrome. The diagnosis depends firstly on recognising the clinical features, including the presence of complications such as thyroid disorders. Then biochemical tests can be carried out, especially chromatographic carbohydrate-deficient transferrin assay and isoelectric focusing of serum transferrin.**

**The prognosis depends on the complications, renal, hepatic, and cardiac, but affected children will be severely handicapped. Therefore treatment consists mainly of coping with the complications, and supporting the child and the family. Oral infusion of mannose can be effective in type Ib disease.**

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Huntlywood, 3 Styal Road, Wilmslow  
SK9 4AE, UK  
N Gordon

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A group of metabolic disorders characterised by a defect in the modification of glycoproteins by carbohydrates was first recognised in the early 1980s.<sup>1</sup> Four types of carbohydrate-deficient glycoprotein syndrome have been recognised, depending on the isoelectric focusing pattern of serum sialotransferrins.<sup>2</sup> The basic defect in type Ia is usually a deficiency of phosphomannomutase, and in type II, a deficiency in Golgi localised N-acetylglucosaminyltransferase II. In the other two types the cause has not been found; they present as a severe encephalopathy with intractable epilepsy and a different cathodal shift on serum transferrin isoelectric focusing from type Ia.

Although a heterogeneous group of disorders many of the clinical findings of the carbohydrate-deficient glycoprotein syndromes are characteristic, the presentation varies with age and type.<sup>2-6</sup> The symptoms and signs which can suggest the diagnosis of these syndromes are shown in the box on the next page.

The commonest variety of the carbohydrate-deficient glycoprotein syndromes is type Ia, and in most instances a deficiency of phosphomannomutase has been recognised. The inheritance is autosomal recessive, and the gene responsible for the disorder has been mapped to chromosome 16p.<sup>2,7</sup> However, in a study from Canada involving 17 families, one of them showed no linkage to chromosome 16p; it is of interest that this family was of French-Canadian origin and the only non-European one, which suggests genetic heterogeneity.<sup>8</sup> Another phosphomannomutase gene has been located on chromosome 22q.<sup>9</sup> Matthijs *et al*<sup>10</sup> cloned the phosphomannomutase gene on chromosome 22q (PMM1), and identified a second human gene on chromosome 16p (PMM2) which encodes a protein 66% identical to PMM1. They also found 11 different missense mutations in the PMM2 gene in 16 patients suffering from the carbohydrate-deficient glycoprotein type Ia syndrome. Missense mutations in this gene have also been reported in Japanese patients, and it is suggested that the principle defect is a disturbance in the synthesis of the dolichol-pyrophosphate-oligosaccharide precursor.<sup>11</sup>

The typical pathology on examination of the brain is atrophy of the brainstem and cerebellum. In about a third there is also atrophy of the cortex.<sup>5</sup> Barone *et al*<sup>12</sup> report on patients with typical type Ia syndromes and radiological evidence of olivopontocerebellar atrophy. There was also supratentorial atrophy but it was considered that the variable mental retardation with special impairment of visuo-perceptual skills, eye-hand coordination, visual memory and language may support the role of the cerebellum and brainstem in the acquisition of these skills.

An example of type Ia syndrome has been described by Veneselli *et al*<sup>13</sup> in an eight-year-old boy, with particular attention to the neurophysiological findings. At 3 months of age he showed delayed development, with hypotonia, hyporeflexia, esotropia, nystagmus, and facial dysmorphism. Feeding difficulties and failure to thrive, mild hepatomegaly, and bilateral cryptorchism were present, and tests showed evidence of liver failure and coagulation abnormalities. A computed tomography scan showed mild cerebral and severe cerebellar atrophy. Over the next few years he suffered from defective growth and episodes of liver failure with occasional seizures. A peripheral neuropathy developed, there was optic atrophy and poor retinal pigmentation with an electroretinogram consistent with photoreceptor dystrophy; he remained severely retarded. The phosphomannomutase activity measured in fibroblasts showed a clear deficiency. Electroencephalograms, and a number of multimodal evoked potentials and nerve conduction velocities, were abnormal, and became progressively more so as the disease progressed.

Stibler *et al*<sup>14</sup> reported the findings in 13 patients with type Ia disease who had passed the age of 15 years. All had presented with the early onset of delayed development, mostly with mild facial dysmorphic features and some degree of hepatic dysfunction; and one patient had a pericardial effusion. About half of them had subcutaneous lipodystrophy and comatose or stroke-like episodes

### Clinical findings at different ages in the carbohydrate-deficient glycoprotein syndromes

#### Infancy

- dysmorphic features (at birth and later): esotropia or roving eye movements, inverted nipples, long fingers and toes, joint restriction at knees and hips, fat pads in the pubic area and above the gluteal region (disappear with time), lipodystrophic changes in the buttocks
- neurological involvement: poor sucking, failure to thrive, developmental delay, alternating internal strabismus, hypotonia, hyporeflexia, occasional seizures, stroke-like episodes
- in some infants only: hepatic, cardiac (cardiomyopathy, pericardial effusions), renal cysts, bone abnormalities, hypogonadism, cataracts, deafness, CNS complications
- in Northern Europeans: high nasal bridge, prominent jaw, large pinnae
- in most affected infants: uneventful pregnancy, full-term birth, appropriate birth weight, head circumference normal at birth
- neuroradiology: cerebellar hypoplasia, brainstem atrophy, occasionally more widespread atrophy (delayed or insufficient myelination)

#### Childhood (3–10 years)

- slow development, ataxia and dysequilibrium, muscle weakness (legs more than arms), stroke-like episodes, low IQ (not progressive), speech limited, some with gross motor handicaps and joint contractures, occasional seizures; often happy
- ocular involvement: esotropia, with bilateral abduction deficiency and nystagmoid movements, occasional retinitis pigmentosa and taporetinal degeneration

#### Adulthood

- muscular atrophy (legs more than arms), long thin limbs, short stature, pigeon-barrel chest, contractures of ankle knee and hip joints, kyphoscoliosis, pre-aged skin and subcutaneous tissue, compressed spider bodies, osteopenia
- neurological involvement: seizures, non-progressive ataxia, peripheral neuropathy
- endocrine disturbances: thyroid-binding globulin deficiency, reduced thyroxin level; females lack secondary sexual characteristics and have no puberty and abnormal hormone levels; males may have decreased testicular volume

during childhood. After the age of 15 the disease was mainly characterised by non-progressive ataxia with cerebellar hypoplasia, stable mental retardation, variable peripheral neuropathies, and strabismus. One-third of them had generalised seizures, and they all had retinal pigmentary degeneration and thoratic deformities. None of the females had passed puberty. All had raised serum concentrations of carbohydrate-deficient transferrin. The authors concluded that this type of the syndrome is mainly a non-progressive condition compatible with a socially functioning but dependent life-style.

A type Ib disease has been reported with a deficiency of phosphomannose isomerase due to mutations in the *PMI1* gene. This phenotype is characterised by a protein-losing enteropathy, but neurological disorders are usually absent. Jaeken *et al*<sup>15</sup> reported on three children with normal phosphomannomutase activity and a deficiency of phosphomannose isomerase, two of whom presented with intestinal and liver disease. The first was normal on neurological examination, but died from an unknown cause at the age of four. The second had a similar clinical picture, mainly of liver disease but with mild neurological signs, which disappeared when solid foods were introduced in infancy. Both these enzymes are active in the pathway leading to the synthesis of complex oligosaccharides, and the dissimilar clinical pictures may be due to the varying roles of the enzymes in the carbohydrate metabolism of different organs. The response of the second patient to solid foods suggested that it was possible to treat this potentially fatal condition with oral mannose.<sup>16</sup> In another report of three siblings suffering from this type it was confirmed that phosphomannose isomerase was deficient and that phosphomannomutase was normal.<sup>17</sup> The possibility of this diagnosis should be considered in any unexplained enteropathy or liver disease.<sup>18</sup>

Examples have also been reported of infants with type Ia syndrome of neonatal onset and normal activity of both phosphomannomutase and of phosphomannose isomerase. They had severe thrombocytopenia and respiratory difficulties, and died in spite of intensive care.<sup>19</sup> In type II, the gene encoding for the Golgi-localised N-acetylglucosaminyltransferase enzyme has been cloned, and located on chromosome 14q.<sup>20</sup> The clinical picture in the few children described is much the same, with marked dysmorphic features and severe developmental retardation, but it is of interest that the two children described by Ramaekers *et al*<sup>21</sup> had marked stereotypical behaviour, which in the case of the girl included tongue thrusting and hand-washing movements, similar to those of children with Rett syndrome. The affected child, reported by Jaeken *et al*,<sup>22</sup> was severely retarded, but there was no peripheral neuropathy and the cerebellum was normal.

Two examples of type III were published by Sibling *et al*.<sup>23</sup> Again there were dystrophic features, and initially hypotonia and severe non-progressive retardation, but tetraparesis with brisk reflexes developed, as well as cerebral and optic atrophy, infantile spasms, and pigmentary changes suggestive of incontinentia pigmenti. The first girl had intermittently elevated liver enzyme levels and at the age of 8 years had a stationary, severe, flaccid tetraparesis with areflexia, daily salaam fits, stable café-au-lait skin changes and scoliosis. The second girl had hepatomegaly, a Dandy Walker malformation and hypoplasia of the corpus callosum. Dystonic features have now developed and the clinical picture is very different from type I (Hagberg, personal communication). There is no evidence of polyneuropathy, retinal degeneration, or cerebellar hypoplasia.

Two infants with a fourth type have been described by Stibler *et al*.<sup>24</sup> Both were microcephalic with severe epilepsy and delayed development, and showed dysmorphic features. Several glycoproteins were abnormal, and it was considered that the clinical and glycoprotein differences were sufficient to establish a separate entity.

### The biochemical disorder

In this condition there is a deficiency of the carbohydrate moieties of secretory glycoproteins. Serum transferrin shows the most pronounced carbohydrate defect, both quantitatively and qualitatively, with half of this glycoprotein apparently missing two or four of its terminal trisaccharides. The deficiency of sialic acid, galactose, and N-acetylglucosamine is found in both serum and the liver, and this failure of glycoconjugate synthesis with an abnormal sialic acid transferrin pattern is a highly specific marker for the syndrome.<sup>25 26</sup>

Many glycoproteins are abnormal, including transport proteins, glycoprotein hormones, complement factors, lysosomal and other enzymes, and enzyme inhibitors. Most enzymes are decreased in the serum but some, such as arylsulphatase A, are increased.<sup>27</sup> No doubt these changes are responsible for many of the syndrome's manifestations, especially the phosphomannomutase deficiency shown to be the major cause of type Ia carbohydrate-deficient glycoprotein syndrome. This enzyme is essential for the biosynthesis of N-linked glycans. It

can occasionally show normal activity, and in type Ib there is a deficiency of phosphomannose isomerase.<sup>28</sup>

In type II there is a deficiency of Golgi-localised N-acetylglucosaminyltransferase II, demonstrated in fibroblasts and mononuclear blood cells, and necessary for the biosynthesis of complex and hybrid N-linked glycans.<sup>2</sup>

### Diagnosis

Reference to the box will show the characteristics which should raise the suspicion that a child who is failing to thrive may be suffering from a carbohydrate-deficient glycoprotein syndrome; the physical findings, such as abnormal fat distribution, will particularly help to confirm this, although dysmorphic features may be minimal.<sup>28</sup> Sometimes difficulties can arise if certain features predominate. In one child bone abnormalities were present before the characteristic lipodystrophy in the first few months of life, and the former suggested dysostosis multiplex.<sup>29</sup> A diagnosis can be made quantitatively by chromatographic carbohydrate-deficient transferrin (CDT) assay, or qualitatively by isoelectric focusing of serum transferrin<sup>4</sup>; the isoelectric focusing of glycoproteins showing a cathodal shift because of a partial deficiency of sialic acid, a negatively charged sugar. Dried blood on a filter paper, serum, or cerebrospinal fluid can be used for this purpose. In the CDT test, levels of transferrin elevated 10–20-fold have been found. Then, as mentioned, in type I the final confirmation is finding decreased phosphomannomutase in leucocytes, fibroblasts, and in the liver.

Additional support for the diagnosis can be obtained by finding evidence of some of the known complications of the syndrome, such as decreased coagulation factor XI and antithrombin III causing coagulopathies, and partial thyroxine-binding globulin deficiency, probably due to decreased levels of transport proteins; some patients may be detected on neonatal screening for congenital hypothyroidism with thyroxine measurement.

It is notable that similar slightly increased carbohydrate-deficient transferrin concentrations can be found in some patients with galactosaemia, fructosaemia, primary biliary cirrhosis, rare genetic D-variants of transferrin, and, more importantly in adults, in some patients with chronic alcoholism.<sup>28 30</sup>

Stibler and Cederberg<sup>31</sup> have reported that the neonatal diagnosis of carbohydrate-deficient glycoprotein syndrome in term and near-term newborns, is possible by immune isoelectric focusing of transferrin.

It was thought that the prenatal diagnosis of type I syndrome would be possible by the analysis of the isoforms of glycoproteins in foetal blood or amniotic fluid.<sup>32</sup> However, Clayton *et al*<sup>33</sup> failed to do this by isoelectric focusing of transferrin and  $\alpha_1$ -antitrypsin in foetal blood obtained at 19 weeks gestation, and only found glycoprotein abnormalities in serum from the affected infant 2–3 weeks after birth (corresponding to 37–38 weeks gestation). Stibler and Skovby<sup>34</sup> also examined a twin pregnancy in a family with a previously affected girl. At 11 weeks gestation, chorionic villus biopsy specimens were taken from the separate placentas, and amniotic fluid was collected from both gestations at 17 weeks. All the samples were analysed by immune isoelectric focusing of transferrin and  $\alpha_1$ -fetoprotein, the latter to exclude the contribution of maternal glycoproteins. Carbohydrate-deficient transferrin and total transferrin were determined quantitatively in the amniotic fluid. The results were considered to be normal compared with age-matched controls. However, at birth both twins showed signs of the disease, confirmed by the relevant tests on the serum. Therefore, with the techniques used, circulating carbohydrate-deficient glycoproteins resulting from the primary biochemical defect must appear sometime between the 19th and 36th gestational week. The diagnostic failure before then may be due to maternal metabolism compensating for the defect in the foetus, or to developmental regulation.

### Prognosis

There is a high mortality in the first few years of life due to severe infections, status epilepticus, liver insufficiency, renal failure, or cardiomyopathy.<sup>10</sup> Jaeken and Casaer<sup>2</sup> record a mortality of about 20% from these causes.

Post-mortem findings include olivopontocerebellar atrophy, loss of neurons and gliosis in the cerebral cortex, basal ganglia, thalamus, and spinal cord. The peripheral nerves show decreased myelin and multivacuolar inclusions in the Schwann cells. Other findings include renal cysts, fibrosis of the liver with steatosis and glycogen storage, fibrosis of the testes, and lymph node abnormalities. The neuropathy suggests an error of macromolecular metabolism,<sup>35</sup> and electron microscopy of liver cells shows lysosomal vacuoles with concentric electron-dense membranes and variable electron-lucent and electron-dense material. In

one report, there was no evidence of progression on a second biopsy.<sup>36</sup> The presence of lysosomal storage of an unknown nature affecting the anterior horn cells has been reported as an unusual finding.<sup>37</sup>

There is no doubt that olivopontocerebellar atrophy is a common finding in this condition, and the cause of the ataxia,<sup>38</sup> although as it can be absent it is not a reliable marker for the disorder.<sup>39</sup> It seems likely, as suggested by Jaeken,<sup>40</sup> that the two siblings with olivopontocerebellar atrophy reported by Harding *et al*<sup>41</sup> were suffering from carbohydrate-deficient glycoprotein syndrome. Similar pathological abnormalities were found in the first example of this disease recorded in Australia<sup>42</sup>; it is certainly recognised that the cerebellar and brainstem pathology is an end point for a number of different clinical and genetic disorders.

### Treatment

It has been reported that mannose was able to correct glycosylation in fibroblasts with phosphomannomutase deficiency in type Ia disorder.<sup>43</sup> Jaeken and Casaer<sup>2</sup> have therefore tried oral and intravenous mannose; however, so far no significant results have been obtained. Mayatepek *et al*<sup>44</sup> gave mannose by continuous intravenous infusion for 3 weeks to an affected boy aged 11 months, but this only resulted in slight biochemical changes. However, infusion of mannose in type Ib can be effective.<sup>16</sup>

As in so many conditions for which there is no specific treatment, it is important to ensure that complications are adequately managed, whether these are renal, cardiac, haematological, or neurological. Speech and occupational therapy may be helpful, and the family will almost certainly need additional support.

### Conclusions

It seems likely that, as suggested by Gahl,<sup>45</sup> there are a number of conditions due to defects in the modification of glycoproteins by carbohydrates still to be discovered. These may affect various organs in the body, and their identification will depend on maintaining a high level of suspicion. They occur world-wide, and as each entity is likely to be rare, this is a field of study that may especially benefit from international cooperation.

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