Venous thromboembolic disease in childhood epidemiology, risk factors and outcome
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Chapter 4

Carbohydrate-deficient glycoprotein syndrome type 1a: a variant phenotype with borderline cognitive dysfunction, cerebellar hypoplasia, and coagulation disturbances.

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Abstract

An 8-year-old boy is described with borderline cognitive impairment, cerebellar hypoplasia, a stroke-like episode, and venous thrombosis of the left leg after a period of immobilization. The pattern of multiple abnormalities in blood coagulation suggested carbohydrate-deficient glycoprotein syndrome type 1a. Isoelectric focusing of serum transferrin was abnormal. The activity of phosphomannomutase in leucocytes and fibroblasts was decreased. Mutation analysis of the \textit{PMM2} gene revealed the R141H/E151G genotype. These results confirm the presence of carbohydrate-deficient glycoprotein syndrome type 1a without severe psychomotor retardation.
Introduction

Carbohydrate-deficient glycoprotein syndromes are genetic disorders affecting multiple organ systems, first described by Jaeken et al. in 1980. The characteristic biochemical feature consists of hypoglycosylation of glycoproteins, readily demonstrated by isoelectric focusing of serum transferrin. Four basic defects have been identified: phosphomannomutase (PMM) deficiency (EC 5.4.2.8.), phosphomannoisomerase deficiency (EC 5.3.1.8.), deficient glucosylation of the dolichol-linked oligosaccharide, and N-acetyl-glucosaminyltransferase II deficiency (EC 2.4.1.143). The most common is CDG syndrome type la, which is caused by PMM deficiency. The gene coding for PMM is on chromosome 16p. The clinical variability of CDG syndrome type la is broad, comprising severe mental deficiency, dysmorphism, cerebellar hypoplasia, and coagulation disturbances.

This report expands the spectrum of CDG syndrome type la with the description of an affected patient with borderline cognitive dysfunction and absent external dysmorphism.

Case report

The patient is an 8-year-old son of non-consanguineous white parents, born at term after a normal pregnancy. His birth weight was 3250 g. No dysmorphism was observed, especially no inverted nipples and no fat pads. Length growth followed the 50th percentile, and weight evolution was between 3rd and 10th percentiles. Examination at 9 months revealed bilateral convergent strabismus with intact range of eye movements on lateral rotation, spasmus nutans, hand dysmetria, and titubation. Cranial computed tomography scan demonstrated cerebellar hypoplasia. At 16 months, he propelled himself by shuffling. At 18 months, he was able to stand with hand support, and he had adequate balancing reactions but displayed postural tremor. Eye pursuit at the time was slow with nystagmus. By 22 months, he could walk without support but was ataxic. At the age of 2 years, receptive language was adequate, but expressive language was delayed. A Reynell language test at 34 months showed receptive language (understanding) at the level of 39 months and general cognition at the level of 32 months. At 6 years of age, reading, writing, and receptive and expressive language were considered appropriate for age by the school. Formal intelligence testing at the age of 8 years disclosed full-scale IQ of 69, verbal IQ of 75, and performance IQ of 68 (Wechsler Intelligence Scale for Children-Revised).

At the age of 7 years, he was admitted to the hospital after sudden onset of left-sided hemiparesis and seizures. Left-sided hemianopia, central left facial paresis, and left hemiparesis were seen with left Babinski’s sign. Hematological parameters were normal. Cerebrospinal fluid showed a normal number of white cells with normal glucose and total protein. Bacterial and viral cultures of cerebrospinal fluid were negative. Brain magnetic resonance imaging demonstrated a diffusely swollen right hemisphere without abnormalities of the white matter, as well as cerebellar hypoplasia (Figure). No signs of
hematoma, thrombosis, or infarction were present. He made a slow but full recovery and was discharged after 10 days. Three months after the episode, the right hemisphere appeared normal on brain magnetic resonance imaging.

Three weeks after discharge, he was readmitted because of a swollen painful left leg. Ultrasonography confirmed the clinical suspicion of thrombosis of the left iliac and femoral veins. Treatment was initiated with standard heparin administered intravenously, followed by oral anticoagulant therapy during 6 months. Plasma levels of coagulation factor V (0.73 U/ml, normal range = 0.8 - 1.4 U/ml), factor VII (0.54 U/ml, normal range = 0.8 - 1.4 U/ml), factor XI (0.34 U/ml, normal range = 0.5 - 1.5 U/ml) and factor XII (0.4 U/ml, normal range = 0.5 - 1.5 U/ml) were decreased, as well as levels of coagulation inhibitors antithrombin (0.49 U/ml, normal range = 0.8 - 1.4 U/ml), protein C (0.26 U/ml, normal range = 0.65 - 1.1 U/ml) and free protein S (0.23 U/ml, normal range = 0.26 - 0.61 U/ml). Both plasma levels of thrombin-antithrombin complex (11.4 μg/L, normal range < 4.6 μg/L) and prothrombin fragment 1 +2 (2.32 nmol/L, normal range = 0.3 - 1.6 nmol/L) were increased. Factor V R506Q mutation and factor II G20210A mutation were absent and anti-phospholipid antibodies were not detectable. Because of the unexplained stroke-like episode and the multiple abnormalities in blood coagulation, the diagnosis of

Figure. T₁-weighted coronal magnetic resonance imaging section of brain demonstrating pancerebellar hypoplasia
Carbohydrate-deficient glycoprotein syndrome type 1a

CDG syndrome was considered. Blood analysis showed an increased level of carbohydrate-deficient transferrin of 125.3 U/L (control subjects, < 30 U/L), and isoelectric focusing of serum transferrin revealed a marked increase of asialo- and disialo-transferrin (type 1 pattern). PMM activity, as described by Van Schaftingen and Jaeken', was decreased in leucocytes (0.5 nmol/mg.min, control subjects [n=10] = 2.5 ± 0.4 nmol/mg.min) and in fibroblasts (Table), confirming the diagnosis of CDG syndrome type 1a. Mutation screening by single-stranded conformational polymorphism analysis and by sequencing showed a combination of the R141H and E151G mutation.

Table. Phosphomannomutase activity in fibroblasts from the patient described in this report, a patient with "classical" type 1a, and healthy control subjects

<table>
<thead>
<tr>
<th></th>
<th>Phosphomannomutase activity (nmol/mg.min)</th>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>Patient described in this report</td>
<td>0.3</td>
</tr>
<tr>
<td>Patient with &quot;classical&quot; type 1a</td>
<td>0.12</td>
</tr>
<tr>
<td>Healthy control subjects (n=6)</td>
<td>4.33</td>
</tr>
</tbody>
</table>

Mean of 6 measurements

Discussion

Since the first report of a patient with CDG syndrome type 1a by Jaeken et all, about 200 patients have been identified. The clinical presentation of CDG syndrome type 1a is characterized by severe neurological abnormalities, dysmorphism, and variable involvement of other organs.[11][12] The neurological features are age-related. Hypotonia, muscular weakness, developmental retardation, and alternating esotropia and hyporeflexia can be observed in the neonatal and infantile periods. After infancy, motor skills develop slowly. Most children can sit without support at the age of 2 years and move independently by shuffling. After the age of 2 to 4 years they are able to stand with support, but only very few patients learn to walk. Muscular atrophy progresses slowly. Tendon reflexes in the lower limbs cannot be elicited after the first 2 to 3 years of life. Cerebellar ataxia and coordination difficulties are common findings. Contractures gradually develop. Stroke-like episodes occur, sometimes in combination with infections, after the age of 4 to 5 years. Retinitis pigmentosa will develop after 3 to 8 years. Mental development is retarded and reaches a median IQ of 40 to 60. The main neuroradiologic finding is cerebellar hypoplasia, which is present in most of the patients.11

Non-neurological features that can be present are slight facial dysmorphism, abnormal subcutaneous fat distribution ("peau d’orange"), inverted nipples, mild
hepatomegaly and hypogonadism. Some patients have pericardial effusions and/or cardiomyopathy. Most of the multi-organ manifestations are present in the infantile period and appear to regress during childhood.

Blood coagulation disorders are a common feature of CDG syndrome type 1a. The most constant findings are reduced activities of antithrombin, protein C, and factor XI. Decreased protein S activity is found less frequently. Although all coagulation factors and inhibitors are glycoproteins, they are not equally affected. The degree of coagulation factor and/or inhibitor deficiency varies among patients and can be severe or mild.

In our patient, cerebellar ataxia and a stroke-like episode causing temporary hemiparesis were the most prominent neurological symptoms. In contrast to previously reported patients with CDG syndrome type 1a, in this patient cognitive dysfunction was borderline and motor retardation was minor, mainly caused by ataxia. Lack of severe psychomotor retardation led to the delay in diagnosis.

Venous thrombosis has been reported in at least 3 patients with CDG syndrome type 1a. One patient had bilateral iliac and pelvic vein thrombosis after 3 weeks of immobilisation for cerebral concussion. Plasma levels of antithrombin and protein C activity were decreased. Our patient also had venous thrombosis after immobilisation. His blood coagulation analysis showed decreased plasma levels of antithrombin, protein C, and free protein S, causing increased thrombin generation as measured by elevated thrombin-antithrombin complex and prothrombin fragment 1+2. In general, venous thrombosis in childhood has multiple causes, and more than 2 laboratory or clinical risk factors are often required to precipitate thrombosis. Thus primary prophylactic anticoagulant therapy for a certain period may be considered in patients with CDG syndrome type 1a and decreased coagulation inhibitors, especially when additional risk factors for venous thrombosis are present.

Mutation analysis revealed the R141H/E151G genotype. The R141H substitution is the most frequent mutation in CDG type 1a patients. It is suggested that R141H is a severe mutation caused by lack of homozygotes for R141H. The E151G mutation has not been described before. E151G is conserved between PMM1 and PMM2. Fungal phosphomannomutases show a histidine at this position, suggesting that E151G might give rise to the mild phenotype as demonstrated in our patient. However, little is known about the relation between the genotype and the clinical phenotype of patients with CDG type 1a patients.

CDG syndrome type 1a should be ruled out in children with cerebellar hypoplasia and/or multiple coagulation disturbances, even in the absence of severe psychomotor retardation and external dysmorphism.

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Carbohydrate-deficient glycoprotein syndrome type 1a

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References


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