TEACHING CASE REPORT

A child with an underrecognized form of developmental delay: a congenital disorder of glycosylation

The case: A 7-month-old boy was referred to the pediatric clinic with developmental delay and failure to thrive. His parents were nonconsanguineous. His family history and antenatal course were unremarkable, and he was delivered vaginally without complications, weighing 2.6 kg.

The child had difficulty swallowing and insufficient caloric intake from birth and had had several episodes of irritability and vomiting, which suggested gastroesophageal reflux. He was delayed in all aspects of development, with substantial global developmental delay and visual problems detected at 3 months of age. At 7 months of age he was unable to lift his head in the prone position and was unable to roll or sit. He had begun cooing and smiling but was not babbling. He was alert to sound but was unable to fix on and follow objects. He had no regression of milestones and had not experienced seizures.

On examination at 7 months of age, the patient weighed 5.84 kg (below 3rd percentile), was 66.8 cm long (below 15th percentile) and had a head circumference of 43 cm (10th percentile). His weight was only 78% of ideal. Find-

ings on cardiovascular examination were unremarkable, and his chest was clear. However, he had inverted nipples (Fig. 1). His liver was slightly enlarged, and no splenomegaly was detected. His testes were undescended. Ophthalmologic consultation revealed strabismus and visual impairment, with rod and cone dysfunction evident on an electroretinogram. The child's face was symmetric. He had central hypotonia, with slightly increased peripheral tone, and reduced deep-tendon reflexes. Plantar reflexes were normal, and there was no clonus. There were prominent fat pads on his fingers (Fig. 2) and in the inguinal and supragluteal regions.

Laboratory investigation showed that the child was not anemic but that his transaminase levels were increased. His γ-glutamyltransferase and albumin levels and international normalized ratio were normal, but his activated partial thromboplastin time was prolonged (39.9 [normal 23–35] seconds). He had proteinuria (3.0 g/L) but no hematuria. Levels of several coagulation factors (factor XI, antithrombin, protein C and protein S) were low.

Fig. 1: Inverted nipples of 7-month-old boy with developmental delay.

Fig. 2: Prominent fat pads on fingers (arrow).

Fig. 3: MRI of the head, showing diffuse loss of cerebellar volume (arrow).

Ultrasound of the abdomen showed hepatomegaly with no ascites. There was a diffuse, coarse, hyperechoic pattern to the liver. MRI of the head revealed marked diffuse loss of cerebellar volume (Fig. 3), including in the vermis, with increased signal and a delayed pattern of myelination.

The child was felt to have a phenotype classic of the congenital disorder of glycosylation type Ia (CDG-Ia). Results of isoelectric focusing of transferrin were abnormal, which suggested CDG. CDG-Ia was confirmed by means of the phosphomannomutase 2 (PMM2) enzyme activity assay on cultured skin fibroblasts and mutation analysis.

The differential diagnosis of developmental delay is broad. However, in a patient such as ours who has many systems affected (brain, eyes, skin, liver, kidneys), a multisystem disease is suggested. In this case, the phenotype matched that of CDG-Ia, and results of specific functional (enzyme assays) and genetic tests confirmed the diagnosis.

CDGs are an inherited group of metabolic disorders due to defects in post-translational modification of glycosylated peptides.[1] This group of disorders was first described in the 1980s. The inheritance pattern is autosomal recessive. Over 500 genes are involved
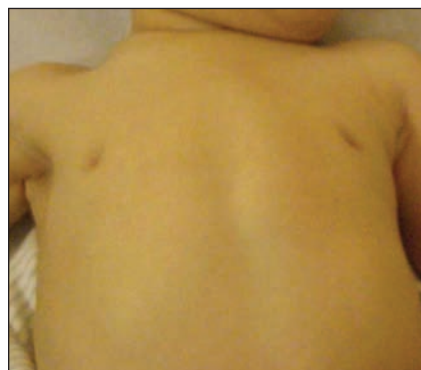
> **Box 1: Clinical features of congenital disorder of glycosylation type Ia**
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> | Skin | Inverted nipples, abnormal subcutaneous fat pads at birth; fat pads disappear with increasing age |
> | Neurologic | Global developmental delay; axial hypotonia, reduced deep-tendon reflexes, cerebellar atrophy, epilepsy; joint contractures, most children do not walk without support; stroke-like episodes |
> | Nutrition/ gastrointestinal | Feeding problems (need for tube feeding common), gastroesophageal reflux, failure to thrive, hepatitis, liver failure |
> | Ophthalmologic | Strabismus, impaired night vision, retinitis pigmentosa |
> | Cardiac | Hypertrophic cardiomyopathy, pericardial effusion |
> | Renal | Nephrotic syndrome early in life, renal cysts |
> | Hematologic | Coagulation disorder (thrombosis or hemorrhage) |

> **Box 2: Differential diagnosis of global developmental delay**
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> - Infection (congenital)
> - Trauma
> - Exposure to toxins
> - Uncontrolled seizures
> - Asphyxia or hypoxic ischemic encephalopathy
> - Structural brain abnormality
> - Genetic, syndromic or neurocutaneous disorder
> - Inborn error of metabolism
> - Endocrinopathy
> - Severe environmental deprivation or neglect
> - Malnutrition or failure to thrive

in glycosylation processes, and half of the body's proteins are glycoproteins. Thus, disorders of glycosylation encompass many diseases with diverse presentations, and they may involve one or many systems.

CDGs are believed to affect people of any ethnic background, and the estimated prevalence is 1.5 per 100 000 population. It is thought that CDGs are underrecognized, with some patients being diagnosed as having cerebral palsy.

CDG-Ia is the most common type of congenital glycosylation disorder reported in childhood.[2] Patients with CDG-Ia may have neurologic disease only or neurologic disease and multisystem involvement (see Box 1). Unlike children with some inborn errors of metabolism, those with CDG do not typically have developmental regression. It is now recognized that some children may have only mild neurologic symptoms with normal intelligence. The rate of death among infants with CDG-Ia is about 20%.

Isoelectric focusing of transferrin is a screening test for CDG. It cannot reliably identify the subtype of CDG, and not all types can be detected this way. This blood test relies on a difference in the number of sialic acid side chains on the glycoprotein, with the resulting change in the net charge of the glycoprotein affecting the migration patterns on the gel. In CDG-Ia, mutations of the *PMM2* gene on chromosome 16p13 result in a deficiency of the PMM2 enzyme. This enzyme converts mannose 6-phosphate to mannose 1-phosphate, and a deficiency results in abnormal glycosylation. PMM is widely expressed in the body, which explains the multi-system disease associated with this condition. The disorder is confirmed by identification of gene mutations or by decreased PMM enzyme activity in fibroblast cultures.

Global developmental delay refers to significant delay in 2 or more developmental domains: motor, speech/ language, cognition, social/personal and activities of daily living. The differential diagnosis of global developmental delay in childhood is broad (see Box 2). A thorough history and physical examination should guide the choice of other laboratory and radiologic investigations. Good algorithms for the evaluation of developmental delay in children are useful tools in practice.[3] Identifying a cause is important for counselling parents on the prognosis and the risk recurrence for future pregnancies, for instituting specific therapies if available and for managing associated conditions.

In the case we have described, features that pointed toward a diagnosis other than cerebral palsy were the child's nonspecific but unusual findings of inverted nipples, fat pads, reduced deep-tendon reflexes and multisystem involvement. CDG is a relatively new group of disorders with an expanding phenotype. CDG should be considered in children with developmental delay, those with gastrointestinal disease such as chronic diarrhea with protein loss or hepatitis, and children with multi-system disease involving neurologic, gastrointestinal, ophthalmologic, cardiac or endocrine systems.

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