

## CASE REPORT

## Neonatal severe intractable diarrhoea as the presenting manifestation of an unclassified congenital disorder of glycosylation (CDG-x)

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### Abstract

**A case of severe and protracted diarrhoea is reported, which started in the neonatal period and progressively associated with neurological impairment, dysmorphism, hepatosplenomegaly, and hepatic insufficiency, from which the patient died at 2 years of age. Isoelectric focusing of serum transferrin showed a congenital disorder of glycosylation type I pattern but the basic defect could not be identified. This observation shows that congenital disorder of glycosylation is a cause of intractable diarrhoea in neonates.**

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Keywords: diarrhoea; protein losing enteropathy; hepatic insufficiency; neurological impairment

Congenital disorders of glycosylation (CDG) are inherited metabolic diseases, characterised by defects in the glycosylation of N-glycoproteins. Type Ia CDG was first reported in 1980 by Jaeken *et al.*<sup>1</sup> This autosomal recessive disease, the result of deficient phosphomannomutase (PMM) activity, is by far the most common CDG and is characterised by neurological impairment, dysmorphism, feeding difficulties, and failure to thrive. A number of other types have been reported since 1980, secondary to deficient phosphomannose isomerase (PMI), diphosphoglucosyltransferase, diphosphomannosyltransferase, dolichol-P-mannose synthase, N-acetylglucosaminyltransferase II, and glucosidase (types Ib, Ic, Id, Ie, IIa, and IIb respectively).<sup>2</sup> Unclassified CDG is named CDG-x. We report on a boy presenting neonatally with severe and protracted diarrhoea, showing a CDG-x with a type I sialotransferrin pattern.

### Case report

Our patient was the first child of healthy unrelated parents without significant medical history. The pregnancy was uneventful. The boy was born at 36 weeks of gestation by spontaneous delivery. Birth weight was 2400 g (35th percentile), length was 46 cm (35th percentile), and head circumference was 33 cm (50th percentile). The Apgar score was 10 at one and

five minutes. Because of premature rupture of the membranes, the patient was admitted to hospital at the age of 2 days. His platelet count was 83 000/mm<sup>3</sup> (normal range 150–300 000/mm<sup>3</sup>), and C reactive protein was 6 mg/l (normal < 3 mg/l). Antibiotic treatment was started and stopped after four days. Bacterial and viral infections were ruled out.

After two weeks of well tolerated feeding with a cow milk formula, he developed severe watery bloodless diarrhoea. This was associated with oedema related to profound hypoalbuminaemia (albumin level 11 g/l; normal range 30–35 g/l), and he was referred to the gastrointestinal unit. Thrombocytopenia persisted (110 000/mm<sup>3</sup>), associated with an increased activated partial thromboplastin time (220 seconds/31 seconds), isolated factor XI deficiency (3%; normal > 60%), and hypogammaglobulinaemia (IgG level 1.4 g/l; normal range 8.5–13.5 g/l; IgA level 0.09 g/l; normal range 0–0.5 g/l; IgM level 0.1 g/l; normal range 0.06–0.16 g/l). Liver function tests were normal. Protein losing enteropathy was confirmed by an abnormal clearance of  $\alpha_1$  antitrypsin (50 ml/24 hours; normal range 1–5 ml/24 hours). Blood, urine, and faecal analyses and stool examinations for pathogens were normal. Total and protein milk specific IgE levels were within normal range, and no systemic autoantibodies were detected. Diarrhoea persisted despite the use of an 85% medium chain triglyceride diet (Portagen; Mead Johnson, Nijmegen, The Netherlands) and led to the use of total parenteral nutrition.

The secretory nature of the diarrhoea was confirmed by its persistence in spite of total parenteral nutrition. There was no biochemical feature suggestive of osmotic diarrhoea as the stool pH  $\geq$  6 and stool osmolality ranged from 295 to 310 mOsmol/l. Radiological, endoscopic, and histological examination (periodic acid-Schiff staining, immunohistochemical investigations, and indirect immunofluorescence) of the upper and lower digestive tract showed it to be normal, ruling out microvillus atrophy, autoimmune enteropathy, and intestinal lymphangiectasia.

The neurological status of the patient progressively worsened, signs including axial hypotonia, psychomotor retardation, and a

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happy appearance without ocular tracking. His dysmorphism was characterised by retrognathia, microstomia with thin lips, small nose with anteverted nose tip, almond eyes, and bilateral clinodactyly of the fifth finger. His lymphocyte karyotype was normal. Electroencephalograms and computed tomography scans of the brain were also normal. No response was observed during auditory and visually evoked potentials.

At 4 months of age, hepatosplenomegaly appeared, associated with slightly increased transaminases (serum glutamate oxaloacetate transaminase 72 IU/l; normal < 40 IU/l; serum glutamate pyruvate transaminase 97 IU/l; normal < 40 IU/l) and evidence of hepatic insufficiency (prothrombin time 45%; normal > 60%). Thrombocytopenia persisted (120 000/mm<sup>3</sup>) associated with low levels of protein C (30% of normal) and antithrombin III (15% of normal). In addition, there were low levels of serum glycoproteins such as hapto-globin (< 0.08 g/l; normal range 0.5–2.5 g/l), transferrin (1.2 g/l; normal range 2.4–3.8 g/l), and thyroid stimulating hormone (0.3 µIU/ml; normal range 0.4–3.6 µIU/ml). Isoelectric focusing of serum transferrin showed a CDG type I pattern: increase in both asialotransferrin and disialotransferrin, and decrease in the tetra, penta, and hexa forms. Oral mannose treatment had no effect, except to intensify the diarrhoea. As analysis of the patient's cultured fibroblasts showed normal PMM and PMI activities, the subtype of this CDG remains to be defined (CDG-x).

At 21 months of age, his weight was 11 kg (0.5 SD below the normal range), his length was 80 cm (– 1 SD), and head circumference was 46 cm (– 2 SD). Because of persistent diarrhoea, the child was still receiving total parenteral nutrition. His neurological status was worsening with generalised convulsions, and the hepatic insufficiency was slowly aggravating (prothrombin time 35%). The patient died at the age of 24 months from hepatic insufficiency.

## Discussion

Protein losing enteropathy, coupled with intractable diarrhoea and liver disease, are the leading signs of type Ib CDG.<sup>2–3</sup> Diarrhoea has also been reported in infants presenting with type Ia CDG.<sup>3</sup> It is well recognised that patients with CDG of the same type may present with appreciable clinical differences; it has recently been suggested that in CDG-Ia the type of mutation in the PMM gene may influence the severity of the phenotype of the disease.<sup>4</sup> Our patient did not present with any of the multisystem abnormalities of type 1 such as abnormal subcutaneous fat deposition, pericardial effusion, cataract, retinitis pigmentosa, and hyperinsulinism. Type Ib CDG is associated with coagulation abnormalities (thrombosis or bleeding resulting from deficiency in protein C, protein S, or antithrombin III), but without any psychomotor retardation.<sup>5–6</sup> Gastrointestinal symptoms characteristic of the type Ib CDG always started after the neonatal period in the eight reported cases (age of onset

ranged from 2 months to 11 months).<sup>5</sup> Digestive symptoms varying from isolated diarrhoea to severe protein losing enteropathy requiring parenteral nutrition, associated with hepatic abnormality (hepatomegaly, cytolysis, or hepatic insufficiency) were reported to improve with mannose treatment or spontaneously with time. However, two of the patients died (at 2 and 4 years) from an unknown cause.<sup>5–7–8</sup> Oral administration of mannose corrected the clinical phenotype as well as the hypoglycosylation of serum glycoproteins in CDG-Ib, but not in the other CDG types.<sup>6</sup> CDG-Ib was enzymatically excluded in our patient.<sup>9</sup> The number of patients with CDG syndrome not belonging to any of the known types is increasing. Most of them show a type 1 pattern of isoelectric focusing of serum transferrin, as did our patient. The basic defect in our patient is still not known.<sup>2</sup> Two previously reported patients with CDG-x, who presented with diarrhoea, protein losing enteropathy, liver disease, and thrombocytopenia, died from respiratory failure at 15 and 58 days of age.<sup>10</sup> Mannose treatment, started before the results of the enzymatic analysis on fibroblasts, was unsuccessful in our patient.<sup>6</sup> Hepatic insufficiency and protein losing enteropathy associated with severe neurological degradation persisted despite 24 months of total parenteral nutrition.

Severe and intractable diarrhoea of infancy is relatively uncommon in industrialised countries and constitutes a heterogeneous group of diseases including post-enteritis syndrome, food intolerance, familial microvillous atrophy, autoimmune enteropathy, intestinal lymphangiectasia, eosinophilic enteropathy, intestinal pseudo-obstruction, and epithelial and basement membrane abnormalities.<sup>11–12</sup> In about half of the cases, the pathogenic diagnosis and cause cannot be defined. From our data, we recommend looking for CDG in cases of severe, protracted, and intractable neonatal diarrhoea.

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