Exceptional Cases

Congenital disorders of glycosylation: a rare cause of nephrotic syndrome

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Abstract

Congenital disorders of glycosylation (CDG) are inborn errors of metabolism presenting with multi-system organ involvement due to defective glycosylation of glycoproteins. We report here a case of microcephaly, hypotonia, seizure disorder and severe developmental delay since infancy in whom screening for CDG with transferring isoelectric focussing (TIEF) revealed a type I pattern. Following investigation, the specific defect in glycosylation remains to be identified; hence, a diagnosis of CDG Ix (type unknown) was made. At the age of 15-months the patient developed nephrotic syndrome and renal biopsy indicated a histopathological diagnosis of diffuse mesangial sclerosis on histopathology. Since cases of CDG Ix may often develop hypoalbuminaemia secondary to malabsorption or liver disease, this case highlights the need for additional regular monitoring for glomerular proteinuria, and indicates that a diagnosis of nephrotic syndrome should be considered in all types of CDG. Furthermore, we propose that early treatment with anti-proteinuric agents may be necessary to limit proteinuria and slow disease progression.

Keywords: congenital nephrotic syndrome; CDG; nephrotic syndrome; proteinuria

Introduction

Congenital disorders of glycosylation (CDG) are a group of inherited disorders due to defects in the synthesis of glycans of glycoproteins or other glycoconjugates, antennalike oligosaccharide structures that are important for their function. N-Glycosylation involves the formation of the nucleotide-linked sugars in the cytosol, the stepwise assembly of the oligosaccharide precursor within the cytosol and endoplasmic reticulum and the subsequent processing of the glycan in the golgi pruning and attaching various sugars to produce the final structure. Due to the ubiquitous distribution of glycosylated proteins, CDGs have multi-organ involvement and therefore present with a variety of symptoms including developmental delay, hypotonia, seizures, protein-losing enteropathy, liver disease and dysmorphic features in some subtypes [1,2]. The majority of CDGs present in infancy.

Congenital nephrotic syndrome (CNS) refers to a presentation of clinical nephrosis before 3-months of age and infantile nephrotic syndrome refers to presentations with clinical nephrosis between 3–12 months of age. The so-called Finnish-type of CNS is the commonest cause of CNS presenting in the first year of life and is due to NPH1 gene mutations.

CNS in patients with CDG has previously been reported in three patients all with CDG type I (one patient CDG Ia; two patients CDG I unclassified) and severe neurological involvement [3–5]. We report here another case of nephrotic syndrome with unclassified CDG type I (CDG Ix) and briefly review the literature describing renal involvement in patients with CDG.

Case description

A term male infant presented at 3 months of age with seizures. At presentation, he was noted to have microcephaly, central hypotonia with peripheral hypertonia, hyperreflexia, roving eye movements and dysmorphic features including high arched palate and narrow palpebral fissures. Seizure activity was confirmed on electroencephalogram (EEG), and magnetic resonance imaging (MRI) of the head revealed a markedly deficient corpus callosum, cerebellar vermis hypoplasia and a generalized reduction in myelination. There was no electrical activity on visual evoked response testing and electro-retinogram, but the brainstem auditory evoked responses were normal. Investigations for a metabolic aetiology performed at this time confirmed normal levels of urine amino acids and organic acids. Urine purine studies were also normal. Blood measurements including levels of plasma amino acid, bile acids, phytic acid, biotinidase, ammonia, urate, vitamin B\(\text{12}\) and lactate...
were normal. Thyroid function was also normal. There was no documented episode of hypoglycaemia, urinary ketones and/or metabolic acidosis. Investigations also ruled out the presence of any disorder of galactose or fructose metabolism.

CDG was diagnosed following atypical distribution of transferrin glycoforms with a type I pattern with increased diasialotransferrin and asialotransferrin with decreased tetrasialotransferrin. A repeat transferrin isoelectric focussing (TIEF) test confirmed the abnormal transferrin glycoform pattern of CDG type I, but white blood cell enzymology excluded CDGs Ia and Ib (phosphomannomutase 1.2 nmol/min/mg protein-control range 0.9–2.3; phosphomannose isomerase 14.1 nmol/min/mg protein-control range 5.3–13.2). Hence, a diagnosis of CDG Ix (type unclassified) was made.

Echocardiogram and abdominal ultrasound studies confirmed a normal heart and no liver abnormalities. Both kidneys were of normal size with normal cortico-medullary differentiation. Clotting studies revealed the presence of low anti-thrombin III and low protein C levels but normal factor VIII, factor XI and protein S levels. His clinical course subsequently was that of a severe seizure disorder requiring multiple anti-epileptic medications and progressive severe developmental delay. There was further clinical deterioration in his seizure control after 9 months of age.

At the age of 15 months, he presented with generalized oedema, oliguria, nephrotic range proteinuria, severe hypoalbuminaemia and hypertension. A percutaneous renal biopsy was performed but was complicated by post-biopsy haemorrhage requiring blood transfusion. Biopsy findings showed early diffuse mesangial sclerosis with focal dilatation of tubules with intra-epithelial protein resorption droplets, but no evidence of interstitial scarring or atrophy. There was diffuse deposition of IgM and C1q. Electron microscopy showed diffuse effacement of foot processes but no electron-dense deposits (Figures 1 and 2).

The review of his case notes, following acute presentation with nephrotic syndrome, confirmed hypoalbuminaemia since early infancy, with a plasma albumin ranging from 36 g/L at 5 months of age to 29 g/L at 9 months of age and 24 g/L at 10 months of age. He developed systemic arterial hypertension in conjunction with nephrotic syndrome and required three-drug combination anti-hypertensive therapy to adequately control his blood pressure. His renal function remained normal during the entire course of his illness. Soon after presentation with NS, he developed a persistent oxygen requirement and continued to deteriorate clinically. In view of an unlikely response to glucocorticoids or other immunosuppressive therapy, his NS was treated conservatively with diuretics and ACE inhibitors. This failed to improve his clinical condition, and he went on to receive palliative care until his death at 17 months of age.

Discussion

CDG is a group of metabolic disorders that develop due to defects in the synthesis of the glycan moiety of glycoproteins or other glycoconjugates [1,2]. The defects in protein N-glycosylation are essentially of two types that constitute a complex pathway involving assembly and processing of proteins and are performed in three cellular compartments, the cytosol, endoplasmic reticulum and the Golgi apparatus. Type I is defects in the assembly and transfer of the lipid-linked oligosaccharide to the recipient protein (mainly
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within the endoplasmic reticulum). Type II is defects in the processing of the protein-bound glycan (within the Golgi). Approximately 40 genes are needed for the assembly and transfer of the oligosaccharide to the protein and at least 20 genes for further processing of the protein-bound glycan. A total of 22 N-glycosylation defects have been defined to date designated CDG Ia to CDG In and CDG IIa to CDG Iih. CDG Ia is by far the most frequent subtype and is due to the deficiency of phosphomannomutase-2 (PMM2). Many remain unidentified and are known as ‘CDG x’.

CDG Ia can present as a multisystem disease with a range varying from a mild to severe degree of clinical organ dysfunction and dysmorphology [6]. Although this patient was not dysmorphic, he showed several characteristic findings of CDG Ia including microcephaly, central hypotonia, seizure disorder, failure to thrive and severe developmental delay [6]. Further clinical evidence for CDG Ia was through the presence of typical neuroimaging findings, including cerebellar and brain stem atrophy [7,8] and clotting factor abnormalities [8]. The clinical diagnosis was further supported by the demonstration of the CDG I pattern on TIEF although finally we were unable to further type the CDG on white blood cell and fibroblast enzyme studies.

Patients with CDG generally do not have overt renal pathology, but renal involvement is often detected in them when investigated for the presence of multisystemic disease. The most common abnormalities are medullary and cortical microcysts occasionally associated with enlarged kidneys [9–11], demonstrated on post-mortem examination [9,11–14]. Hertz-Pannier et al. recently reported bilateral hyperechoic kidneys on ultrasonography in patients with multisystem involvement with CDG Ia, one patient with CDG Ib and one with CDG Ix [14]. In addition, Olczak et al. have reported abnormal glycosylation of the Tamm–Horsfall protein in one patient with CDG I [15].

All three patients with CDG I (one patient CDG Ia; two patients CDG I unclassified) and congenital NS have been previously reported in the literature [3–5]. The patient with CDG Ia presented with neurological involvement but without the characteristic ponto-cerebellar atrophy [4]. The renal biopsy findings of this patient also showed evidence of early diffuse mesangial sclerosis and focal dilatation of tubules with protein resorption droplets. IgM and C1q deposits were identified by immunoperoxidase with diffuse effacement of the foot processes confirmed by electron microscopy as with the case reported here. Two other groups have reported the association of NS in patients with multisystem involvement and CDG I [3,5]. One patient had thickening of several peripheral glomerular tufts as the only abnormality on histopathology. There were no reported microcystic tubular changes but evidence of hyaline droplets in tubules. Podocyte foot process fusion was also described [5]. The patient with CDG Ia and congenital NS has been subsequently identified to have disease linked to chromosome 16p13 and mutations identified in the PMM2 gene. This female patient was identified to have a heterozygote mutation with the genotype, R141H/D188G [16].

Proteoglycans, a unique class of heavily glycosylated glycoproteins, are important components of the glomerular filter in that perlecan, agrin and collagen VIII contribute to the negative charge of the glomerular basement membrane and may be important for charge selectivity and glomerular filtration barrier function [17] and treatment with puromycin
downregulates proteoglycan expression in glomerular endothelial cells inducing a nephrotic syndrome [18]. It is likely that the specific inherited defects in glycosylation may alter proteoglycan function, which in turn has an impact on glomerular function.

Diffuse mesangial sclerosis (DMS) is often reported in patients with infantile nephrotic syndrome and is usually associated with the rapid onset of renal failure. In the majority of cases, DMS occurs as part of a syndrome such as the Denys Drash syndrome (resulting from WT1 gene mutations) or Pierson syndrome. A small proportion of patients have non-syndromic idiopathic DMS and may have autosomal recessive inheritance [19]. Gbadegesin et al. recently reported PLCE1 mutations in 28.6% (14 children from 10 families) and WT1 mutations in 8.5% (3 children from 3 families) of a large cohort of 40 patients from 35 families with non-syndromic idiopathic DMS [20]. Amongst consanguineous offspring, 36% had no PLCE1, WT1 or LAMB2 mutations.

One of the potential weaknesses of this report is that we have not excluded mutations in podocyte genes (NPHS1, NPHS2, WT1, LAMB2 or PLCE1) responsible for CNS in our patient. No mutational analysis was performed in our patient, as the phenotype was strongly suggestive of CDG despite the lack of detection of specific CDG gene mutations to date. Moreover, there is no reported association between CDG and either Finnish-type congenital NS or syndromic or non-syndromic DMS. We thought that the chances of finding dual pathology in our patient were therefore extremely low, especially as the presentation was also classical for CDG. Unfortunately, as the patient died we are unable to look into this further.

Our patient developed hypoalbuminaemia by 5 months of age that continued to deteriorate, as indicated by declining plasma albumin measurements leading to the acute presentation with nephrotic syndrome at 15 months. Since hypoalbuminaemia in patients with CDG is common and usually due to malnutrition, or gastrointestinal and/or liver involvement, this led to a delay in the detection of proteinuria in this case. Although proteinuria is a relatively unusual cause of hypoalbuminaemia in patients with CDG Ia, in a patient such as this where other causes of hypoalbuminaemia such as gastrointestinal disease and malnutrition are not evident, it is clear that urinary protein estimation at least by dipstick is the key. Steroid resistance is expected, but supportive treatment with antiproteinuric agents and antihypertensive agents would be of great therapeutic benefit in controlling symptoms.

In conclusion, we report a patient with CDG Ia who developed proteinuria during infancy and highlight CDG as a rare cause of nephrosis during infancy. This is comparable to previous reports and suggests that a diagnosis of CDG should be considered in all patients with microcephaly, neurological disease and nephrotic syndrome. Additionally, we would advocate regular urine dipstick testing in all patients with CDG type I and that if significant proteinuria is detected, this should be managed by the use of antiproteinuric agents to limit the onset of nephrotic syndrome.

Conflict of interest statement. None declared.