DMP1-CDG (CDG1e) with Significant Gastrointestinal Manifestations; Phenotype and Genotype Expansion

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Abstract The literature describes eight cases of mutations in the *DPM1* gene generating DMP1-CDG, causing similar phenotype of early onset seizures, microcephaly and developmental delay. Investigations of these patients revealed associated abnormal findings on brain imaging, elevated CK, abnormal clotting factors and mildly deranged serum transaminases. We describe the ninth case of DMP1-CDG, whose clinical presentation includes severe gastrointestinal involvement, i.e. food protein induced enterocolitis syndrome (FPIES). Gastrointestinal manifestations (GIT) of

the congenital glycosylation disorders have included deranged liver function, hepatomegaly, liver fibrosis, steatosis and protein-losing enteropathy. This is the first report of a congenital glycosylation disorder being associated with FPIES.

Introduction

Glycosylation is the post-translational modification of proteins and lipids which occurs in the membrane compartment of endoplasmic reticulum (ER), Golgi complex and lysosomes of cells (Scott et al. 2014; Freitas and Cayuela 2000; Cumming 1992; Meynial-Salles and Combes 1996; Yang et al. 2013; Dancourt et al. 2006; Imbach et al. 2000; Kim et al. 2000; García-Silva et al. 2004; Ashida et al. 2006; Schenk et al. 2001; Maeda et al. 2000), and involves the addition of a glycan oligosaccharide to a protein and lipid backbone (Dancourt et al. 2006; Imbach et al. 2000; Kim et al. 2000; García-Silva et al. 2004; Ashida et al. 2006; Schenk et al. 2001; Maeda et al. 2000). These glycans affect the conformation and activity of these ‘background’ proteins, and the resulting glycoproteins are involved in many cellular and physiological processes, such as signal transduction and immune response (Dancourt et al. 2006; Imbach et al. 2000; Kim et al. 2000; García-Silva et al. 2004; Ashida et al. 2006; Schenk et al. 2001; Maeda et al. 2000). Congenital disorders of glycosylation (CDGs) are rare genetic disorders which affect this post-translational modification of proteins, and various subtypes exist with protean clinical presentations (Maeda et al. 2000). To date, eight cases (Yang et al. 2013; Dancourt et al. 2006; Imbach et al. 2000; Kim et al. 2000; García-Silva et al. 2004) of DMP1-CDG (OMIM 608799) have been described in the literature.

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The CDGs exhibit protean clinical manifestations. Previously reported gastrointestinal manifestations (GIT) of the congenital glycosylation disorders include deranged liver function with elevated transaminases, hepatomegaly, liver fibrosis, steatosis and protein-losing enteropathy, as well as non-specific feeding problems, vomiting, diarrhoea and failure-to-thrive (Scott et al. 2014). Protein-losing enteropathy is common in children with MPI-CDG (OMIM 602579, CDG-1b) and has also been reported in types PMM2-CDG (OMIM601785, CDG-1a), ALG6-CDG (OMIM 603147, CDG-1c), ALG12-CDG (OMIM 607143, CDG-1g), ALG8-CDG (OMIM 608104, CDG-1h), as well as in several cases of unclassified CDG (CDG-1x) (Höck et al. 2015; Damen et al. 2004; Agarwal et al. 2007; McKenzie et al. 2007; Kranz et al. 2007; Krasnewich 2014).

Food protein induced enterocolitis syndrome (FPIES) has not been reported in a CDG patient to the best of our knowledge. FPIES is a non-IgE-mediated reaction to food proteins, most commonly cows' milk, soy or rice, which results in profuse vomiting and diarrhoea commencing 1–3 h after ingestion. Onset is in the first year of life, and reactions can be severe, inducing dehydration, hypotension and acidosis. Herein we present a 9th case of DMP1-CDG, who expands the clinical phenotype to involve severe GIT involvement in the form of FPIES.

Clinical Report

Our case is a 10-year-old girl from a non-consanguineous Caucasian family. She was delivered via a spontaneous vaginal delivery at 40 weeks gestation after an uncomplicated pregnancy. Apgar scores were 9 at 1 min and 10 at 5 min. Her birth weight was 3.8 kg and head circumference was 35 cm and length 50 cm.

Her early life was complicated by severe and refractory seizures, global developmental delay, and postnatal microcephaly with her head circumference tracking below the 3rd percentile. Seizures occurred from infancy and were semiologically diverse, including myoclonic, atonic, tonic and absence events. Electroencephalograms demonstrated bilateral epileptogenicity with emphasis on the bilateral central and left posterior regions and a suggestion of focal onset for some of the events, particularly during sleep. Multiple anticonvulsants failed to achieve satisfactory control, and a trial of the ketogenic diet was also unsuccessful. In recent years, however, her seizures have become quiescent, with tonic convulsions occurring once or twice a year and occasional absence seizures which do not affect her activities of daily living or quality of life. She has been weaned off anticonvulsants. She is ambulatory over short distances, has lower limb spasticity, has no verbal expressive language but has receptive and nonverbal language. A combination of oral

aversion and vomiting generated a requirement for gastrostomy feeding from an early age. Dysmorphic features include a depressed nasal bridge, prominent glabella, down slanting palpebral fissures, hypertelorism, smooth philtrum, carp shaped mouth, bilateral knee contractures and long great toes with a wide sandal gap.

An MRI scan of her brain at 3 years of age was normal. Consistently elevated creatine kinase (CK) levels, combined with the dysmorphic features prompted consideration of a CDG. APOC-III mass spectrometry revealed a normal pattern. Transferrin isoforms revealed increased levels of disialotransferrin and no asialotransferrin, which is an abnormal pattern typical of *N*-glycosylation defects. DMP1-CDG was suspected and subsequently confirmed at the molecular level.

Utilising next generation sequencing (Otogenetics) we identified two sequence variations in the DPMI gene, i.e. NM_003859 c.1A>C p.(Met1Leu) which was inherited from her father, and an NM_003859 c.274C>G p.(Arg92Gly) which was inherited from her mother. These mutations were confirmed in the proband and the parents via sanger sequencing (myGenomics). The NM_003859 c.1A>C p.(Met1Leu) mutation is reported in dbSNP with an allele frequency of 0.0002 and a BLOSUM score of 2, and is predicted to interfere with translation initiation. There are however no reports of this variant associated with DMP1-CDG. The NM_003859 c.274C>G p.(Arg92Gly) variant has been previously reported to be associated with DMP1-CDG (Kim et al. 2000).

The patient had a history of profuse vomiting and irritability in the first year of life, which raised suspicion of a cows' milk protein allergy. Extensive skin prick and patch allergy testing (including to pea, soy, rice and target formulas) have all proven negative to date. The first documented episode of FPIES occurred at age 7, when Nutrini Energy formula was switched to Nutrison. After resolution, Nutrini was tolerated for 2 feeds, and the reaction recurred almost immediately when Nutrison was subsequently reintroduced. In retrospect, a similar attack had occurred at almost 4 years of age, when she was inadvertently given a ketogenic formula, possibly Ketocal, instead of her usual formula PediaSure. A ketogenic diet with Ross Carbohydrate Free formula had been used in the past without incident. FPIES was characterised by hypersalivation during the feed, followed by severe vomiting with haematemesis and profuse mucousy diarrhoea with frank PR bleeding. These acute episodes occurred within 90 min of changing formula, and often left the patient very lethargic and required hospitalisation for intravenous fluid rehydration on three occasions.

Aside from her inborn error of metabolism, this child had multiple risk factors for food protein allergies and intolerances. This included her personal history of severe irritability

and vomiting in infancy, suggesting cows' milk allergy. She had a tendency to decompensate rapidly during gastroenteritis infections, suggesting underlying subtle chronic food protein enteropathy. Her half-siblings had similar symptoms, which in one child resolved on a dairy free formula.

Discussion

Dolichol phosphate mannose (DPM) is the sole donor substrate in various glycosylation processes, and has recently shown to be involved in four glycosylation processes: *N*-glycosylation, *O*-mannosylation, *C*-mannosylation and glycosylphosphatidyl inositol (GPI) anchor assembly (Yang et al. 2013; Dancourt et al. 2006; Imbach et al. 2000; Kim et al. 2000; García-Silva et al. 2004; Ashida et al. 2006; Schenk et al. 2001; Maeda et al. 2000; Lefeber et al. 2009). DPM is synthesised from GDP-mannose and dolichol phosphate, which is catalysed by the enzyme DPM-synthase (Freitas and Cayuela 2000; Cumming 1992; Meynial-Salles and Combes 1996; Yang et al. 2013; Dancourt et al. 2006; Imbach et al. 2000; Ashida et al. 2006; Schenk et al. 2001; Maeda et al. 2000). This membrane-bound catalyst is composed of 3 protein subunits (DPM1, DPM2 and DPM3); of which DPM1 (a soluble cytoplasmic catalytic subunit) is anchored to the ER membrane and stabilised by DPM2 and DPM3 (Freitas and Cayuela 2000; Cumming 1992; Meynial-Salles and Combes 1996; Yang et al. 2013; Dancourt et al. 2006; Imbach et al. 2000; Ashida et al. 2006). In DPM1-CDG, the biosynthesis of DPM is disrupted through a defect in the DPM-synthase (specifically the gene for the DPM1 subunit) (Yang et al. 2013; Dancourt et al. 2006; Imbach et al. 2000; Kim et al. 2000; García-Silva et al. 2004; Ashida et al. 2006). To date, eight cases (Yang et al. 2013; Dancourt et al. 2006; Imbach et al. 2000; Kim et al. 2000; García-Silva et al. 2004) of DPM1-CDG have been described in the literature, with varying *DPM1* mutations. The clinical features of these patients are summarised in Table 1. A clue to the diagnosis of DPM1-CDG is the elevated CK in keeping with an alpha-dystroglycanopathy (Meynial-Salles and Combes 1996; Yang et al. 2013). Previous links have been suggested between homozygous DPM3 mutations and DPM2-CDG and alpha-dystroglycan-type muscular dystrophy (Lefeber et al. 2009; Barone et al. 2012).

Our patient experienced episodes resembling severe FPIES, which is a non-IgE-mediated allergy to certain foods triggers (McDonald et al. 1984; Sicherer 2000; Mane and Bahna 2014; Fiocchi et al. 2014; Caubet and Nowak-Węgrzyn 2007; Katz et al. 2011). The pathogenesis of FPIES in infants and young children is not completely understood (Sicherer 2000; Mane and Bahna 2014). Several hypotheses have been proposed, and some research has

suggested the involvement of antigen-specific T-cells and their pro-inflammatory cytokines which may act to alter the permeability of the intestinal barrier (Mane and Bahna 2014; Fiocchi et al. 2014; Caubet and Nowak-Węgrzyn 2007). The age of onset of FPIES in our patient outside of the infant period is very unusual, and at least 90% of FPIES-affected children experience resolution by 3 years which is not the case with our patient (Katz et al. 2011).

The most recently proposed diagnostic criteria for FPIES are as follows (Miceli Sopo et al. 2013) (Miceli Sopo et al. 2013):

1. Less than 2 years of age at first presentation (frequent feature but not mandatory).
2. Exposure to the incriminated food elicits repetitive and important vomiting, pallor, hyporeactivity and lethargy within 2–4 h. Diarrhoea may be present, much less frequently and later. The symptoms last a few hours, usually less than 6 h.
3. Absence of symptoms that may suggest an IgE-mediated reaction.
4. Avoidance of the offending protein in the diet results in resolution of symptoms.
5. Re-exposure or oral food challenge elicits typical symptoms within 2–4 h. Two typical episodes are needed to deliver the definitive diagnosis.

The diagnosis rests entirely on the satisfaction of these clinical criteria, although there are frequently observed but non-specific laboratory findings such as neutrophilia and thrombophilia (Miceli Sopo et al. 2013). Our patient does meet these new criteria which have dispensed with the previously inflexible requirement for presentation in infancy. A neutrophilia was noted during episodes, but no thrombocytosis.

The possibility that our patient displays an incidental association between DPM1-CDG and FPIES cannot be excluded. The cumulative incidence of FPIES is significant, with a 0.34% cumulative incidence in one large cohort study (Katz et al. 2011). The likelihood of a chance association between a very rare disorder and an uncommon one is low; however, such associations do occur and in monogenic disorders their detection is increasing with new diagnostic technology. However, the unusual presentation of FPIES in our patient with a late age at onset and persistence at age 7 poses questions about whether the development of FPIES, its longevity, or both are related to her glycosylation disorder.

In PMM2-CDG, where GIT are common, inflammatory cells and intestinal villous blunting have been observed on microscopic examination of the small intestine. The changes are similar to that seen in food allergy, but no response was observed to elimination diets (Kristianson et al. 1998). The mechanism for protein-losing enteropathy

Table 1 Review of reported cases of DPMI-CDG

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Current Case
<i>DPMI</i> mutations	c.274C>G (R92G) homozygous	c.274C>G/13bp deletion (c331-343)	c.274C>G/c.628delC	Homozygous C742T>C (S248P)	Homozygous g.1VS4-5T>A	Homozygous g.1VS4-5T>A	c.455G>T p.Gly152Val /302bp deletion	c.1A>C p.(Met1Leu) c.274C>G p.(Arg92Gly)
CNS	Seizures, hypotonia, developmental delay	Seizures, hypotonia, developmental delay	Seizures, hypotonia, developmental delay	Seizures, hypotonia, developmental delay, neonatal encephalopathy, ataxia	Febrile seizures, hypotonia, developmental delay, ataxia	Hypotonia, developmental delay	Seizures, hypotonia, developmental delay	Seizures, developmental delay, spasticity
Microcephaly	+ (postnatal)	+	+ (postnatal)	+ (postnatal)	+ (by 6 months)	+ (postnatal)	borderline	+ (postnatal)
MRI brain	Delayed myelination?	Delayed myelination, hypoplastic L inferior frontal lobe, cerebellar atrophy	Widening of frontal temporal lobe and ventricles	Transient basal ganglia hypodensities, delayed myelination	N at 4.5 years. Later mild pontocerebellar atrophy, dentate nucleus hypersignal	Cerebral atrophy, dentate nucleus hypersignal	Mild cerebral volume loss	Normal at 3 years
Dysmorphic features	Flat occiput, flat nasal bridge, hypertelorism, high narrow palate, inverted V mouth, short limbs	Inverted nipples	Gothic palate, micro-gentalia, hypertelorism, gothic palate dysplastic nails, contractures	Trigonocephaly, hypertelorism, gothic palate micrognathia, smooth philtrum, prominent fatty cheeks, long 1st toe, sandal gap	Nil	Nil	Camptodactyly	Low nasal bridge, Hypertelorism, Smooth philtrum, Prominent glabella, Carp shaped mouth, Downslanting palpebral fissures, Contractures (knees), Long great toes, wide sandal gap
Muscle	CK+++	CK+	CK+++	CK+	Normal	Normal	CK+++	CK+
Eyes/vision	Cortical blindness	Cortical blindness, strabismus	Absent visual fixation	Optic atrophy, Alternating endotropia, nystagmus	Retinopathy	Strabismus, nystagmus	Partial optic nerve atrophy	Normal
GIT	Low antithrombin III	Low antithrombin III, protein C and S, elevated transaminases	Elevated transaminases, hepatosplenomegaly	Low antithrombin, protein C and S, factor XI	Decreased protein C and S	Slight hepatomegaly	Elevated transaminases, low protein C and S, antithrombin III, elevated D dimer	FPIES
Other		FTT			Peripheral neuropathy, FTT	FTT		
Reference	Kim et al. (2000)	Kim et al. (2000)	Imbach et al. (2000)	García-Silva et al. (2004)	Dancourt et al. (2006)	Dancourt et al. (2006)	Yang et al. (2013)	Current

in CDGs and other disorders is thought to involve loss of heparan sulphate proteoglycans from the basolateral surfaces of intestinal epithelial cells which directly leads to protein leakage as well as increasing the effects of other factors such as inflammatory cytokines (Bode and Freeze 2006). It is possible that a perturbed intestinal *N*-glycan microenvironment may have predisposed our patient to develop sensitisation to food allergens due to increased gut permeability and/or an altered cytokine environment. This may have contributed to her more severe presentation with FPIES, compared to family members with more subtle food reactions. Gastrointestinal involvement has not been described in any of the DPM1-CDG patients recorded in the current literature (Yang et al. 2013; Dancourt et al. 2006; Imbach et al. 2000; Kim et al. 2000; García-Silva et al. 2004), and as such our patient differs phenotypically from the other patients in the spectrum of this rare disease.

Compliance with Ethics Guidelines

Conflict of Interest

David Coman, Carolyn Bursle, Dominique Brown, Frances Connor, John Cardinal and Sophie Calvert declare that they have no conflicts of interest

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

Author Contributions

Dr Carolyn Bursle has driven the manuscript development, and been involved in patient care.

Dr Dominique Brown has driven the manuscript development, and been involved in patient care.

Professor David Coman is a metabolic physician coordinating care of patient, and has coordinated the manuscript development and design.

Dr Sophie Calvert is a Paediatric Neurologist, providing neurology care for the patient, and has been involved in the manuscript development.

Dr John Cardinal is a Medical Scientist who has been involved in the manuscript development.

Dr Frances Connor is a Paediatric Gastroenterologist involved in the patient's care and has been involved in the manuscript development.

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