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Glycobiology and the Paediatric Eye in Health and Disease

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Abstract

The Congenital Disorders of Glycosylation (CDG) are a clinically and genetically heterogeneous family of inherited diseases. Their clinical manifestations are truly multi-system. While the ophthalmological manifestations of CDG are not life threatening, they carry the potential for significant disease burden for the child and their family.

In this brief review we highlight the ophthalmological manifestations in patients with CDG, and discuss the importance of ocular glycobiology in health and disease.

Introduction

Glycosylation is a ubiquitous post translational modification (PTM) of proteins and lipids [1]. PTM of proteins and lipids is essential for their proper folding, stability, cell signalling and interactions. The transfer of initial sugar(s) to glycoproteins or glycolipids occurs in the endoplasmic reticulum (ER) or on the ER membrane. The subsequent addition of the many different sugars that make up a mature glycan is accomplished in the Golgi apparatus. Golgi membranes are embedded with glycosidases, glycosyltransferases, and nucleotide sugar transporters from the *cis*-Golgi to the *trans*-Golgi network (TGN). *N*-glycosylation starts primarily in the ER while *O*-glycosylation occurs in the Golgi.

In eukaryotes the linkage of glycans to proteins and lipids is carried out by eleven biosynthetic pathways [1], six of which are associated with human genetic disorders known as the congenital disorders of glycosylation (CDG). The last decade has seen an explosion in the identification of genetic glycosylation disorders, predominantly in the individual *N*-linked and *O*-linked protein glycosylation pathways (16 and 8 diseases respectively), while combined defects in both the *N*- and the *O*-glycosylation pathways, or other pathways e.g. *O*-Mannosylation have also been described (17 diseases).

The clinical features observed in CDG are protean, those that incur the highest disease burden involve the central nervous system, gastrointestinal and cardiac disease systems [2]. In this brief review we discuss the ophthalmological manifestations in CDG and the role glycosylation has in normal ocular function.

Clinical Ophthalmological Manifestations of Congenital Disorders of Glycosylation

Gylcosylation is a ubiquitous cellular process; approximately 1% of the human genome is dedicated to glycosylation [1]. The CDG are an eclectic group of disorders with a multisystem phenotype. Common clinical features associated with CDG involve developmental delay and intellectual impairment, ataxia, seizures, hepatic dysfunction, coagulopathies, failure to thrive, cardiomyopathy and pericardial effusion, hydrops fetalis, endocrine abnormalities, renal dysfunction, skeletal defects, early lethality, dysmorphic features, and ophthalmological features [3]. Glycosylation is essential for normal development and function of the human eye and visual pathways from cornea to the occipital cortex, so purturbed glycosylation produces clinical phenotypes throughout the visual system (Table 1).

PMM2-CDG (OMIM 212065) is the most common CDG with an estimated incidence of 1 in 20,000 live births, with the biochemical block being in the assembly of *N*-glycan structures [1,2]. The multi-system clinical presentation, while often involving ophthalmological features, is dominated by potential for severe end organ disease which is life limiting in 20% of affected infants [1]. Ophthalmological features are often present at diagnosis but can be over looked due to the emerging severity of end organ disease and the neurological and neurodevelopmental disease burden imparted by CDG. Common features include esotropia, reduced visual acuity, cone-rod dysfunction, and delayed visual maturation (Table 1). PMM2-CDG patients can develop photoreceptor degeneration which ultimately causes a pigmentary retinopathy with specific dysfunction in the "on-pathway" in the retina [4,5]. Electroretinography demonstrates characteristic attenuation of the b-wave with relative sparing of the a-wave, which localises the dysfunction to the Muller cells or ON-bipolar cells. In less common CDG, the ophthalmological manifestations can be a key component in making the diagnosis. Anterior chamber defects such as iris coloboma and glaucoma are a key diagnostic clue for the newly described defect in Dolichol metabolism SRD5A3-CDG (Table 1).

In recent years specific CDG disease phenotypes have been associated with unique defective glycosyltransferases, in which the ophthalmological features are main components of the clinical presentation. Key examples include Peters Plus Syndrome (OMIM 261540) and the alpha-dystrogylcanopathy family.

Peters Plus syndrome is an autosomal recessive disorder with the main clinical features involving anterior chamber defects, short stature, developmental delay and cleft lip/palate [6-8]. Reported ophthalmological manifestations include deficiency of the corneal endothelium and Descemet membrane (causing a corneal opacity), iridocorneal adhesions and congenital glaucoma [7,9,10]. It is caused by mutations in beta-1,3-galactosyltransferase-like gene (*B3GALTL*) which encodes a β1,3-glucosyltransferase [6], which adds glucose to an O-Linked fructose and hence is a CDG, B3GALTL-CDG.

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Clinical Feature	Type of Glycan Defect	Reference
Myopia	*N*-glycan	[20,29]
Corneal opacity	*O*-Glycan	[7,9]
Iridocorneal adhesions	*O*-Glycan	[30]
Iris colobomata	*N*-glycan	[7,9,29,30]
Congenital cataracts	*N*-glycan, *O*-Glycan	[30]
Microphthalmia	*N*-glycan, *O*-Glycan	[29]
Enopthalmos		[30]
Hypertelorism	*N*-glycan, *O*-Glycan, *N*- and *O*-glycan	[28,31]
Esotropia	*N*-glycan	[16,17]
Vitreous haemorrhage	*N*-glycan	[32]
Retinal haemorrhage	*N*-glycan	[33]
Macular hypoplasia	*N*-glycan	[4,5,20,29,34,35]
Retinitis pigmentosa	*N*-glycan, *O*-Glycan, *N*- and *O*-glycan	[4,5,20,29]
Rod dysfunction	*N*-glycan, *O*-Glycan	[20,29]
Cone dysfunction	*N*-glycan	[20,29]
Attenuated retinal vessels	*N*-glycan	[29,30]
Retinal colobomata	*N*-glycan, *O*-Glycan, *N*- and *O*-glycan	[28]
Visual Field loss	*N*-glycan	[7,9,30]
Glaucoma	*N*-glycan, *O*-Glycan	[28]
Optic neuropathy	*N*-glycan	[30,36]
Optic nerve atrophy/ hypoplasia	*N*-glycan, *O*-Glycan, *N*- and *O*-glycan	[37]
Eye movement disorder	*N*-glycan	[20,29,30]
Nystagmus	*N*-glycan	[20]
Ptosis		
Delayed visual maturation	*N*-glycan	[20]

Table 1: Reported Clinical Manifestations of the CDG.

Congenital muscular dystrophy (CMD) is a clinically and genetically heterogeneous group of syndromes. Hypoglycosylation of alpha-dystroglycan (aDG) accounts for a grouping subset of CMD. Currently 15 genes associated with PTM of aDG have been implicated in clinical disease phenotypes *POMT1* (OMIM 607423), *POMT2* (OMIM 607439), *POMGNT1* (OMIM 606822), *FKTN* (OMIM 607440), *FKRP* (OMIM 606596), *GTDC2* (OMIM 614828) *LARGE* (OMIM 603590), *DPM2* (OMIM 603564), *DPM3* (OMIM 605951), *DOLK* (OMIM 610746), *B3GNT1* (OMIM 605581), *B3GALNT2* (OMIM 610194), *ISPD* (OMIM 614631) and *TMEM5* (OMIM 605862) [11,12]. These genes have PTM roles associated with *O*-mannosylation, dolichol synthesis, glycosyltransferases and glucuronyltransferase activity, and some have uncharacterised functions. aDG plays a vital role in basement membrane stability via its interactions with Lamin and Integrins, in which the *O*-mannosylation PTM is an essential step. The aDG clinical phenotypes are heterogenous and include Walker-Warburg syndrome (WWS), Fukuyama Muscular Dyrtrophy (FCMD), limb-girdle muscular dystrophy (LGMD) and Muscle-Eye-Brain disease (MEB) [13]. Neuronal migration defects, muscular dystrophy, and ophthalmological manifestations (retinal dystrophy, cataracts) are central to considering a diagnosis of an aDG defect.

Galactosaemia (OMIM 600999) is an autosomal recessive metabolic disease in which secondary abnormalities of glycosylation are observed and are part of the disease process [14]. Coagulation factors are heavily glycosylated and coagulopathy is common place in the initial clinical presenting features of neonate with galactosaemia [15]. Vitreous haemorrhage has been reported as a rare neonatal complication of Galactosaemia secondary to coagulopathy [16,17].

Discussion

PTM via glycosylation plays a key role in the function of the normal visual pathways, and primary and secondary derangements in glycosylation are central to the clinically relevant ophthalmological manifestations.

PTM results in mature collagen I and II through N-glycosylation of the C-terminal procollagen and subsequent cleavage of the N- and C-terminal propeptide domains. Aberrant *N*-glycosylation of collagen and proteoglycans has been implicated in the pathogenesis of component of the skeletal manifestations of the CDG [3]. The human sclera is rich in collagen, proteoglycans and non-collagenous glycoproteins, and the biochemical and biomechanical properties of the sclera can play a role in the refractive capabilities of the eye [18,19]. Myopia is commonly identified in CDG patients, especially those with PMM2-CDG [4,5,20,29]. This raises the possibility that altered *N*-glycan PTM of the human sclera constituant proteins could predispose to refractive errors in patients with CDG.

Glycoproteins are highly expressed on the ocular surface including glycosyltransferases, proteoglycans, Notch signalling molecules, and glycan degradation products such as mucins and lectins [21,22]. These play a vital role in lubrication, prevention of bacterial adherence and endocytosis, and maintenance of the epithelial layer [21,22]. The Mucin family of *O*-glycoproteins in particular have an essential role in maintaining corneal and conjunctival epithelia [22]. Corneal histological samples from patients with Peters Plus syndrome (B3GALTL-CDG.) revealed abnormal stromal connective tissue, corneal thickening and absence of the endothelium Descemet and Bowman layers [23], perhaps indicating that a loss of corneal stromal proteoglycans may play a role in the significant corneal manifestations of B3GALTL-CDG. Ocular glycobiology therefore plays an integral role in maintenance of the ocular surface in both health and disease.

Glycan PTM plays a vital role in normal synaptic signalling processes in the human eye. aDG ligand proteins such as Lamin, Fukutin, FKRP and LARGE, rely on *O*-Mannosylation for their interaction. Pikachurin is a newly discovered DG ligand protein which localises to the synaptic cleft in the photoreceptor synapse. Pickachurin-DG interactions are essential for the proper alignment of the retinal bipolar cell dendritic tips to the photoreceptor ribbon synapse, which ultimately results in impaired synaptic signal transmission [24]. Pikachurin knockout models also reveal disorded synaptogenesis between the photoreceptor and bipolar cells [25]. ERG studies in patients with PMM2-CDG demonstrate attenuation of the a-wave placing the site of retinal dysfunction at the level the synapse between the photoreceptors and the bipolar cells [4,5]. There are likely to be more complex PTM DG ligand retinal synapse interaction partners identified in time for example, FKRP and Synaptophysin. The precise role that FKRP played in Lamin deposition in the retina is unclear [26]. Synaptophysin is an abundant presynaptic protein involved in synaptic vesicle recycling, undergoes PTM via N-glycosylation [27]. Reduced synaptophysin in the diabetic rat retina has been porstualed to be secondary to dysregulated PTM [27]. Retinal disease is a key clinical clue to the a-DG group of conditions, especially the MEB group. PTM of DG and PTM induced interations of DG ligand proteins like Pikachurin are important for understanding the basis of disease processes and for producing novel treatment strategies.

Eye movement disorders reported in CDG patients are likely to be multifactorial with central neurological causes being the prime

reason. Nystagmus in PMM2-CDG patients most commonly results for concomitant cerebellar malformations and cerebellar dysfunction [28].

Conclusion

The CDG are an eclectic group of diseases in whom multi-system disease processes compete and collude to impact the functional status of the patient with respect to activity of daily living. The neurological and life limiting manifestations associated with CDG often burden and dominate the clinical phenotype. While the ophthalmological manifestations of CDG may not be life threatening, they have major implications for a child's functional status and potential quality of life. Delayed visual maturation, severe myopia, ocular movement disorders, retinal dysfunction, cataracts and glaucoma are all commonly noted in the CDG as a family and all can combine to impair the child's ability to function independently and to reach their full potential.

Neurosensory difficulties in patients with centrally driven developmental disabilities and intellectual impairments can serve to profoundly impact on the child's function further. As such, attention to ocular disorders in patients with CDG is an important health care strategy in reducing disease burden for the child, the family, and their respective health systems.

The CDG are clinically heterogeneous in their clinical presentations. Ophthalmologists should consider a CDG in the differential diagnosis of a child with ocular disease as part of a multi-system disease process, especially when the ocular features include coloboma and retinitis pigmentosa.

Improved understanding the glycobiology of the eye, especially at the retinal synaptic level, sheds light on basic disease processes while opening opportunities for tailored treatment modalities.

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