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SHORT COMMUNICATION

High myopia and congenital myopathy with partial pachygyria in cutis laxa syndrome

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PURPOSE. *Several types of inborn errors of the O-glycan biosynthesis are known, leading to clinically very distinct phenotypes. Children with O-mannosyl glycan biosynthesis defects commonly present as a severe form of congenital muscular dystrophy with decreased alpha-dystroglycan staining, congenital eye anomalies, and brain migration defects. Alpha-dystroglycan is an O-mannosylated glycoprotein with additional mucin type O-glycans.*
METHODS. *Based on overlapping clinical features with O-mannosyl glycan defects, especially with muscle-eye-brain disease, the authors performed a muscle biopsy in a child with severe congenital hypotonia, high myopia, partial pachygyria, mental retardation, cutis laxa, and an inborn error affecting the biosynthesis of both mucin type O-glycans and N-linked glycans.*
RESULTS. *The histology showed no signs of muscle dystrophy, but a mild myopathy with slight increase in the muscle fiber diameter variability and type I fiber predominance. No significant decrease in the alpha-dystroglycan staining was detected; therefore, in spite of the phenotypic similarities the authors could not confirm the role of abnormal dystroglycan in the etiology of the muscle weakness and the developmental anomalies.*
CONCLUSIONS. *High myopia, muscle weakness, and cortical neuronal migration abnormalities are common in disorders of O-mannosylation and also observed in the authors' patient. However, compared to the severe generalized defect observed in mannosyl glycan defects, in this child the cerebral white matter and cerebellum were spared, and no muscle dystrophy could be confirmed. This is the first description of high myopia in cutis laxa syndrome in combination with congenital disorders of glycosylation. (Eur J Ophthalmol 2006; 16: 190-4)*

KEY WORDS. *Autosomal recessive cutis laxa, High myopia, Pachygyria, Myopathy, O-glycosylation, N-glycosylation*

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INTRODUCTION

Previously we described a female patient diagnosed with an inborn error affecting the biosynthesis of both N- and O-linked glycans (1). She presented with severe congenital hypotonia, joint contractures, ocular symptoms (high myopia and strabismus), central nervous system abnormalities (pachygyria with microcephaly, mental retardation, and epilepsy), as well as skeletal anomalies and generalized cutis laxa. Some of these features, except for cutis laxa and skeletal malformations, have been observed in patients with O-mannosylation defects as well.

Several types of inborn errors of the O-glycan biosyn-

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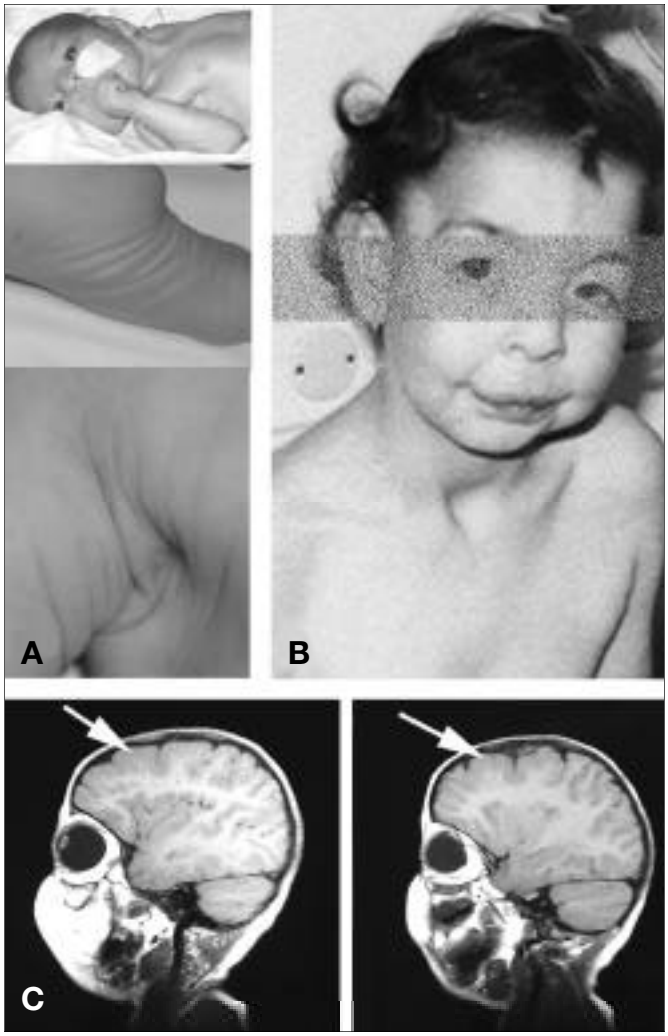

Fig. 1 - (A) *Facial and skin features of cutis laxa at 3 months,* **(B)** *facial features at age 5 years,* **(C)** *frontal pachygyria on cranial magnetic resonance imaging at age 4 years.*

thesis are known, leading to clinically distinct phenotypes (2-5). Children with O-mannosyl glycan biosynthesis defects characteristically have a congenital muscle dystrophy (CMD) characterized by a decreased alpha-dystroglycan staining in the muscle tissue (2). Alpha-dystroglycan is a glycoprotein with an O-mannosyl glycan structure (2) containing additional mucin type O-glycans (6). Some of the known alpha-dystroglycanopathies, like Fukuyama muscle dystrophy, muscle-eye-brain disease, or Walker-Warburg syndrome, are multiple malformation syndromes associated with brain migration defects and congenital eye anomalies. The defective protein mannosylation causes abnormal binding of the sarcolemma to the extracellular matrix (ECM) through an alpha-dystroglycan hypo-glycosylation, and leads to central nervous system developmental defects through disrupted cell interactions with the ECM and abnormal receptor signaling in the embryonic period (7). Skin and connective tissue anomalies, except for the secondary contractures due to fetal hypokinesis, are not common in these patient groups.

Cutis laxa is combined with abnormal elastic fiber structure and joint anomalies, microcephaly, development delay, hypotonia, skeletal malformations, and retarded growth in patients with the autosomal recessive form of cutis laxa syndrome (ARCL type II; MIM 219200) (8, 9). Central nervous system malformations and eye anomalies, however, are uncommon findings (9). In most patients the genetic etiology of the syndrome is not known.

Case report

The female patient (1) was born as the first child of healthy parents of Turkish origin who were first cousins. The patient presented at term with a birth weight of 3605 g (+1 SD), length of 53 cm (+1 SD), microcephaly (31.5 cm; -2.5 SD), strabismus, severe muscle hypotonia, generalized cutis laxa, clubfeet, bilateral clinodactyly of the IVth and Vth fingers, and hyperflexible joints (Fig. 1A). Further studies detected bilateral hydronephrosis due to pyelo-urethral stenosis. A skeletal survey showed a large, open fontanel, and hypoplastic iliac wings and acetabulae. At the age of 16 months she had a generalized tonic-clonic seizure and was given anticonvulsive therapy for 2 years. Seizures have never recurred since then. Electroencephalography was normal at the ages of 3 weeks, 1.5 years, and 4.5 years. Cranial MRI showed partial, bilateral frontal pachygyria (Fig. 1C), without other abnormalities, including a normal structure of the white matter and cerebellum. Creatine kinase levels in blood were normal. Chromosome analysis and blood and urine analysis including initial screening metabolic analysis were normal, except for the transferrin isoelectric focusing. The patient was diagnosed with CDG type IIx (1). Further specific analysis of mucin-type O-linked glycans showed a combined defect of N- and O-glycosylation in serum (1). A skin biopsy was performed. The histology showed a slight hyperkeratosis. The Gleason staining detected shorter, thin collagen fibers and

short elastic fibers, which were severely fragmented. The electron microscopy detected a severe decrease in the amount of elastic fibers. The fibers present were all abnormal in structure.

Ocular examination showed hyperlaxity of eyelids without true ptosis and downslanting palpebral fissures. There was strabismus (esotropia) of the left eye with normal fixation and free ocular motility. Objective measurement of the ocular refraction showed myopia of 4.5 diopters in both eyes. The intraocular pressure was normal. The vision was normal with appropriate glasses. No cataracts or unusual ophthalmoscopic findings were detected. Visual evoked potential studies showed a symmetric Flash-VEP with delayed latency after stimulation.

A muscle biopsy was performed at 2.5 years of age demonstrating mild myopathic features with slightly increased variability of the muscle fiber diameters and type I fiber predominance. No sign of muscle dystrophy was observed. The muscle fibers showed no internal nuclei. There was no endomysial fibrosis, nor an increase of fat cells. The immune staining for dystrophin, merosin, and alpha-sarcoglycan was normal. Immune staining with antibodies against the O-mannosyl glycan carbohydrate portions of alpha-dystroglycan (clone VIA4 Upstate Biotechnology, Lake Placid, NY) showed a slight, not significant decrease in intensity compared to controls (Fig. 2).

Currently at the age of 5 and a half years the child still has a developmental delay (mean IQ 59), hypotonia, and generalized cutis laxa (Fig. 1B). By neurologic examination there is a suboptimal strength (but no paresis), and low tendon reflexes with normal plantar responses, compatible with a mild myopathy. A recent ophthalmologic evaluation showed progression of myopia (6.0/6.5 diopters).

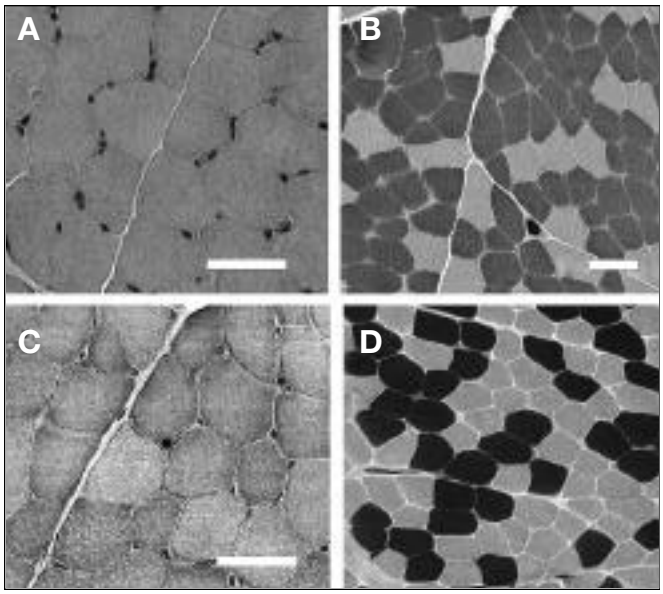

Fig. 2 - *Histology of quadriceps muscle.* **(A)** *Hematoxylin-phloxine stain. No presence of internal nuclei and other structural abnormalities.* **(B)** *Myosin ATPase (after preincubation at pH 4.2). Type I fiber predominance with slight hypertrophic fibers (especially type II fibers).* **(C)** *Immune histochemical staining with antibodies (clone VIA4-1) against carbohydrate parts of α-dystroglycan reveals slight sarcolemmal staining.* **(D)** *Muscle histology of an age-matched control patient: normal myosin ATPase staining. Bars represent a distance of 50 µm.*

DISCUSSION

Protein glycosylation is a complex biochemical process in which different monosaccharides are sequentially added to proteins in the endoplasmatic reticulum and in the Golgi apparatus. This posttranslational modification is essential for protein stability, secondary structure, and function, important for molecular recognition events, cell growth, and organ differentiation (10). We detected a combined N- and mucin type O-glycan biosynthesis defect in our proband. The phenotype observed was similar to that of ARCL type II regarding many features. In patients with cutis laxa the elastic fiber system has major structural and functional defects. Elastin, a non-glycosylated extracellular matrix (ECM) protein found in skin and connective tissue, is present in association with several microfibril-associated glycoproteins, which contribute to elastic fiber assembly, structure, and function. The abnormal glycosylation process causes an abnormal structure of several extracellular matrix glycoproteins, leading to a subsequent malfunction of different tissues and organs (11).

Central nervous system abnormalities are generally not present in cutis laxa syndrome. Pachygyria and brain migration defects have been reported in children with O-glycan biosynthesis defects, especially in O-mannosylation defects, whereas cerebellar hypoplasia is common in the congenital disorders of N-linked glycosylation (CDG) (12). Previous studies revealed that dystroglycan, a highly mannosylated protein, targets different proteins to their functional sites

in the central nervous system through interactions with extracellular matrix proteins (2 ,6, 13). An inborn error of glycosylation leads to defective receptor signaling and developmental defects, like pachygyria, already in the early embryonic period (14, 15). In our proband we have found cortical neuronal migration abnormalities in combination with mental retardation and epilepsy. In severely affected patients with O-mannosyl glycan defects the cerebral white matter and cerebellum are also affected, but – in line with the relatively mild phenotype – these structures were spared in our patient.

Additional to the neural migration defects, in both Walker-Warburg syndrome and muscle-eye-brain disease, congenital myopia is a characteristic finding. In Walker-Warburg syndrome microphthalmia and cataract occur as well. The underlying etiology of the development of the myopia in O-mannosyl glycan disorders is not fully understood (15, 16).

Alpha-dystroglycan is a muscle membrane protein, carrying both mucin type and mannosyl O-glycan groups. Abnormal biosynthesis of O-mannosyl glycans altering posttranslational modification disrupts the binding activity to its ligands, known to cause a congenital muscle dystrophy. In our proband, however, in spite of the clinical similarities with O-mannosyl glycan defects, the histology of the muscle biopsy sample showed no signs of a muscle dystrophy, but was compatible with a mild myopathy. Immunohistologic analysis revealed no decrease in the expression of alpha-dystroglycan compared to controls. Our results suggest that the muscle involvement and pachygyria in this patient most likely occur due to a developmental defect different from that observed in O-mannosyl glycan defects.

Here we describe a child with clinical symptoms similar to the autosomal recessive form of cutis laxa, who additionally had a severe muscle hypotonia, high myopia, partial pachygyria, and was known to have an inborn error of the biosynthesis of the N- and the mucin type O-glycans. Based on the abundance of glycosylated proteins in the extracellular matrix and the importance of glycosylation in the secondary structure of the connective tissue proteins, the defective glycosylation is most likely an important factor in the occurrence of the skin and joint symptoms and the occurrence of high myopia in the patient. Regarding the observed congenital central nervous system developmental anomalies, defective receptor signaling and the abnormal protein interactions with the ECM may both play a role.

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