Intracranial Hemorrhage as the Initial Manifestation of a Congenital Disorder of Glycosylation

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ABSTRACT

Intracranial hemorrhage in a term neonate is a rare event in the absence of an identifiable precipitating factor such as severe thrombocytopenia, mechanical trauma, asphyxia, infections, or congenital vascular malformations. Congenital disorders of glycosylation are a genetically and clinically heterogeneous group of multisystem disorders characterized by the abnormal glycosylation of a number of glycoproteins. Although bleeding caused by abnormal glycosylation of various coagulation factors is a well-known clinical complication of several types of congenital disorders of glycosylation, intracranial hemorrhage has not been reported as an initial manifestation of this entity. Here we report the detailed history of a family with 2 consecutive male infants, both born at term with intracranial hemorrhage diagnosed within the first 24 hours of life. The diagnosis of a congenital disorder of glycosylation was established in the second infant by an abnormal glycosylation of serum transferrin detected by electrospray-ionization mass spectrometry. Both infants showed significant neurologic deterioration during the first month of life, and both died at 5 months of age. Intracranial hemorrhage in a term neonate without a potential precipitating factor represents yet another clinical feature that should raise the suspicion for a congenital disorder of glycosylation.
abnormalities associated with an abnormal transferrin pattern.

Disorders affecting O-glycosylation defects are associated with different forms of muscular dystrophy such as Walker-Warburg syndrome, muscle-eye-brain disease, Fukuyama congenital muscular dystrophy, limb-girdle muscular dystrophy type 2I, and congenital muscular dystrophy type 1D.6,7 In addition, progeria syndromes8 and bone disorders such as hereditary multiple-exostoses syndrome9 are caused by alterations in O-xyllose-linked glycosaminoglycan formation.

Here we describe perinatal intracranial hemorrhage as a novel, initial presentation of a CDG, and we emphasize to the broad group of pediatric health care providers that screening for this heterogeneous group of disorders via a simple and inexpensive blood test should be considered for any patient with an unusual clinical finding and/or any multisystem disease of unknown etiology.

CASE REPORTS

A young, healthy white couple came to medical attention because of postnatal complications of their newborn son. The patient’s mother is of German extraction, and the father is of Native American and Northern European extraction. Consanguinity was denied. The family history was remarkable for a 7-year-old daughter with terminal ileal intestinal duplication who was in good health after resection of the intestinal duplication at 7 months of age. The second pregnancy resulted in a live-born male infant described as case 1. The proband was born from a third pregnancy and is described as case 2. Both patients were evaluated by a clinical geneticist, pediatric hematologist, and neurologists as part of their comprehensive clinical care. Skin biopsy of the proband was obtained after an appropriate consent procedure.

CASE 1. A male infant was evaluated at 2 months of age for hypotonia, failure to thrive, and respiratory distress. He was born at an outside hospital to a gravida 2 para 1001 (1 term, 0 preterm, 0 abortions, 1 live) then-22-year-old mother at 39 weeks’ gestation. During pregnancy, the mother had 3 fetal ultrasounds at 20, 28, and 35 weeks’ gestation without any detectable abnormalities. The mother had a history of anti-E antibodies, diagnosed 5 years before this pregnancy. Labor was complicated by maternal fever and failure to progress, with forceps being used to assist during delivery. At delivery, the infant had respiratory distress that required intubation, and his Apgar scores were 4 and 7 at 1 at 5 minutes, respectively. His birth weight was 3.69 kg (75th–90th percentile), birth length was 54.0 cm (95th percentile), and head circumference was 37 cm (95th percentile). The immediate postnatal course was complicated by hydrops, seizures, a large subdural hematoma and cephalohematoma, and hyperbilirubinemia. The infant had persistent severe feeding difficulty and remained hospitalized for 3 weeks after birth. During the interval from discharge until readmission at 2 months of age, he had recurrent episodes of apnea (which were later thought to be caused by seizures) and perioral cyanosis associated with crying. The mother also reported recurrent rhythmic bilateral upper extremity movements of unclear duration and frequency. By 2 months of age, the child’s initial hypertonic state changed to diffuse hypotonia with contracted joints.

Physical examination at 2 months revealed an emaciated, pale male infant with a weight of 3.7 kg (–1 SD), length of 54.6 cm (10th percentile), and head circumference of 37.4 cm (10th percentile). The metopic ridge and lambdoidal sutures were prominent, and the anterior fontanel was barely palpable. Palpebral fissures appeared small, and there was bilateral ptosis. Inner canthal distance was 2.2 cm (–1 SD), interpupillary distance was 4 cm (25th–50th percentile), and outer canthal distance was 5.8 cm (–4 SD). Microtretrognathia was present, and the palate was high-arched. His ears were low-set but had no anomalies. His chest was narrow with an internipple distance of 8 cm (3%). Cardiovascular examination was normal. His abdomen was soft, without hepatosplenomegaly or masses. The right testicle was descended, and the left was in the canal; otherwise, the genital examination was unremarkable. A coccygeal pit was present. The extremities had decreased muscle mass, but all large joints (elbows, hips, knees, wrist) were tight, with limited active and passive mobility. Linear creases were noted on the dorsal surface of the right foot at the metatarsalphalangeal joint. Neurologic examination was significant for poor axial and appendicular tone and equivocal Moro reflex. In resting position, his knees were slightly bent and hands fist tight. Few spontaneous movements were noted throughout the examination. No tracking or response to visual threat was noted, and he had equivocal response to loud noise.

Head ultrasound on day-of-life (DOL) 1 showed bilateral subdural hematomas in the parietal, occipital, and right frontotemporal regions, with normal ventricles, cephalohematoma, and no calcifications. An echocardiogram on DOL 3 showed no structural abnormalities, patent ductus arteriosus, patent foramen ovale, trivial pericardial effusion, and decreased right ventricular function. Electroencephalography (EEG) on DOL 3 showed abnormal, low-voltage, paucity of background activity consistent with encephalopathy and no seizure activity. A brain MRI (DOL 9) showed normal ventricles and bilateral subdural hematomas with possible calcifications. The laboratory workup on DOL 2 revealed a normal complete blood cell count including a normal platelet count, prothrombin time, and partial thrombin time.

Evaluations performed during the admission at 2 months of age included urine organic acids, plasma amino acids, serum lactate, cerebrospinal fluid lactate,
serum ammonium, calcium, magnesium, very-long-chain fatty acids, karyotype, and urine sulfites. The results from these tests were normal, and his karyotype was 46,XY. A skeletal survey was unremarkable. A brain MRI showed small extra-axial fluid collections noted over frontal and temporal regions, with normal cortex and myelination for age and no evidence of heterotopia. Renal ultrasound detected bilateral hydronephrosis, which had resolved on follow-up examination. The cholelithiasis (several stones) was observed incidentally during an abdominal ultrasound. Ophthalmologic ultrasound documented absent central retinal arteries with greater neuronal bulk and perineuronal blood flow on the right than left. Follow-up EEG showed bilateral temporal sharp waves consistent with epileptiform activity.

The patient continued to show neurologic deterioration with intractable seizures and died at 5 months of age as a result of respiratory failure.

CASE 2. The proband, a male infant, was born at 38 weeks’ gestation to the same, then-26-year-old gravida 3 para 2001 (2 term, 0 preterm, 0 abortions, 1 live) mother via scheduled cesarean section secondary to breech presentation. The mother was monitored for anti-E sensitization throughout her pregnancy, with maternal anti-E titers never exceeding 1:8. The pregnancy history was remarkable for decreased fetal movements throughout the pregnancy. Results of serial fetal ultrasounds performed at 15, 20, 28, 32, and 36 weeks’ gestation, however, were normal. There were no reported maternal illnesses, and nicotine, alcohol, and drug exposures were denied. No invasive prenatal testing was performed.

The proband’s birth weight was 3.39 kg, length was 49 cm, and head circumference was 34.5 cm (all at the 50th percentile). His Apgar scores were 6 and 8 at 1 and 5 minutes, respectively. Shortly after birth, the proband developed respiratory distress, which required continuous positive airway pressure, and he was subsequently transferred to the NICU for additional monitoring and evaluation. In addition to the respiratory distress, the patient was noted to have increased muscle tone, multiple mild contractures of his extremities, and a right club foot. On the second DOL, a head ultrasound revealed bilateral intraventricular hemorrhages (grade I on the right and grade III on the left). A subsequent MRI confirmed hemorrhage in both lateral ventricles, left more than right (Fig 1). The brain parenchyma was of normal signal intensity, and myelination was normal for age. Magnetic resonance angiography and magnetic resonance venography did not show any significant abnormalities, and a diffusion scan did not show evidence of an acute stroke-like event. Repeat head ultrasound on DOL 8 showed resorption of the hemorrhages, with mildly dilated lateral ventricles, and no parenchymal pathology.

The first clinical genetics physical examination on DOL 3 revealed slightly deep-set eyes with normal palpebral fissures. His ears had bilaterally prominent antehelices but were of normal size and position, without pits or tags. His posterior fontanel was closed. His anterior fontanel was open but small, and mild metopic and lambdoid ridging was present. His facial features were not grossly dysmorphic, and his mouth was small, with down-turned corners. The chest had normal configuration, and initially both nipples were assessed as hypoplastic but not inverted. His lung, heart, and abdominal examinations were unremarkable, and cardiac evaluation by echocardiography demonstrated a patent foramen ovale but no structural defects. He had a normal penis and bilaterally descended testes. The upper and lower extremity examination documented mild joint contractures and abnormal implantation of the digits on both feet. The neurologic examination initially revealed an increased tone of upper and lower extremities, with normal Moro, suck, grasp, and deep-tendon reflexes. Episodes of bradycardia and apnea developed in the second week of life.

The proband was discharged from the hospital at 1 month of age, and on a follow-up evaluation at 2 months he was found to be lethargic, with poor oral intake, and heavily dependent on feedings through a nasogastric tube. Inverted nipples were noted on this visit. He had very limited response to external stimuli and minimal eye movements, suggesting ophthalmople-
gia. His neurologic examination showed axial hypotonia, increased peripheral muscle tone, and ankle clonus. The parents reported frequent episodes of hiccups and rapid jerking movements of the extremities but no obvious tonic-clonic seizures. EEG was declined, and the parents strongly felt that the symptoms of the proband were identical to those of his deceased sibling. Within the next month, his neurologic status dramatically declined. He became profoundly hypotonic and lethargic, with an inability to move his extremities, and significant head lag. He required nasogastric tube feeding and developed a tonic-clonic seizure disorder that was resistant to antiepileptic treatment. He died at the age of 5 months secondary to respiratory arrest.

Hematologic Evaluation
The unusual finding of bilateral intraventricular hemorrhages in the absence of prematurity and the previous history of a brother with intracranial hemorrhage prompted a detailed hematologic workup. An initial complete blood cell count did not reveal any abnormalities and included a normal platelet count. The proband’s prothrombin time and partial thrombin time were normal, as was his fibrinogen level (310 mg/dL). D-dimers were elevated at 6.51 mg/L (reference range: 0.43–2.24 mg/L), and his α-2 antiplasmin level was 41% (reference range: 80%–120%). These findings were thought to be a result of low-grade disseminated intravascular coagulopathy secondary to the intracranial bleeding. Both factor IX and factor VIII activities were within the reference range (55% and 166%, respectively). Platelet adhesion and aggregation functions in response to adenosine diphosphate, collagen, and epinephrine were normal as measured by the PFA-100 test (PFA-100 in vitro diagnostic system; Dade Behring, Deerfield, IL). The family recognized very similar patterns between their sons and objected to additional evaluation. No clinically significant bleeding diathesis was observed after the perinatal episode of intraventricular hemorrhage.

Genetic and Biochemical Workup
The genetic workup included karyotype with subtelomeric fluorescence in situ hybridization analysis, plasma amino acids, urine organic acids, and acylcarnitine profile. The results of these tests were normal. His skeletal survey documented mild left hip dysplasia and more vertical orientation of the talus and calcaneus bilaterally but was otherwise unremarkable. The ophthalmologic evaluation was also unremarkable, and transorbital ultrasound documented normal central retinal arteries bilaterally. An ultrasound of his kidneys and heart did not reveal any significant abnormalities. Given the history of profound and rapid neurologic deterioration in the patient’s brother that could not be fully explained by intracranial hemorrhage, an ESI-MS screening test for CDG was performed (Mayo Clinic, Rochester, MN) to measure the ratio of transferrin isoforms carrying 0, 1, or 2 oligosaccharide chains (normal transferrin contains 2 chains). The ratio of transferrin molecules carrying 1 sugar chain/2 sugar chains was 1.10 (reference: ≤0.074), and the ratio of nonglycosylated transferrin to those with 2 chains was 0.563 (reference: ≤0.022). This pattern was suggestive of a CDG-I assembly defect. A repeat CDG assay performed at 1 month of age confirmed the previous finding.

A skin biopsy was obtained, and fibroblast enzymatic assays documented normal activity of both phosphomannomutase and phosphomannose isomerase, the enzyme defects of which cause CDG-Ia and -Ih.10 Labeling of the patient’s lipid-linked oligosaccharides with [2-3H]mannose, with size separation of the liberated oligosaccharides,11 showed that the patient’s cells produced normally sized lipid-linked oligosaccharides. According to this study, CDG-Ic through CDG-Ih were excluded as potential causes for the patient’s symptoms. Although the spectrum of clinical features is very broad, no previously described patients of known type have shown this constellation of clinical and biochemical features (see below and Table 1); therefore, the possibility of a novel type of CDGI (currently denoted as CDG-Ix) needs to be considered in these brothers. The inheritance pattern of the condition described in this report would be consistent with either autosomal recessive or X-linked.

DISCUSSION
These case reports suggest that intracranial hemorrhage in the newborn period can be an initial presentation of a CDG, and this group of disorders should be considered in any newborn with unexplained intracranial bleeding. Intracranial hemorrhage in neonates can occur as a result of prematurity, birth/mechanical trauma, platelet disorders (congenital, alloimmune, maternal autoimmune), coagulation disorders, infections, and hypoxia. The incidence of subdural hematoma after spontaneous vaginal delivery is ~1%.12 It should be noted that in infants without a coagulopathy, the incidence of intracranial hemorrhage after forceps-assisted vaginal deliveries is on the order of 1 in 600.13 On the bases of our observations in these 2 infants, we suggest that CDG may predispose to the development of intraventricular hemorrhage and/or subdural hematoma in the perinatal period. The assumption that forceps-assisted delivery was the sole etiology of hemorrhage in the first case described may have precluded the possible diagnosis of a coagulopathy or CDG.

To our knowledge, there has not been a report of intracranial hemorrhage as the presenting clinical feature of a CDG. The main reason for considering this disease entity originated from the family history of a brother who also presented with subdural hemorrhage in the newborn period and subsequently developed neurologic problems within the first few weeks of life. We
<table>
<thead>
<tr>
<th>CDG Type</th>
<th>No. of Patients</th>
<th>Abnormal Screening</th>
<th>Head Size</th>
<th>Seizures</th>
<th>Developmental Delay</th>
<th>Hypotonia</th>
<th>Liver/GI Problems</th>
<th>Coagulation Defects</th>
<th>Dysmorphic Features</th>
<th>Other Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia20,21</td>
<td>~600</td>
<td>+</td>
<td>N</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Osteopenia, cerebellar hypoplasia, strabismus, inverted nipples, retinitis pigmentosa, renal cysts, cardiomyopathy, endocrine abnormalities</td>
</tr>
<tr>
<td>Ib22-25</td>
<td>20</td>
<td>+</td>
<td>N</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>Hypoinsulinemic hypoglycemia, responsive to oral mannosae supplementation</td>
</tr>
<tr>
<td>Ic26</td>
<td>~25</td>
<td>+</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Endocrine abnormalities</td>
</tr>
<tr>
<td>Id27</td>
<td>6</td>
<td>+</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Optic atrophy, coloboma</td>
</tr>
<tr>
<td>Ie28,29</td>
<td>5</td>
<td>+</td>
<td>N</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Delayed myelination</td>
</tr>
<tr>
<td>Ic30,31</td>
<td>5</td>
<td>+</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Dwarfism, ichthyosis</td>
</tr>
<tr>
<td>If32,33</td>
<td>5</td>
<td>+</td>
<td>N</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>Genital hypoplasia</td>
</tr>
<tr>
<td>Ig34,35</td>
<td>5</td>
<td>+</td>
<td>N</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>Cholestasis</td>
</tr>
<tr>
<td>Ih36</td>
<td>1</td>
<td>+</td>
<td>N</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ij37</td>
<td>2</td>
<td>+</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ik38,40</td>
<td>4</td>
<td>+</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>Il31</td>
<td>2</td>
<td>+</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Cardiomyopathy, nephrotic syndrome</td>
</tr>
<tr>
<td>Il32</td>
<td>2</td>
<td>+</td>
<td>N</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Bronchial asthma</td>
</tr>
<tr>
<td>Il43</td>
<td>4</td>
<td>+</td>
<td>N</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Intraventricular hemorrhage in newborn period</td>
</tr>
<tr>
<td>Il44,45</td>
<td>3</td>
<td>-</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Stereotypic hand movements</td>
</tr>
<tr>
<td>Ij46</td>
<td>1</td>
<td>+</td>
<td>H</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Abnormal urine oligosaccharides</td>
</tr>
<tr>
<td>Ik51</td>
<td>2</td>
<td>+</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Short stature, neutropenia, recurrent bacterial infections</td>
</tr>
<tr>
<td>Ipm52</td>
<td>1</td>
<td>ND</td>
<td>N</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>Dandy-Walker cyst</td>
</tr>
<tr>
<td>Il53</td>
<td>1</td>
<td>ND</td>
<td>N</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>Cholestasis, absence of long bone epiphyses and abundant shiny skin</td>
</tr>
</tbody>
</table>

CDG screening via transferrin testing is warranted for any patient with nonspecific nervous system abnormalities as well as in any otherwise-unexplained disease involving multiple organ systems. GI indicates gastrointestinal; N, normal; ND, not determined. +++, prominent feature; ++, often present; +, present feature; MI, microcephaly; MA, macrocephaly; H, hydrocephaly; ND, not determined.

a Stroke-like episodes.

b Patients described in this article.
therefore suggest that the diagnosis of CDG be considered in the diagnostic evaluation of newborns with intracranial hemorrhages when common causative factors are not present or when the clinical presentation is disproportionately severe.

The hematologic evaluation demonstrated no significant clotting deficiencies, but the α-2 antiplasmin level was slightly low in our proband at 41%. α-2 antiplasmin is a glycosylated protein\(^{14}\), and although this was felt to be a potential contributory factor to the intracranial bleeding, it is unlikely to have been the sole cause. Generally, bleeding is not seen in α-2 antiplasmin deficiency unless much lower levels are present. More importantly, this factor can be decreased in disseminated intravascular coagulopathy, which would fit with the fact that the proband had elevated D-dimers, probably secondary to his intracranial bleed and brain injury. Because the patient’s family asked to withhold additional hematologic evaluations, we were not able to definitely rule out a deficiency in coagulation-factor XIII, which is known to cause central nervous system bleeding without alteration of the bleeding cascade; however, factor XIII deficiency is usually associated with delayed bleeding after cord separation, which was not present in either child.\(^{15}\) Abnormalities of hemostasis are a well-described feature of CDG. This is not surprising, because many proteins involved in the clotting pathway require glycosylation for proper function. Interestingly, patients may present with thrombotic events that cause stroke-like episodes or massive bleeding. Individuals with CDG show a variety of coagulation-factor abnormalities including markedly decreased activity of factor XI and coagulation inhibitors such as antithrombin III and protein C.\(^{16,17}\) Moreover, glycosylation defects are not exclusively detected in secreted plasma proteins but are also present in functional membrane glycoproteins such as the glycoprotein Ib/IX/V complex of platelets. It is possible that a perturbation of the equilibrium of the clotting cascade in conjunction with other functional membrane proteins ultimately causes either bleeding or stroke-like episodes. Van Geet et al\(^{17}\) demonstrated that reduced glycoprotein Ib-mediated platelet activity with vessel wall components under blood-flow conditions in patients with CDG-IIa (see below) may explain the bleeding tendency of these patients. Unfortunately, we were not able to analyze platelet function in more detail in our patient or his brother; however, it is possible that similar alterations of the platelet glycoprotein complex in our patients were responsible for the initial intracranial hemorrhage.

The clinical and genetic characterization of new disease entities caused by abnormal glycosylation of proteins has increased rapidly over the past 6 years. The first patients with CDG were described by Jaeken et al\(^{18}\) in 1980, after the observation of abnormal processing of arylsulfatase-A and thyroxin-binding globulin in patients with severe developmental delay and neurologic deficits. Approximately 13 years later, phosphomannomutase deficiency was found to be the basis of the most frequent variant of CDG-Ia.\(^{19}\) Today, a total of 25 different CDG types have been characterized (17 identified within the past 6 years), making this disease category a “booming chapter of pediatrics.”\(^{1}\) As summarized in Tables 1 and 2, diseases caused by abnormal N- and O-glycosylation can affect virtually every organ system; therefore, it is important for primary care providers as well as various subspecialists to be familiar with CDG. There is a reliable and inexpensive screening test that will identify a significant number of N-glycosylation defects. Biochemical and genetic characterization of the glycosylation defects may offer the opportunity for prenatal diagnosis. We therefore recommend that CDG testing be considered for all patients with unexplained nervous system or hemorrhagic symptomatology or in any patient with multisystem dysfunction of unknown etiology.

### Table 2: Disorders Associated With Abnormal O-Glycosylation

<table>
<thead>
<tr>
<th>O-Glycosylation Disorder</th>
<th>Inheritance</th>
<th>Gene</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>O-mannosylglycan glycosyltransferase defects</td>
<td>AR</td>
<td>POMT1</td>
<td>Muscular dystrophy, lissencephaly, eye abnormalities</td>
</tr>
<tr>
<td>Walker-Warburg syndrome(^a)</td>
<td>AR</td>
<td>POMGnT1</td>
<td>Muscular dystrophy, structural brain abnormalities, eye abnormalities</td>
</tr>
<tr>
<td>Muscle-eye-brain disease(^a)</td>
<td>AR</td>
<td>PGM1</td>
<td>Muscular dystrophy, structural brain abnormalities, eye abnormalities</td>
</tr>
<tr>
<td>Putative O-mannosylglycan glycosyltransferase defects</td>
<td>AR</td>
<td>Fukutin</td>
<td>Muscular dystrophy, structural brain abnormalities with mental retardation and seizures, eye abnormalities</td>
</tr>
<tr>
<td>Fukuyama congenital muscular dystrophy(^a)</td>
<td>AR</td>
<td>FKRP</td>
<td>Broad range of phenotype ranging from very severe to mild onset of skeletal muscle weakness; often cardiomyopathy and respiratory failure; can have brain abnormalities</td>
</tr>
<tr>
<td>Limb-girdle muscular dystrophy type 2(^a) and congenital muscular dystrophy type 1(^a)</td>
<td>AR</td>
<td>LARGE</td>
<td>Muscular dystrophy, abnormal neuronal migration, eye abnormalities</td>
</tr>
<tr>
<td>Congenital muscular dystrophy type 1D(^a)</td>
<td>AR</td>
<td>B4GALT1</td>
<td>Premature aging, joint hypermobility, hyperelastic skin, macrocephaly</td>
</tr>
<tr>
<td>Glycosaminoglycan-synthesis defects</td>
<td>AD</td>
<td>EXT1/EXT2</td>
<td>Osteochondromas on the ends of long bones, self-limiting disease</td>
</tr>
<tr>
<td>Ehlers-Danlos progeroid variant(^a)</td>
<td>AR</td>
<td>B4GALT(^a)</td>
<td>Premature aging, joint hypermobility, hyperelastic skin, macrocephaly</td>
</tr>
<tr>
<td>Multiple-exostoses syndrome(^a)</td>
<td>AD</td>
<td>EXT1</td>
<td>Premature aging, joint hypermobility, hyperelastic skin, macrocephaly</td>
</tr>
</tbody>
</table>

\(^{a}\) For review see ref 6.
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