Initial diagnosis of the congenital disorder of glycosylation PMM2-CDG (CDG1a) in a 4-year-old girl after neurosurgical intervention for cerebral hemorrhage

Case report

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The congenital disorder of glycosylation characterized by a deficiency of phosphomannomutase 2 (PMM2-CDG) is the most common variant of congenital disorders of glycosylation. Besides typical clinical features, such as dysmorphism and abnormal body fat distribution, coagulation abnormalities often lead to thromboembolic and hemorrhagic events in these patients. However, only 2 cases of intracerebral bleeding in patients with PMM2-CDG have been described so far.

A 4-year-old girl who initially presented with symptoms resulting from raised intracranial pressure underwent acute neurosurgical intervention for intracranial hemorrhage. The differential diagnoses after MRI included arteriovenous malformation and intraparenchymal brain tumor. However, clinical investigations promoted the diagnosis of PMM2-CDG, which was supported further by neuropathological findings and finally confirmed by isoelectric focusing and mutational analysis. No major complications or neurological deficits were evident after surgery, and the patient was able to attend an integrated kindergarten.

Unexplained intracranial hemorrhage should raise suspicion of a metabolic disorder and should be discussed with specialists to rule out an orphan disease such as PMM2-CDG.

Key Words - CDG1a - PMM2-CDG deficiency - intracerebral hemorrhage - disordered blood clotting - vascular disorders

Congenital disorders of glycosylation (CDG) were first recognized in the 1980s.6 The growing numbers of cases and different subtypes of disease6 revealed the most common type to be PMM2-CDG, which is characterized by a deficiency of the enzyme phosphomannomutase 2 (PMM2), 1 of 2 enzymes that catalyze the conversion of mannose-6-phosphate to mannose-1-phosphate.19 Because phosphomannomutase 1 is not able to compensate for PMM2,19 its dysfunction leads to early disruption of the N-glycan assembly of glycoproteins5 due to a deficit in guanosine diphosphate-mannose.4,19

It is still an underdiagnosed autosomal recessive genetic disorder with an approximate incidence of 1:20,000, and there are more than 700 affected patients worldwide. The mortality rate reaches up to 25%4–6 in children with PMM2-CDG.

Depending on patient age, 4 stages of the disease may be observed: the infantile multisystemic stage, the childhood ataxia–mental retardation stage, the teenage leg atrophy stage, and the adult hypogonadal stage.7

All organ systems may be involved in the disease process, and there is high clinical variability even in monozygotic twins. As a rule, the peripheral and central nervous systems are always affected, resulting in muscular hypotonia and psychomotor developmental delay, and cerebellar ataxia.8 Especially in patients younger than 15 years in a catabolic state due to infection or immobilization,1–5,7,16,17,20–22,24 the coagulation system may be altered. These changes may lead to thrombotic and hemorrhagic complications, including stroke-like episodes as the major neurological feature. Acute vascular events are especially seen.

The diagnosis of PMM2-CDG is confirmed by isoelectric focusing of transferrin, which should be followed by an enzyme assay and mutational analysis of the PMM2 gene.5,14 Treatment is currently only supportive; few experimental approaches, including cellular, genetic, and metabolic options, exist.4

Although thrombotic or hemorrhagic complications occur frequently in patients with PMM2-CDG, only 2 cases of neonates with cerebral hemorrhage and fatal outcome have been mentioned in the literature so far.10,18

In this report, we describe an additional case of a patient who experienced an intracerebral hemorrhage requiring neurosurgical intervention and was diagnosed with PMM2 deficiency during the postoperative course.

Abbreviations used in this paper: AT III = antithrombin III; CDG = congenital disorder of glycosylation; PMM2 = phosphomannomutase 2; PNET = primitive neuroectodermal tumor.

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This article contains some figures that are displayed in color online but in black-and-white in the print edition.
PMM2-CDG diagnosed after surgery for intracerebral hemorrhage

Case Report

A 4-year-old girl was taken to a tertiary pediatric center after a 4-day history of reduced propulsion, projectile vomiting, and fever. As she became soporous, MRI of the brain revealed a large tumor in the right trigonal area, with a massive hemorrhage and marked midline shift but no contrast enhancement (Fig. 1A). MR angiography results were unremarkable, but a cerebellar atrophy and an asymmetry of the temporal lobes were noted (Fig. 1B). The radiological differential diagnoses included primitive neuroectodermal tumor (PNET) and atypical teratoid/rhabdoid tumor.

The patient’s initial serum coagulation parameters showed a decreased prothombin time (37%; reference range 75%–140%) and a prolonged activated partial thromboplastin time (42.2 seconds; reference range 27.0–41.0 seconds). The serum hemoglobin (11.5 g/dl; reference range 12.0–15.0 g/dl) and hematocrit (33.5%; reference range 35.0%–55.0%) concentrations, mean cellular volume (73.8 fl; reference range 78.0–98.0 fl), serum calcium level (2.12 mmol/L; reference range 2.20–2.70 mmol/L), and total serum protein concentration (56.9 mg/dl; reference range 60–80 mg/dl) were slightly reduced. Furthermore, the aspartate aminotransferase (98 U/L; reference range < 35 U/L), alanine aminotransferase (78 U/L; reference range 5–21 U/L), lactate dehydrogenase (422 U/L; reference range 100–300 U/L), and C-reactive protein (2.18 mg/dl; reference range < 0.5 mg/dl) levels were increased.

At the pediatric intensive care unit, the patient became comatose and exhibited bilateral mydriasis. After first-line high-dose cortisone and mannitol treatment, she was immediately transferred to the neurosurgical operating theater.

After craniotomy and opening of the dura, fresh bleeding was observed at the cortical surface. A diffuse tumor with massive hemorrhaging was accompanied by a multitude of thrombotic veins beside and at the bottom of the resection (Fig. 1C and D). The intraoperative differential diagnoses included a hemorrhagic tumor such as a PNET, an arteriovenous malformation, and secondary bleeding after venous thrombosis.

After surgery, the patient’s pupils were narrow and reactive to light again. The postoperative cranial CT scan showed gross-total extirpation of the intraparenchymal hemorrhage without secondary bleeding or ischemia.

A histopathological workup revealed no signs of a tumorous lesion in the specimen. Instead, loosely orga-
nized, partially thrombotic, partially ruptured thin-walled meningeal vessels with abundant bleeding remnants were detected. In the CNS tissue, a laminar type of ischemia was observed in the white matter (Fig. 1A), with abundant intracytoplasmic PAS-positive granular material (Fig. 1F) were found. Neither inflammation nor demyelination was detected in the specimen.

A detailed postoperative analysis of the patient’s coagulation factors after suspicion of PMM2-CDG revealed decreased activity levels of factors II (49%; reference range 75%–130%), VII (46%; reference range 75%–160%), X (38%; reference range 70%–150%), and XI (17%; reference range 60%–140%). Her protein C and antithrombin III (AT III) activity levels were reduced to 17% and 12%, respectively. The protein C and S quantities were also reduced to 21% and 30%, respectively.

The diagnosis of PMM2-CDG was suspected due to the patient’s constellation of typical symptoms: strabismus convergens alternans, psychomotor retardation, developmental speech delay with dysarthria, muscular hypotonia, ataxia with cerebellar atrophy on MRI, and, finally, the coagulation disturbance that led to intracranial bleeding. The diagnosis of PMM2-CDG was confirmed by isoelectric focusing of serum transferrin and subsequent mutational analysis, which revealed two known mutations at the DNA level, c.422G>A (p.Arg141His) and c.682G>T (p.Gly228Cys).

The patient had been born spontaneously at term after an uncomplicated pregnancy as the first child of unrelated parents. A heterozygote deficiency of coagulation factor V in the mother was evident. The patient’s psychomotor development had been delayed, with sitting beginning at 18 months, crawling and standing at 30 months, walking with someone holding her hands at 48 months, and talking at 20 months. She was able to attend an integrated kindergarten and showed good developmental progress. Neither cerebral seizures nor retinitis pigmentosa had appeared previously.

Six months later, the patient had stabilized clinically and metabolically. Thus, results of follow-up testing of her serum coagulation parameters showed low values for only AT III activity (52%), whereas her protein C and S quantities (71% and 67%, respectively) were at baseline. Up to the time of this writing, the patient had not shown any major complications, only mild residual neurological deficits after the hemorrhagic event.

Discussion

Herein, we present the case of a patient with PMM2-CDG who was diagnosed with her disease after intracerebral hemorrhage requiring neurosurgical intervention.

Clinical or chemical coagulation abnormalities are a common feature in patients with PMM2-CDG.12,20 Published case reports usually describe transient stroke-like or comatose episodes in up to 50% of patients and, very rarely, cerebellar infarctions. Hemorrhages in general are reported for up to 25% of patients during childhood and adolescence, but only a few case reports of cerebral bleeding have been published so far. However, in these patients, there are no consistent coagulation system changes, which can include reduced levels of the vitamin K–dependent coagulation factors II, VII, IX, and X; proteins C and S; AT III; and factors V and XI.12,20

In our case, nearly all of these factors showed reduced activities or quantities, suggesting a complex combination of functional disturbances in the coagulation system with a typical misbalance between coagulation factors and inhibitors. These changes may be attributed to impaired hepatic synthesis or protein excretion,12,20 as well as rapid clearance of proteins or weak intrinsic activities due to hypoglycosylation.10 A recent study showed an increased risk of thromboembolic complications for patients who undergo invasive procedures and those who are immobilized but not for those with infection or fever.12 However, these clinical features have been attributed to a trigger mechanism, possibly dehydration and resulting metabolic derangement,1,13 as was seen in our case. Hepatic cytolysis and serum coagulation parameters normalize with time due to metabolic stabilization.13

So far, the cases of only 2 patients with PMM2-CDG and cerebral hemorrhage have been described.3,10,18 One patient presented with thalamic and intraventricular bleeding on the 10th postnatal day, and a fatal outcome due to organ failure with cardiac arrest after 29 days was observed. In that case, levels of the patient’s coagulation factors IX and XI and AT III were reduced, and multivisceral involvement was confirmed by autopsy.18 In a Scandinavian series,10 another cerebral hemorrhage due to hypoprothrombinemia was evident in 1 child in the infantile alarming multisystem stage.

Another case report described the fatal outcome of a patient with deficiency of subunit 6 of the conserved oligomeric Golgi complex (COG6-CDG) and cerebral bleeding due to vitamin K deficiency.13

Interestingly, the patient in our case was diagnosed with PMM2-CDG after cerebral hemorrhaging that required neurosurgical intervention due to the volume effect and raised intracranial pressure. The clinical aspects of muscular hypotonia, strabismus convergens, and psychomotor retardation were indicative of PMM2-CDG, although the usual dysmorphic features of this disorder, such as inverted nipples and atypical body fat distribution, were missing. However, the typical cerebellar atrophy on MRI was evident.

In a neuroradiological examination, a vascular lesion was ruled out originally due to unremarkable MR angiography results, which should have revealed the presence of an arteriovenous malformation. The impressive mass of the lesion with midline shift and slight contrast enhancement initially led to the diagnosis of a malignant brain tumor, such as atypical teratoid/rhabdoid tumor or PNET, which are among the most common malignant supratentorial brain tumors in children.15,23

This initial impression was maintained during surgery. However, thrombotic dural veins were evident, suggesting a secondary hemorrhage after venous thrombosis rather than a primary hemorrhage. However, on histopathological examination, thin-walled vessels, as seen in cavernous malformations, became evident. Glycogen deposits around
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the vessels raised the suspicion of a glycogen storage disease originally. Also, vacuolar degeneration of smooth muscle cells in addition to local accumulation of glycogen may render arterial vessel walls fragile and predispose for hemorrhagic events. Unfortunately, vacuolar degeneration of smooth muscle cells was detected only by electron microscopy, which was not performed in this case.

Conclusions

CDG syndrome rarely presents with cerebral hemorrhage, although it involves a complex dysfunction of coagulation factors and inhibitors. Because hemorrhagic and thrombotic events may occur in the same patient, the use or avoidance of antithrombotic therapy cannot be recommended. Unexplained cerebral hemorrhage in the pediatric neurosurgical setting should raise suspicion of a metabolic disorder and should be discussed with specialists to rule out the presence of an orphan disease, such as PMM2-CDG, by screening for inborn errors of metabolism.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Matula, Stefanits, Konstantopoulou. Acquisition of data: Stefanits, Konstantopoulou, Kuess, Milenkovic. Analysis and interpretation of data: Stefanits, Konstantopoulou, Kuess, Milenkovic. Drafting the article: Stefanits. Critically revising the article: Matula, Stefanits, Konstantopoulou, Milenkovic. Reviewed submitted version of manuscript: Matula, Stefanits, Konstantopoulou, Milenkovic. Approved the final version of the manuscript on behalf of all authors: Matula. Study supervision: Matula.

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