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Association between acute complications in PMM2-CDG patients and haemostasis anomalies: Data from a multicentric study and suggestions for acute management

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ABSTRACT

Objectives: Patients with PMM2-CDG develop acute events (stroke-like episodes (SLEs), thromboses, haemorrhages, seizures, migraines) associated with both clotting factors (factor XI) and coagulation inhibitors (antithrombin, protein C and protein S) deficiencies. The aim of the study was to correlate acute events to haemostasis and propose practical guidelines.

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Haemorrhages
Emergency protocol

Methods: In this multicentric retrospective study, we evaluated clinical, radiological, haemostasis and electroencephalography data for PMM2-CDG patients hospitalized for acute events. Cerebral events were classified as thrombosis, haemorrhage, SLE, or "stroke mimic" (SM: normal brain imaging or evoking a migraine).
Results: Thirteen patients had a total of 31 acute episodes: 27 cerebral events with 7 SLEs, 4 venous thromboses, 4 haemorrhages (3 associated with thrombosis), 15 SMs at a mean age of 7.7 years; 4 non-cerebral thromboses, one of which included bleeding. A trigger was frequently involved (infection, head trauma). Although sometimes normal at baseline state, factor XI, antithrombin and protein C levels decreased during these episodes. No correlation between haemostasis anomalies and type of acute event was found.
Discussion: Acute events in PMM2-CDG are not negligible and are associated with haemostasis anomalies. An emergency protocol is proposed for their prevention and treatment (https://www.filiere-g2m.fr/urgences). For cerebral events, brain Magnetic Resonance Imaging with perfusion weight imaging and diffusion sequences, electroencephalogram and haemostasis protein levels guide the treatment: anticoagulation, antithrombin or fresh frozen plasma supplementation, antiepileptic therapy. Preventing bleeding and thrombosis is required in cases of surgery, prolonged immobilization, hormone replacement therapy.
Conclusion: Acute events in PMM2-CDG are associated with abnormal haemostasis, requiring practical guidance.

1. Introduction

Due to the importance of glycosylation for the function of many proteins, impairment of this process results in broad multisystem manifestations [1,2]. Phosphomannomutase 2 is a cytosolic enzyme involved in the mannose pathway that is required for the first steps of the N-glycosylation process [3]. Phosphomannomutase 2 deficiency, or PMM2-CDG, is the most common disorder of N-glycosylation [4]. The clinical presentation varies among patients, but neurological symptoms are almost always present, including hypotonia, developmental delay, cerebellar atrophy and hypoplasia with ataxia, peripheral neuropathy, and less frequently, epilepsy [1,2]. In addition to neurological signs, visceral features can be present including cardiac features, feeding difficulties, liver or other organ features. Coagulation abnormalities are also frequent, including low levels of both clotting factors (factor XI (FXI) and, less frequently, factor IX) and coagulation inhibitors (especially antithrombin (AT), protein C (PC) and protein S (PS)) [2,5–8], which lead to haemostatic unbalance and is often accompanied by a procoagulant phenotype [9]. In addition to the chronic symptoms of the disease, patients with PMM2-CDG can present acute neurological events such as seizures [10,11], stroke-like episodes (SLEs) [2,12], cerebral sino-venous thrombosis (CSVT) [13], or haemorrhagic strokes [2]. SLEs are the most frequent acute neurological event [2,6,12,14]. Systemic thrombosis and haemorrhage are also reported [13]. In a cohort of 96 patients, we retrospectively reported 20 acute events in 19 patients (mostly SLE, more rarely cerebral thrombosis, cerebral haemorrhages and peripheral venous thrombosis), with no detail on haemostasis in regards [2]. Moreover, the radiological data have not been controlled by a same neuroradiologist while the definition of cerebral complications is crucial, e.g. SLE. More recently, of about 50 patients, De Graef et al. reported in a prospective study 36% of patients with bleeding (from easy bleeding to hematemesis), 18% of patients with SLE and 10% with thrombosis [5]. These acute events most often present with confusion, acute mono- or hemiparesis, epileptic seizure, or headache [1]. They are often triggered by fever or head trauma. We aimed to address the association between such acute complications and the coagulation unbalance in PMM2-CDG patients. Here, we describe 31 acute events, including neurological episodes and non-cerebral thrombosis or bleeding, occurring in 13 patients with PMM2-CDG. We discuss the physiopathology and management of these events, from diagnosis to treatment.

2. Patients and methods

This multicentric retrospective study included PMM2-CDG patients with biochemical and genetically proven diagnosis (transferrin isoform analysis by capillary electrophoresis or western blotting and *PMM2* gene mutation analysis) [15] followed at Necker Hospital or other reference or competence centers for rare inherited metabolic diseases in France for whom our group of experts (Necker metabolicians, hematologists, neurologists) had been contacted for at least one acute episode until 2021, with sufficient data available. Clinical, radiological (tomography and/or magnetic resonance imaging), biological and electroencephalography data during acute episodes were collected from the medical records. We noted the time for clinical recovery (<24 h or >48 h) and acute treatments. Absence of recovery was considered if clinical signs were still reported at six months after the acute episode.

Levels of coagulation proteins (prothrombin time (PT), AT, FXI, PS and PC) were recorded in the basal state and during acute events, when available. Mean levels of coagulation proteins were calculated, when the patient had multiple biological assessments.

Because the definition of neurological complications remains crucial, available images were reviewed by the paediatric neuroradiologists of the French center for paediatric stroke (Necker Hospital, Paris). According to imaging findings, neurological events were classified as 1) cerebral sino-venous thrombosis, 2) cerebral haemorrhage, 3) stroke-like episode (SLE) as defined in the literature for mitochondrial diseases (acute neurological symptoms (motor and/or language deficit, visual field deficit) associated with hypersignal on DWI (diffusion weight imaging) MR sequence not restricted to an arterial territory without sinovenous thrombosis; with a specific imaging pattern differentiating it from stroke, e.g. initial vasogenic edema (normal or high ADC sequence) that can also be mixed with cytotoxic edema (restriction of ADC), and local hyperperfusion) [16], and 4) "stroke mimic" (SM), which corresponds to acute neurological clinical symptoms without signs of arterial thrombosis (ischaemic stroke), venous thrombosis, haemorrhage, or stroke-like on brain imaging. Brain imaging can be normal or shows only perfusion weight imaging (PWI) abnormalities (in arterial spin labelling (ASL) sequence) and no diffusion abnormality, suggesting postictal state or migraine. We also classified as "stroke mimic" episodes those without available brain imaging ($n = 1$). For some episodes, brain imaging showed more than one type of event.

Electroencephalography was considered abnormal if asymmetry, slow waves, spikes or epileptic seizures were mentioned in the report.

2.1. Statistical analyses

The Shapiro–Wilk test was employed to assess the normality of variable distribution. Normally distributed continuous data are summarized as means ± standard errors of means (SEMs) and non-normally distributed continuous data as medians with interquartile range (IQR). Parametric tests were performed when data were normally distributed; otherwise, nonparametric tests were used. For normally distributed data, an unpaired *t*-test was applied for comparisons of 2 groups. Welch's correction was performed when variances were unequal. In the case of nonnormally distributed data, the Mann–Whitney test was used to compare 2 groups. For comparisons of more than two groups, the significance of changes was examined with a one-way ANOVA followed by

a Fisher's Least Significant Difference (LSD) post hoc test when data were normally distributed. Unpaired t-test with Welch's correction was performed when variances were unequal. Prism 9.3.1 (GraphPad Software, San Diego, CA) was used for the data analysis. Significant differences are indicated as * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, and **** $p < 0.0001$.

2.2. Ethics

We collected medical data from French Hospitals where PMM2-CDG patients were hospitalized for acute events (non-scheduled admission). The medical management was prescribed by physicians as part of routine care in case of acute events related to the PMM2-CDG disease. According to French legislation, during medical consultations and routine care, we informed the patients and/or their parents or legal representatives that their medical data could be collected for research purpose.

Unless specifically declined, their reticence was taken as consent, and it was noted in their medical record. All data were anonymised and stored in a secure, password-protected database, and remain confidential, in accordance with the French and European legislation and regulations on data protection.

3. Results

3.1. Patient description

Of the 58 patients with PMM2-CDG followed up in one of the centers participating in the study, thirteen patients (22%) have had at least one acute episode up to the end of 2021. Thirteen patients (born between 1995 and 2020; 8 males and 5 females) experienced a total of 31 documented acute episodes, with 27 acute neurological events (one was associated with non-cerebral thrombosis) and 4 non-cerebral venous thromboses, one of which was associated with bleeding. All patients had previous neurological or radiological chronic symptoms of PMM2-CDG: cerebellar syndrome ($n = 13$), developmental delay (n = 13), neuropathy ($n = 6$), strabismus ($n = 8$), cerebellar atrophy and hypoplasia on brain MRI (n = 13). Multivisceral symptoms were present in 10 patients, including failure to thrive ($n = 9$) or pericardial effusion (n = 6) (Table 1).

3.2. Neurological acute episodes

a. *Clinical symptoms*

The 27 neurologic acute events occurred at a mean age of 7.7 years old (range: 1 month-17 years). Some events ($n = 4$) included several types of complications (e.g. thrombosis and haemorrhage in the same event). Five patients presented several events at different times during their follow-up (max. 7 per patient), of different types (see focus Patient 3). The mean age for the first episode was 5.6 years old. The most frequently reported acute symptoms were hemiparesis ($n = 16$), altered consciousness ($n = 15$), aphasia or dysphasia ($n = 11$), seizure ($n = 10$), emesis (n = 10), headache ($n = 7$), and facial palsy ($n = 5$). A trigger was noted for 24/27 episodes, the most frequent being concurrent infection, with ($n = 18$) or without ($n = 2$) fever, and recent head trauma (<48 h; $n = 8$), usually minor. Clinical recovery was fast in most cases: <24 h for 10 episodes and <48 h for 4 episodes. No patient had persistent neurologic sequelae 6 months after the acute episode.

b. *Brain imaging*

Brain imaging was available for all acute neurologic events except one, including 23 MRIs and 3 brain CTs. In most cases, imaging was

Table 1
Clinical and biological characteristics of 13 patients with PMM2-CDG.

Patient	Year of birth	Age at diagnosis (months)	Clinical presentation of PMM2-CDG	Haemostasis proteins in the basal state in % (PT, AT, FXI, PS, PC)	Mutations in the *PMM2* gene
1	2004	24	N (developmental delay, swallowing and sucking trouble, neuropathy) O (strabism, nystagmus)/C (conotruncal cardiac malformations and pericarditis) failure to thrive, deafness (mild)	100/82/100/66/100	R141H/E139K
2	1999	10	N (developmental delay, ataxia, peripheral neuropathy) O (strabism)/C (pericarditis)/feeding difficulties, scoliosis	97/38/31/63/53	R141H/T237M
3	2011	9	N (developmental delay, ataxia, headache, neuropathy) O (strabism)/C (pericardial effusion)	100/57/45/79/69	R141H/I153T
4	1999	2	N (developmental delay, epilepsy, neuropathy, ataxia) O (retinitis pigmentosa, strabism)/feeding difficulties, elevated transaminases, renal tubulopathy, hyperinsulinaemic hypoglycaemia	93/56/17/41/50	P113L/C9fs
5	2010	10	N (developmental delay, headache) O (strabism)	86/−/32/−/−	R141H/L244R
6	2015	< 1	N (developmental delay) O (strabism)/C (pericardial effusion)/feeding difficulties	100/63/62/52/90	V129M/F157S
7	2001	48	N (developmental delay, ataxia, behavioural problems, dysarthria, epilepsy)	89/89/80/−/−	R21G/V129M
8	2010	1	N (developmental delay, swallowing and sucking troubles, neuropathy) C (pericardial effusion)/nephrotic syndrome, diarrhoea, failure to thrive, elevated transaminases	NA	V129M/R141H
9	2019	5	N (developmental delay)/diarrhoea, failure to thrive, elevated transaminases	−/21/−/20/61	R123Q/V231M
10	1995	NA	N (developmental delay, ataxia, epilepsy, neuropathy)	NA	R141H/I132T
11	2020	1	N (developmental delay) O (strabism)/failure to thrive, elevated transaminases	NA	R141H/T237M
12	2015	12	N (developmental delay, neuropathy) failure to thrive, diarrhoea, hypothyroidism	67/36/27/48/40	G117C/G117C
13	2009	7	N (developmental delay, epilepsy)/feeding difficulties, elevated transaminases C (pericarditis)/hypothyroidism, scoliosis, nephrotic syndrome, feeding difficulties, hyperinsulinism	100/92/68/69/104	R141H/F119L

All patients presented cerebellar syndrome. N: neurologic; C: cardiac; O: ophthalmologic; NA: not available. PT: prothrombin time; AT: antithrombin; FXI: factor XI; PS: protein S; PC: protei.

performed <24 h after symptom onset ($n = 17$) or between 24 and 48 h ($n = 6$). After reanalysing the data by the paediatric neuroradiologists of the French center for paediatric stroke, we found 7 SLE, 4 venous thrombosis, 4 haemorrhage and 15 remaining episodes that have been defined as "stroke mimics" (Table 2).

Except for one, the cerebral venous thromboses were triggered by fever ($n = 2$) or sinusitis (n = 1).

Among the 4 cases of cerebral haemorrhage, 3 were associated with thrombosis. These haemorrhages were probably a direct complication of the thrombosis having occurred during this acute event; for one patient, the episode of thrombosis and haemorrhage was inaugural and occurred at the age of only one month old. The isolated episode of cerebral haemorrhage occurred after sepsis following primitive peritonitis and preventive anticoagulant therapy administered before insertion of central venous access because of abnormal haemostasis (Patient 9, Tables 1 and 2).

Among the 15 "stroke mimics" (SMs), there were 5 episodes with slight MRI anomalies evoking postictal state or migraine with aura, 9 with normal brain imaging except for cerebellar atrophy and hypoplasia (3 tomography without MRI and 6 MRI without details of the sequences or at least no interpretable perfusion sequences), and 1 episode with only clinical symptoms (altered consciousness) but no brain imaging available.

c. *Electroencephalography*

Table 2
Levels of haemostasis proteins during each acute episode.

Episode n° (Patient)	Type of episode	PT (%)	AT (%)	FXI (%)	PS (%)	PC (%)
1 (P1)	SLE	100	52	63	-	79
2 (P1)	SM	-	-	-	-	-
3 (P1)	SM	39	32	-	-	-
4 (P2)	SM	68	-	-	-	-
5 (P2)	SM	-	-	-	-	-
6 (P2)	SM	-	-	-	-	-
7 (P2)	SM	-	-	-	-	-
8 (P3)	SLE	63	24	-	75	25
9 (P3)	Th + Hem	47	13	9	-	-
10 (P3)	SM	62	16	21	58	-
11 (P3)	SM	69	26	26	52	18
12 (P3)	SM	84	13	24	45	18
13 (P3)	SM	67	24	-	-	-
14 (P3)	SM	67	21	25	52	8
15 (P4)	SLE	73	37	13	41	48
16 (P4)*	SLE + Th^P	–	-	-	-	-
17 (P4)	SM	-	-	-	-	-
18 (P4)	SM	-	-	-	-	-
19 (P4)	Th^P	-	-	-	-	-
20 (P5)	Th + Hem	55	10	15	-	-
21 (P6)	SLE	60	22	39	39	-
22 (P6)	SLE	67	69	46	-	-
24 (P7)	Th	64	24	33	70	43
25 (P8)	SLE	-	-	-	-	-
26 (P9)	Hem	93	36	24	-	-
27 (P10)	Th^P	-	-	-	-	-
28 (P11)	Th + Hem	-	12	14	35	10
29 (P12)**	SM	55	36	39	-	-
30 (P13)	Th^P + Hem^P	-	-	-	-	-

SLE: Stroke-like event; SM: stroke mimic; Th: cerebral thrombosis; Th^P: peripheral (non-cerebral) thrombosis; Hem: cerebral haemorrhage; Hem^P: peripheral Haemorrhage PT: prothrombin time; AT: antithrombin; FXI: factor XI; PS: protein S; PC: protein C.

* No quantitative values available but disseminated intravascular coagulation with "all factors low" mentioned in the medical report of this event.

** This patient presented before this recent episode (the only one documented and included in this study) with 5 other episodes of SM between 4 and 6 years of age revealed by a hemicorporeal deficit, which evolved favourably between 24 h and 4 days, spontaneously or after AT infusion.

Electroencephalography performed during 15 episodes was always abnormal. EEG showed either diffuse slowing (11 episodes), asymmetry (12 episodes), seizures or spike-and-wave discharges (8 episodes).

d. *Haemostasis proteins assessed in the basal state*

Haemostasis proteins assessed in the basal state were available for 9 of the 11 patients with acute neurological events (Table 1). Overall, mean PT (92%; $n = 9$, min-max: 67%–100%; normal range > 70%) and PC (71%; $n = 8$, min-max: 40%–104%; normal range > 70%) values were normal. In contrast, mean AT (59%; n = 9, min-max: 21%–92%; normal range > 80%), FXI (51%; n = 9, min-max: 17%–100%; normal range > 70%) and PS (55%; n = 8, min-max: 20%–79%; normal range > 70%) values were low (Fig. 1). Importantly, 2 patients had normal or subnormal basal haemostasis values (P1, who displayed 1 SLE and 2 SM; P7, who had 1 cerebral thrombosis). Baseline values were normal for PT in 8 patients, for AT in 3 patients, for FXI in 2 patients, for PS in 1 patient, and for PC in 3 patients.

e. *Mean value of coagulation proteins during acute episodes*

During acute episodes, the mean value of coagulation proteins tended to decrease significantly compared to baseline values for PT, AT, FXI and PC (reduction of 30 to 40% depending on the type of proteins) (Fig. 1). In all patients, at least one abnormal coagulation protein level was detected (Fig. 1, Table 2). FXI and AT values were never normal; PT, PC and PS values were occasionally normal (Fig. 1, Table 2). Considering the coagulation profile by type of acute neurologic episode, AT and FXI, and even PC when available, were very low in thrombosis and haemorrhage episodes (Fig. 2). These proteins also decreased in SM. Although often abnormal, they were higher in SLE than in other types of acute episodes (Fig. 2). Notably, there were fewer available levels for PC and PS during acute episodes.

f. *Treatments*

Treatments during acute episodes included anticoagulation (low molecular-weight heparin-LMWH, or unfractionated heparin (UFH)) prescribed at curative doses in 3 of 4 episodes of cerebral thrombosis (of which 2 were complicated with haemorrhage). One patient did not receive anticoagulation because of haemorrhage.

AT infusion was administered during 8 neurologic episodes: 3 thromboses (1 in Patient 3 who was not given anticoagulation because of an associated haemorrhage and 2 more in association with LMWH (of which 1 complicated by haemorrhage), 3 SLEs (1 secondary to non-cerebral venous thrombosis), 1 SM and 1 haemorrhage). During this last haemorrhage episode, AT was administered in association with prophylactic LMWH before providing central venous access in a patient experiencing sepsis and peritonitis and presenting a low blood level of AT. This patient also showed neurologic acute symptoms, which led to a diagnosis of subdural haematoma.

Fresh frozen plasma (FFP) was administered in association with AT in 4 episodes (1 haemorrhage combined with thrombosis, 1 non-cerebral venous thrombosis associated with SLE, and 2 isolated SLEs) and was administered alone in 2 episodes of SM. In 3 episodes (2 SMs and 1 SLE), clinicians noted almost instant recovery of coma immediately after infusion of FFP.

Aspirin at anti-aggregate doses was administered to 2 patients after SLE or SM, outside of an acute episode, but both patients experienced other acute episodes (SLE or SM) under this treatment.

Anti-epileptic drugs were applied in 7 acute neurological episodes.

Notably, arginine was prescribed after an episode of SM in Patients 1 and 2 (after their third and fourth acute events, respectively). For another patient, arginine was prescribed as a preventive treatment for SLE a few months after diagnosis of PMM2-CDG. He presented with cerebral thrombosis associated with cerebral haemorrhage under this

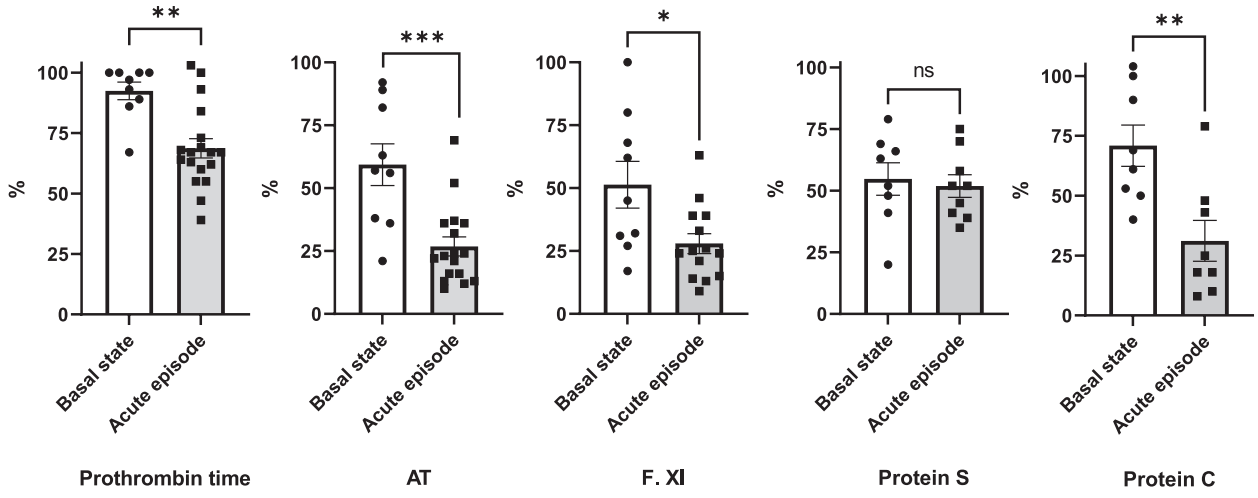

Fig. 1. Evolution of mean levels of haemostasis proteins (in percentage) during acute episodes. Levels of coagulation proteins in the basal state (white) and during acute episodes (grey) were compared using an unpaired t-test. Welch's correction was performed when variances were unequal. Graphs represent means ± SEMs. Significant differences are indicated as * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, and **** $p < 0.0001$. AT: antithrombin; FXI: factor XI.

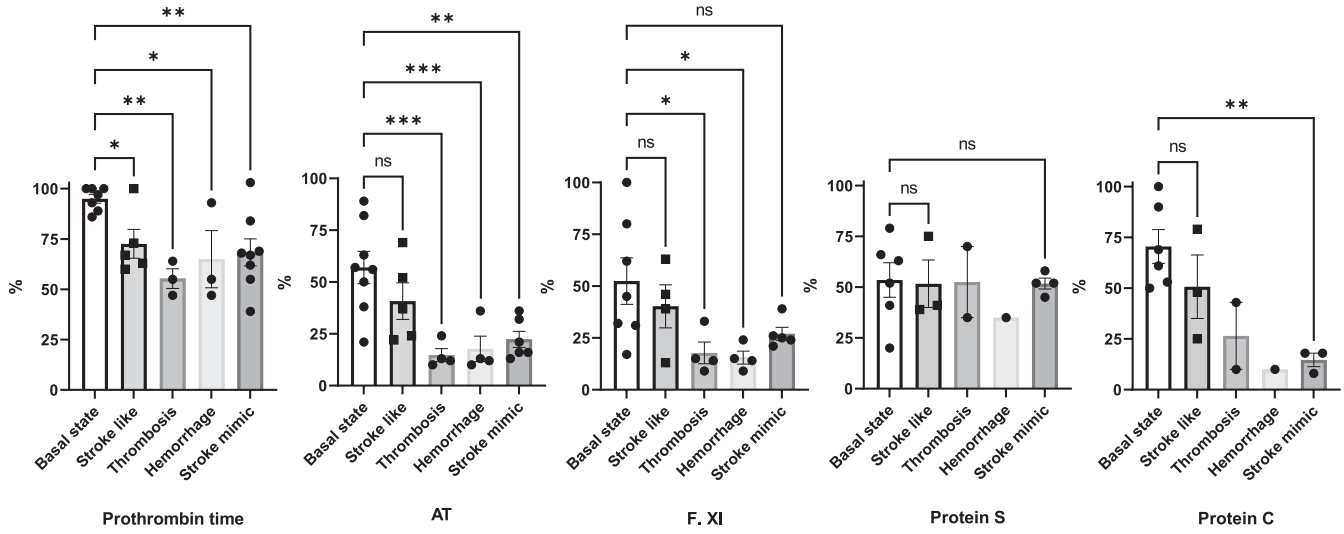

Fig. 2. Evolution of mean levels of haemostasis proteins (in percentage) during acute episodes according to the type of episode. Levels of coagulation proteins in the basal state (white) and during each types of episodes (grey) were compared using a one-way ANOVA followed by a Fisher's Least Significant Difference (LSD) post hoc test. Graphs represent means ± SEMs. Significant differences are indicated as * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, and **** $p < 0.0001$. AT: antithrombin; F.XI: factor XI.

treatment.

3.3. Non-cerebral venous and arterial events

We also found 4 episodes of non-cerebral vascular events. 1) One case of arterial thrombosis in the right ilio-femoral artery in Patient 4 at the age of 6, occurring after arteriography because of asymmetry in the pulses and temperature of the right lower limb. The patient presented post arteriography fever and finally developed right hemiparesis and right facial palsy. His brain MRI showed evidence of SLE. All coagulation proteins were low (DIC), lower than in the basal condition (Tables 1 and 2). He was treated with FFP and AT infusion but not by anticoagulation because of the DIC and risk of haemorrhage. 2) The second episode, a thrombosis of the iliac vein, occurred in the same patient 13 years later, when he was under anti-aggregant treatment, without any trigger. The anti-aggregant treatment was then switched to an inhibitor of factor Xa (Rivaroxaban). 3) The third episode occurred in Patient 10 at the age of 23 years old, with thrombosis in all the left tibial posterior veins. No trigger was found. His coagulation levels were low (Table 2). UFH followed by antivitamin K treatment was prescribed. 4) The last episode occurred in Patient 13 at 13 years old, 3 days after surgery for her scoliosis and placement of a central venous line. The patient had normal or subnormal baseline coagulation levels (Table 1). This episode started with severe oesophageal haemorrhage caused by dilaceration of the mucosa after use of a nasogastric tube associated with nonsteroid anti-inflammatory treatment. One day later, the patient presented complete thrombosis of the femoral vein, with extension to the external iliac vein. UFH therapy was initiated, associated with AT supplementation to potentiate their action, despite risk of recurrence of the haemorrhage (FFP was planned). Her coagulation protein levels during this acute episode were low (Table 2).

None of the patients had sequelae at 6 months after the non-cerebral

episode, except for one who still presented with lower limb oedema at 6 months after thrombosis of the posterior tibial vein.

3.4. Focus on Patient 3: multiple acute neurological events

To illustrate the diversity of these acute episodes, which sometimes occurred in a single patient, we describe the clinical history of Patient 3 (Table 1), who presented 7 episodes during follow-up (1 SLE, 1 cerebral thrombosis with haemorrhage, 5 SMs; Table 2). There was no history in the family of such events, especially no vascular issues. The first coagulation assessment showed normal PT and PS but low AT, FXI and PC (Fig. 3 and Table 1). Moreover, her coagulation proteins decreased from baseline levels in each acute episode (Fig. 3 and Table 2).

At 4 years of age, she presented with mild head trauma, fever and sore throat, with feeding difficulties. After a few days, she presented a disturbance in consciousness, opisthotonos and abnormal eye movements evoking seizures. The seizures stopped with anti-epileptic treatment (diazepam and clonazepam), and right hemiparesis was observed. EEG showed diffuse slowing. Brain MRI showed important increased perfusion in left hemisphere and in left thalamus consistent with a "stroke-like" episode (Fig. 4A). Cerebellar and vermian atrophy with a hypotrophic brain stem was also present (already known). She recovered within two days, with no specific treatment.

At 6 years of age, she developed otitis with fever, feeding difficulties, and progressive decline in her general condition. After 7 days, she experienced a severe headache, central left facial palsy, emesis with arterial hypertension evoking elevated intracranial pressure and one short episode of loss of consciousness with eye rolling. Initial EEG was asymmetric, slow on the right side, with brief infraclinical seizures on the left fronto-centro-temporal area. In the next days, it improved with more physiologic elements on the left side, and finally slow spikes on the right fronto centro temporal area. Brain MRI showed ischemic and haemorrhagic changes in the right central area secondary to adjacent venous cortical thrombosis (Fig. 4B). Because of the imaging results and decreased haemostasis proteins (Fig. 3 and Table 2), FFP and AT infusion were administered during the first 48 h of hospitalization. Her clinical symptoms disappeared within 48 h, and blood tests returned to the basal state on day 5.

At 7 years of age, she had 2 distinct episodes of moderate headache secondary to fever in both cases. The first time, no brain imaging was performed. The second time, early injected brain tomography was normal. Because of the previous history of cerebral thrombosis and presence of disturbed coagulation proteins (Fig. 3 and Table 2), preventive infusion of AT was administered during the first episode. Her symptoms disappeared within 24 h in both episodes. These episodes were categorized as SM.

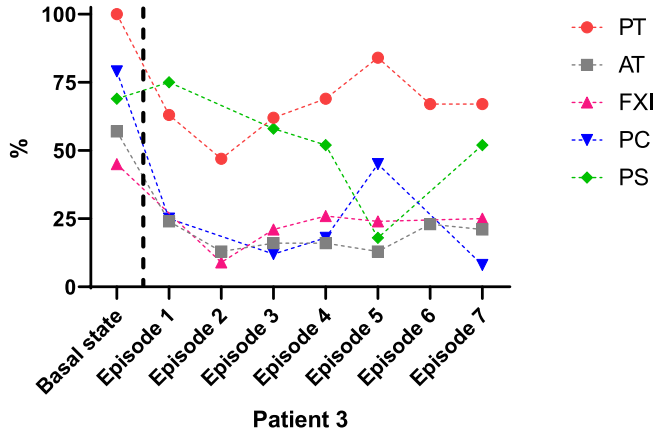

Fig. 3. Evolution of haemostasis proteins during follow-up of Patient 3 (in percentage).
PT: prothrombin time; AT: antithrombin; FXI: factor XI; PC: protein C; PS: protein S.

At 8 years of age, she presented again with fever after a small head trauma and neurological symptoms with elocution troubles, headache, drowsiness, right upper limb defect and vomiting in the ensuing hours. EEG was asymmetric, slower on the left side, with right temporo-occipital spikes diffusing to the left side, evoking a postictal state. Brain MRI showed in the left temporoparietal area an important ASL hypoperfusion and a major increase in the visibility of veins in susceptibility weighted imaging (SWI), equivalent to migraine with aura or postictal defects (Fig. 4C). Because of these results and the repetition of episodes of headache in a patient at risk of seizure, topiramate was introduced. The patient recovered within a few days (>48 h).

At 9 years of age, after a mild head trauma and then fever, she presented moderate troubles of consciousness, with no focal neurologic defect. Brain tomography was normal, and no EEG was performed. She recovered within 72 h with antalgic treatment.

At 11 years of age, another episode of altered consciousness, vomiting and headache occurred concomitant with fever. Enterovirus and rhinovirus were detected in nasopharyngeal smears. Coagulation profile was similar to those under basal conditions. As when she was 8 years old, brain MRI showed FLAIR hypersignal and ASL hypoperfusion in the hippocampal and left temporal areas but no anomalies in SWI sequences, also evoking a migraine with aura or postictal state but perhaps less severe. EEG was slow and nonreactive to external stimuli. After 48 h of traditional treatment for migraine (ibuprofen), she underwent lumbar puncture and treatment with amitriptyline because there was no improvement in consciousness. An FFP infusion was performed just prior to the procedure because her coagulation proteins worsened after 48 h (Fig. 3 and Table 2). Both treatments allowed her to improve dramatically within a few hours.

4. Discussion

We reported herein 31 acute events, of which 27 neurological episodes and 4 non-cerebral venous thromboses (one with bleeding) occurred in 13 patients with PMM2-CDG. The 27 neurological episodes included different types of events (thrombosis, SLE, haemorrhage, SM) reviewed by the paediatric neuroradiologists of the French center for paediatric stroke, and SLE and SM were the most frequent, in line with literature [2,12]. During acute episodes, the mean value of measured coagulation parameters tended to decrease and was significantly lower than basal levels for PT, AT, FXI and PC. Although strokes and SLE are well known to occur in PMM2-CDG patients, migraine with aura has been less described [1]. Different types of events can occur in the same patient during follow-up (see focus Patient 3). Overall, the variability in the type of acute events, even in a single patient, is challenging for medical management.

Importantly, the clinical severity of the disease was not related to the occurrence of these acute events. Indeed, 3 patients (Patients 5, 7 and 10) presented a neurologic form of the disease without peripheral signs; these 3 patients displayed only thrombotic events, cerebral ($n = 2$) or non-cerebral ($n = 1$), and their basal levels of haemostasis proteins were either normal (Patient 7) or low (Patient 5).

Although coagulation proteins were abnormal at each acute episode for AT and FXI and most often for PC, we could not anticipate an acute episode for these patients, as at least 3 patients had normal or subnormal coagulation levels at baseline, as previously mentioned for Patient 7. Even in the multivisceral form of the disease, coagulation proteins may be normal at baseline (e.g., Patient 1 showed normal AT, FXI and PC levels). Similarly, we could not correlate levels of coagulation proteins in acute situations with the type of acute event, as AT, FXI and PC were low in thrombosis, haemorrhage and SM episodes but tended to be higher in SLE.

In our study, acute episodes were found in 22% of the patients with PMM2-CDG followed up in one of the participating centers. A recent prospective study on 50 patients reported complications in 23 patients

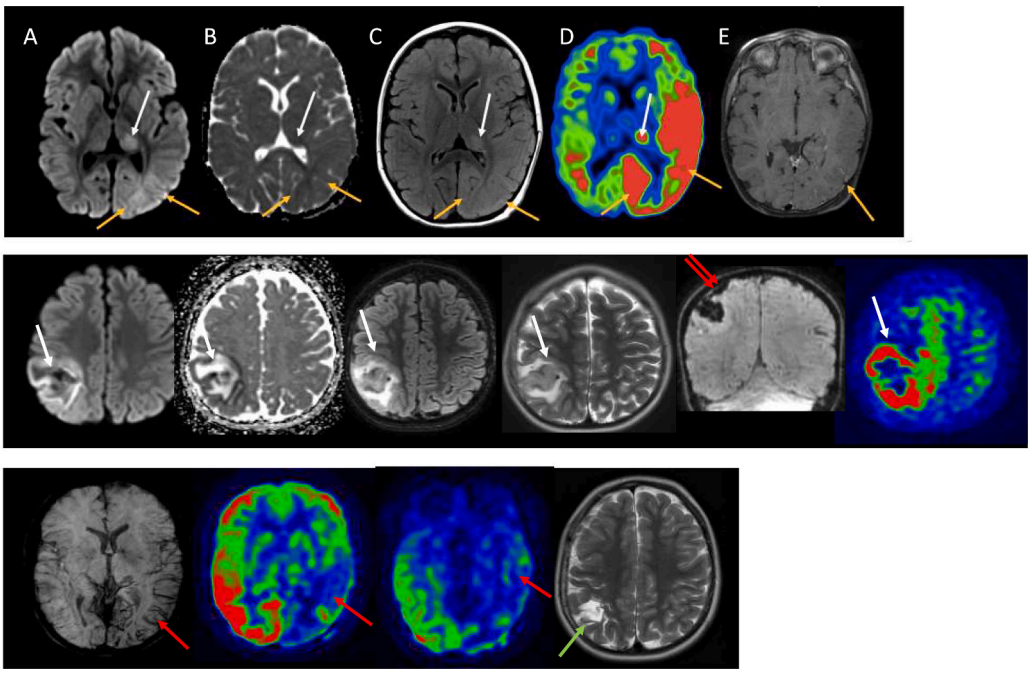

Fig. 4. Cerebral MRI during three acute neurologic events in Patient 3.
A: Brain MRI showed increased perfusion in left hemisphere and in left thalamus consistent with a "stroke-like" lesion. In details, hypersignal diffusion (A) with ADC restriction (B), hypersignal on FLAIR sequence (C), and ASL hyperperfusion (D) were shown in the left thalamus (white arrow) and in the left temporo-parieto-occipital cortico-subcortical area with additional sulcal hyperaemia after gadolinium injection (E) (yellow arrows). B: Cortical thrombosis (red arrow on SWI sequence) responsible for a right frontoparietal ischaemic-haemorrhagic accident (white arrows). C: Brain MRI showed in the left temporoparietal area an important ASL hypoperfusion and increased visibility of veins in susceptibility weighted imaging (SWI) and no abnormality in diffusion (red arrows), equivalent to migraine with aura or postictal defects. The green arrow in T2 demonstrates the sequelae of the ischaemic haemorrhagic episode on cortical thrombosis with focal right parietal atrophy. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(46%), including bleeding (36%), deep venous thrombosis (10%) and SLE (18%). [5] Bleeding was probably underestimated in our study as we did not include either easy bleeding/bruising or epistaxis. AT deficiency was described as the most frequently abnormal in PMM2-CDG patients [5] while in our study FXI was similarly decreased. However, AT activity positively correlated with FIX activity [5]. This recent study concluded that there was no significant increase in the risk of thrombotic events when the AT activity levels were higher than 65%. Nevertheless, at least one of our patients who experienced cerebral thrombosis had normal baseline AT. In this recent study, haemostasis protein values during acute episodes were not available except for 4 patients with deep venous thrombosis [5].

The same team published the case of a PMM2-CDG patient who underwent liver transplantation for severe liver disease, with normalization of haemostatic protein levels and no acute complications during 3 years of post-transplant follow-up [17], highlighting the link between haemostasis and complications.

In our study, infection and head trauma were the most frequent triggers. Clinical symptoms were variable, ranging from focal neurologic defects, impaired consciousness, seizure, and emesis to headache. Overall, clinical symptoms were not sufficient to define what type of event the patient experienced. Nevertheless, all patients with SLE in our cohort presented hemiplegia or hemiparesis. Seizures seem to be a factor of severity because they were present in all episodes of haemorrhage, 3 of 4 episodes of thrombosis and 6 of 7 episodes of SLE, as already described in the literature [2]. In contrast, seizures were absent in SM episodes. A quick and near complete recovery was observed for all SLE and SM patients, also as described in the literature [1].

Brain imaging, specifically brain MRI, with usual sequences but also perfusion-weighted imaging (such as arterial spin labelling ASL), seems to be key to better characterizing and treating these episodes, in association with EEG and the level of coagulation proteins. For SM, the ASL sequence was useful to diagnose the postictal state or migraine with aura (5 episodes), as they showed modifications of blood flow. In contrast, 9 brain images defined as normal probably included insufficient information (MRI without ASL sequences or tomography).

In SLE, brain MRI reveals vasogenic or cytotoxic oedema that is not restricted to arterial territories [12,18,19]. Although coagulation abnormalities can easily explain thrombosis and bleeding events [1,20], the role of haemostasis in the pathophysiology of SLE has not yet been characterized. There is no evidence of ischaemic occlusion during SLE episodes in the CDG [6,21,22], but the hypercoagulability state with elevated thrombin generation observed in patients with SLE [9,12] may still contribute, at least in part, to the occurrence of SLE and SM episodes [2,9]. Moreover, hyperthermia, which is the most common trigger of SLE, reduces the activity of PMM2 [23] and accentuates glycosylation defects, including those of coagulation proteins that are largely glycosylated [24]. Hyperthermia can also induce a conformational change in the AT protein, increasing risk of thrombosis [25,26]. Finally, platelet hyperaggregability during catabolic stress has been described in these patients as another ischaemic risk [27,28]. Without being able to affirm it, these different points could perhaps be involved in the acute manifestations during febrile episodes.

In migraine, the changes in blood flow might be explained by a suggested physiopathology of aura, consisting of cerebral microembolism that triggers cortical spreading depression (CSD), without causing an obvious or enduring tissue signature [29]. It is also known that patients with migraine with aura have increased risk of other cerebral acute vascular events, especially ischaemic stroke [30]. The occurrence of a transient ischaemic attack cannot be ruled out [19,31–33], and the role of hypercoagulability as a link between migraine, especially with aura, and stroke has been proposed [34]. In some other diseases, such as CADASIL syndrome, in which small blood vessels are affected, evolution during follow-up is first marked by

migraine with aura followed by transient ischaemic attacks or stroke [35]. Therefore, all these acute neurologic events might be initially triggered by hypoperfusion, clinical and radiological characteristics differ according to the severity of the initial hypoxic event (only migraine with aura for mild hypoperfusion to real SLE or stroke for severe or prolonged hypoxia). As already suggested in the literature for migraine [29], we could consider the neurologic acute events occurring in PMM2-CDG as a continuum of vascular complications.

We observed spectacular clinical improvement in some patients with SM or SLE after FFP administration that provides all the haemostasis proteins. The clinical neurological improvement was indeed very fast, the transfused FFP brings coagulation proteins but probably also other deficient proteins in this period of stress in patients with PMM2-CDG.

Interestingly, Izquierdo-Serra et al. [19] found similarities between PMM2-CDG and channelopathies related to familial hemiplegic migraine (FHM), as caused by mutations in *CACNA1A,* encoding a subunit of the neuronal high voltage-activated Ca^{2+} channel Cav2.1. Indeed, in both diseases, ataxia, SLE triggered by mild head trauma or fever, and cerebellar atrophy occur [36,37]. This analogy led the authors to show a possible common physiopathology for SLE: gain of function of the Ca^{2+} channel Cav2.1 (either by mutations in *CACNA1A* or hypoglycosylation of the protein in PMM2-CDG) results in cortical excitatory neurotransmission, which promotes generation and propagation of cortical spreading depression (CSD), that may explain the symptoms of aura in migraine. In this hypothesis, fever or mild head trauma would trigger SLE in PMM2-CDG by increasing excitatory neurotransmission [19]. Findings to date have paved the way for possible new treatments for PMM2-CDG patients: in FHM, verapamil (Ca^{2+} channel antagonist) or acetazolamide improves symptoms and prevents acute events [19,38].' In PMM2-CDG, acetazolamide improves neurological symptoms and some coagulation parameters. [39] By analogy with chronic treatment sometimes used for migraine and epilepsy [31], we administered topiramate to patient 3, who nevertheless presented another episode of SM two years after its introduction. Topiramate is a voltage-dependent Na^{+} channel antagonist, but perhaps we should focus on the Ca^{2+} channel antagonists or carbonic anhydrase inhibitors in the future [39].

The consequences of haemostasis anomalies in PMM2-CDG patients are not easy to predict, since pro- and anticoagulant proteins decrease in all types of events (from thrombosis to bleeding), and because basal proteins can be normal in these patients. Prevention and treatment of acute episodes remain a challenge, as recently discussed [5]. In conditions associated with thrombosis risk, preventive anticoagulation is needed from adolescence because the patients often exhibit a procoagulant phenotype [9], but preventive treatment of thrombosis can increase the risk of bleeding. For example, since 2021 (end of our data collect), one of the participating centers had one patient aged 13 months who died from haemorrhage during a surgery, and another patient presented with phlebitis and pulmonary embolism at age 35 years (personal data). Because we need to anticipate and prevent these complications, we proposed an emergency protocol for our patients. This protocol was written by a multidisciplinary working group from the French G2M rare disease network representing all French reference and competence centers for IMDs, by colleagues from other specialties such as hematologists, neurologists and radiologists, by physicians from emergency and intensive care units, and by patient associations. The emergency protocol is given to patients and is also on the web page from the French G2M rare disease network (https://www.filiere-g2m.fr/urgences).

In case of an acute neurological episode, perform brain MRI with PWI or ASL and diffusion sequences in the first hours to precisely characterize the event, a systematic EEG to optimize potential anti-epileptic treatment (epileptic manifestations are not always clinically obvious), and a dosage of coagulation proteins compared to the basal state of the patient (made yearly), with at least measurement of PT, AT and FXI, but ideally also PS, PC. After performing these different examinations, we propose the following recommendations.

—In case of thrombosis (central or peripheric): Anticoagulation treatment with LMWH following current recommendations. Anti-Xa activity monitoring is essential due to potential deficiency of AT (target: 0.5–1 IU/ml 4 h after the 3rd SC injection in a child, in case of LMWH administration) [40]. If the level of AT is <70% or 20% or more lower than the basal level, we recommend an associated human AT infusion (bringing an anticoagulant effect and limiting the resistance to LMWH that may appear with AT deficiency). It may be possible to replace LMWH with anti-vitamin K after assessment of the patient's risk of bleeding. Rivaroxaban is now a possible therapeutic alternative in children, with respect to precautions of use (evaluation of renal function and hepatic assessment). If there is a bleeding risk on anticoagulation, FFP is not contraindicated if all haemostasis proteins are low.

—In case of haemorrhage or disseminated intravascular coagulation: infusion of FFP to correct the deficit in procoagulant proteins while maintaining a balance with anticoagulant proteins. If the haemorrhagic manifestations are not controlled despite administration of FFP, administration of human prothrombin complex (PPSB) (can only be considered after checking clotting factors and prefer medicinal products containing protein C and protein S such as Confidex ® or Octaplex ®). We contraindicate use of isolated procoagulant factors such as plasmatic concentrate FXI or recombinant activated FVII because of the associated risk of thrombosis.

—In the case of SLE, if coagulation proteins are 20% lower than the basal state or AT is <70% and/or Factor XI <40%, we suggest infusion of FFP rather than AT infusion to maintain the haemostatic balance between procoagulant and anticoagulant proteins. Corticosteroids may be added in cases of oedema with disorder of consciousness.

—In the case of migraine, symptomatic treatment with paracetamol or nonsteroid anti-inflammatory drugs (only if there is no portal hypertension) is suggested. The question of administration of FFP is not resolved (see focus Patient 3).

In the case of planned surgery, assess levels of all coagulation proteins at the anaesthetic consultation. Prophylactic administration of FFP in immediate preoperative care +/− AT infusion depending on clotting factor deficiencies, risk of bleeding during surgery, and risk of postoperative thrombosis should be discussed. Postoperatively, in cases of haemorrhagic complications, FFP transfusion is proposed; LMWH prophylaxis should be considered on a case-by-case basis, notably in cases of prolonged immobilization, after assessing the balance of bleeding vs. thrombosis risk relating to the patient and the surgical procedure, associated with support stockings.

Prevention of thrombosis in situations at risk such as prolonged bed rest, a cast, etc., should be discussed individually with prepubertal children depending on the medical history of the patient and coagulation profile, especially when there is an AT deficiency, associated with support stockings and hyperhydratation. Concerning the adults, we suggest following the usual recommendations for postoperative preventive anticoagulation. We propose LMWH; if started, anti-Xa monitoring is essential due to the potential deficiency of AT (target: 0.2–0.4 IU/ml 4 h after the 2nd or the 3rd SC injection in a child). If the anti-Xa target is difficult to obtain, consider administration of AT (target after perfusion: AT at the patient's baseline level, check 12–24 h after administration).

If hormone replacement therapy is needed (ovarian failure), oral estrogens are contraindicated to limit risk of thrombosis, however subcutaneous estrogen may be used. If contraception is needed, we recommend progestin contraception only or intra uterine device. Contraception with estrogen is contraindicated regardless the route of administration.

In case of fever, patients/parents and medical teams should routinely administer antipyretics and search more exhaustively for treatable infections, as fever is often associated with acute episodes.

5. Conclusion

Acute neurologic events are common in PMM2-CDG and are triggered by fever or trauma, including multiple types of events associated with abnormal haemostasis even when basal coagulation levels are normal. Brain MRI with specific sequences, electroencephalography and coagulation protein dosages may permit characterization of the event and management. Although their physiopathology is not well understood, all these complications may be part of a vascular continuum, from simple migraine with aura, which involves microcirculation, to SLE, thrombosis or haemorrhage, which are probably the consequence of larger vessel involvement. Based on these hypotheses, we propose an emergency protocol to provide highly practical guidance for prevention and immediate management of PMM2-CDG patients with acute events.

Author contributions

Camille Wicker, Annie Harroche, Pascale de Lonlay: Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data; provision of patient care.

Charles-Joris Roux: review of all brain images.

Yvan de Feraudy, Manoelle Kossorotoff, Tiffany Parscreau, Delphine Borgel: revision of the manuscript for content; analysis or interpretation of data.

Louise Goujon: Major role in the acquisition of data.

Marie Hully, Anais Brassier, Claire-Marine Bérat, Nicole Chémaly, Arnaud Wiedemann, Lena Damaj, Marie-Thérèse Abi-Warde, Dries Dobbelaere, Agathe Roubertie, Aline Cano, Alina Arion, Sabrina Da Costa, Nathalie Boddaert: provision of patient care, revision of the paper.

Anna Kaminska: EEG data.

Arnaud Bruneel, Sandrine Vuillaumier: diagnosis of PMM2-CDG.

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Declaration of Competing Interest

The authors Camille Wicker, Charles-Joris Roux, Louise Goujon, Yvan De Feraudy, Marie Hully, Anais Brassier, Claire-Marine Bérat, Nicole Chémaly, Arnaud Wiedemann, Lena Damaj, Marie-Thérèse Abi-Warde, Dries Dobbelaere, Agathe Roubertie, Aline Cano, Alina Arion, Anna Kaminska, Sabrina Da Costa, Arnaud Bruneel, Sandrine Vuillaumier, Nathalie Boddaert, Delphine Borgel, Tiffany Pascreau, Manoelle Kossorotoff, Annie Harroche, and P de Lonlay declare that they have no conflict of interest.

Data availability

The manuscript has no associated data.

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