RHEUMATOLOGY

Letter to the Editor (Other)

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Presentations and outcomes of juvenile dermatomyositis patients admitted to intensive care units

Rheumatology key message

- JDM exacerbations, especially vasculopathy-related complications, were the main cause of admission to the intensive care unit.

Sir, JDM may be complicated by life-threatening conditions requiring paediatric ICU (PICU) management [1, 2]. Here, we report on a retrospective study of JDM patients admitted to two French hospital PICUs, describing the causes, treatment and outcomes of these severe, little-known complications in order to improve their management.

We included patients with JDM (diagnosed according to Bohan and Peter's criteria) who were followed between 2005 and 2013 in two French referral centres for paediatric rheumatology and hospitalized in PICUs. Patients were registered, after parental consent (in accordance with the Declaration of Helsinki), in the national CEntres MAladies RAres (CEMARA) database approved by the French National Committee on Informatics and Liberty. No additional approval was required to use data from the CEMARA database in this study. The first line of treatment consisted of prednisone alone until 2012, and a combination of prednisone with MTX thereafter. We retrospectively reviewed the medical chart at admission to the PICU, the causes for admission to ICU, therapy and outcomes. The causes of admission were classified at PICU discharge either as certain or probable primary JDM involvement, therapy-related event or infection-related event. Gastrointestinal (GI) involvement was defined by severe abdominal pain, dysphagia, digestive haemorrhage and/or bowel obstruction or perforation. Complete remission of JDM was defined according to the PRINTO criteria as a Childhood Myositis Assessment Scale of $\geqslant$48, the absence of skin disease and a Physician's Global Assessment Score of $<$1.

Of the 116 JDM followed during the considered period, 11 (9.5%) were hospitalized once or twice (patients 5, 7) in the PICU. The median age at diagnosis of JDM was 9 years (range, 3–13.5). The median disease duration from the JDM diagnosis to the first admission to PICU was 9.0 months (range, 0–86.9), and six patients were admitted within 4 weeks following the diagnosis. The median Childhood Myositis Assessment Scale and manual muscle testing (MMT) scores at admission to PICU were 17/52 (range 0–28) and 48/80 (range 44–64), respectively. The median creatine phosphokinase value was 6135 IU/l (range 34–21208). Myositis-specific autoantibodies were present in the three patients who were tested [anti-NXP2 ($n=2$) and anti-MDA5 ($n=1$)]. Causes of PICU admission, treatments and outcomes are shown in Table 1. Complications were considered as certain ($n=8$) or possible ($n=1$) primary complications, as certain ($n=2$) or possible ($n=2$) treatment-related complications and/or as certain infection ($n=1$). Certain JDM-related complications consisted of gastro- ($n=4$) and cardiac ($n=2$) involvement, and thrombotic microangiopathy (TMA) ($n=2$). TMA was suspected and considered as a possible primary complication in patient 9, who had thrombocytopenia, haemolytic anaemia and proteinuria, but without assessment of schizocytosis. Three patients (patients 5, 7, 9) had a combination of a primary JDM complication and treatment toxicity. Certain treatment-related complications were posterior reversible encephalopathy syndrome in patient 9, who had a possible pre-existing TMA and anaphylactic shock secondary to a third infusion of rituximab (patient 10). The diagnosis of posterior reversible encephalopathy syndrome was supported by the occurrence of hypertension, seizures and typical lesions on brain imaging, 21 days after initiation of oral ciclosporin (5 mg/kg/day). In addition, we considered high doses of CSs as a probable predisposing factor for the development of bowel perforations in patients 5 and 7, who presented with severe abdominal pain suggestive of JDM vasculopathy-related intestinal disease. The short time span between the drug initiation and the development of perforation (5 and 3 days), and the reports of digestive perforations after steroids therapy in JDM patients with pre-existing severe abdominal pain [3, 4], support this probable causal relationship. Finally, patient 11 died from acute respiratory distress syndrome due to *Pneumocystis jirovecii* pneumonia, despite an appropriate cotrimoxazole therapy. Thus, most of the life-threatening complications resulted from specific JDM complications, especially from vasculopathy (GI vasculopathy or TMA). Indeed, digestive involvement has been linked to inflammatory vasculopathy with luminal narrowing or complete occlusion of multiple small and medium arteries, causing GI ulceration and perforation [3]. TMA, which has been rarely reported in adult and paediatric DM [5], is also due to endothelial damage. Altogether, our series confirms the recent study of Gitiaux *et al.* [6] emphasizing that severe outcome is linked to vasculopathy.

Prednisone ($n=9$) and plasma exchange (PE) ($n=7$), alone or in combination with rituximab or CYC were given to the nine patients who developed a certain or possible primary JDM-related complication; seven of them were previously unresponsive to a sustained course of CSs in combination with immunosuppressive drugs. PE was well tolerated, without any serious side effects. All the primary JDM complications completely remitted after

Table 1 Causes, treatments and outcomes of the patients admitted to PICU ($n = 11$)

Patient sex/age at JDM diagnosis (in years)	Disease duration/ activity before admission	Causes of admission in PICU	Treatment before PICU	Specific treatment of JDM in PICU	Others treatments in PICU	JDM disease status after PICU (MMT)	Treatment after discharge
		Certain primary JDM complications					
1/M/11.1	26 days (active)	Cardiac arrest	Pred[b] 2 mg/kg/day, MTX[b], MP	Pred 10 mg/kg/day, IVIG (2), plasma exchange (7), CsA	MV, VP, PhysioT	PR 34/80	Pred, HCQ CYC
2/F/13.4	2 years (active)	Digestive haemorrhage and ulcerations	Pred[b] 1.5 mg/kg/day, MTX[b], IVIG sub,[b] CsA[b]	Pred 1.5 mg/kg/day, IVIG sub, MTX, plasma exchange (9), RTX (4)	PN, ATB, PhysioT	PR 56/80	AZA, EN
3/F/7.9	21 days (active)	Renal thrombotic microangiopathy	Pred[b] 1.5 mg/kg/day, IVIG sub,[b] MP, CsA	Pred 2 mg/kg/day, IVIG sub, plasma exchange (13), RTX (4)	VP, ATB PhysioT	CR 75/80	None
4/F/8.2	6 days (active)	Digestive involvement, dysphagia	Pred[b] 2 mg/kg/day	Pred 2 mg/kg/day, IVIG (2), Plasma exchange (4), MTX	PN, ATB, PhysioT	PR 65/80	Pred, MTX, IVIG, RTX
5a/F/10.8	17 days (active)	Digestive sub-occlusion	Pred[b] 1.5mg/kg/day, MP, MTX	Pred 1.8 mg/kg/day, Plasma exchange (11), MTX	MV, PN, ATB, PhysioT	PR NA	Pred, MTX
5b/F/11.3	9 months (active)	Digestive perforation[a]	Pred[b] 0.6 mg/kg/day, MMF,[b] MP	Pred 2 mg/kg/day, IVIG sub, plasma exchange (15), RTX (4), MMF	MV, PN, ATB PhysioT	PR 34/80	Pred, MMF, EN
6/M/7.5	0 days (active)	Renal and retinal thrombotic microangiopathy		Pred 4 mg/kg/day, MP (4), IVIG (2), plasma exchange (5)	MV, PhysioT	CR 80/80	None
7a/F/11.2	10 months (active)	Bowel perforation[a]	Pred[b] 1.3 mg/kg/day, IVIG sub,[b] CsA, MP	Pred 1 mg/kg/day, MP (2)	MV, ATB, PhysioT	PR 65/80	None
7b/F/11.2	21 months (active)	Bowel perforation[a]	Pred[b] 1 mg/kg/day, CYC[b], MTX, MP	Pred 1 mg/kg/day, IVIG sub, RTX (2), CsA	PN, ATB, PhysioT	PR 54/80	EN
8/F/4.5	0 days (active)	Bradycardia		Pred 2 mg/kg/day, MP (4), CsA	EN, PhysioT	CR NA	None
		Certain treatment-related complications					
9/F/9.7	21 days (active)	PRES due to ciclosporin[a]	Pred[b] 2 mg/kg/day, CsA[b] MP	Pred 2 mg/kg/day, IVIG (2), Plasm[a] exchange (11)	MV, ATB, PhysioT	PR 76/80	Pred, HCQ, MMF, IVIG
10/M/3.7	7 years (active)	Anaphylactic shock due to rituximab	Pred[b] 1.5 mg/kg/day, RTX[b] CYC[b] MP,[b] IVIG sub,[b] HCQ	Pred 2 mg/kg/day, CsA	VP, ATB, PhysioT	PR 65/80	IVIG, HCQ
		Certain infection-related complications					
11/F/8.9	5 months (active)	ARDS (*Pneumocystis jirovecii* pneumonia)[a]	Pred[b] 1.5 mg/kg/day	Pred 2 mg/kg/day, MP (3), CYC	MV, VP, ATB (cotrimoxazole) PhysioT	Death	

Disease activity before ICU was classified as active or complete remission according to the PRINTO criteria (a Childhood Myositis Assessment Scale of $\geqslant 48$, the absence of skin disease and a Physician's Global Assessment Score of <1). [a]Mixed form of aetiologies (therapy-related and primary complication). [b]Ongoing treatment at admission to ICU. a/b: first/second hospitalization; F: female; M: male; NA: not available; Pred: prednisone; MP: methylprednisolone; CsA: ciclosporin; MV: mechanical ventilation; VP: vasopressors; PhysioT: Physiotherapy; PR: partial remission; sub: substitutive; RTX: rituximab; PN: parenteral nutrition; ATB: antibiotics; EN: enteral nutrition; CR: complete remission; PRES: posterior encephalopathy reversible syndrome. The numbers into brackets refer to the number of plasma exchanges, and to the number of infusions of methylprednisolone, IVIG or Rituxamab.

a median length of hospitalization in the PICU of 13.5 days (range, 1–88). Three patients remained dependent on enteral nutrition after PICU discharge before being weaned 2, 4 months and 2 years later. These findings suggest that prompt PE and CSs, possibly associated with rituximab, are an efficient therapeutic option for the treatment of life-threatening primary JDM complications, especially in the subset of patients with severe vasculopathy. Such efficacy of PE in the rescue therapy for juvenile and adult DM in the acute phase has been previously reported in a few studies of patients with severe muscle weakness or complications unresponsive to conventional therapy [7, 8].

In conclusion, primary JDM vasculopathy-related complications were the most common causes for admission to PICUs, and had a favourable outcome despite severe life-threatening events. Larger studies are warranted to confirm the efficacy of PE for treating these severe complications.

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