Children with immune-mediated necrotising myopathy: a case series

Sirs,

Immune-mediated necrotising myopathy (IMNM) can be divided into three groups according to myositis-specific antibodies (MSAs): anti-signal-recognition particles (anti-SRP), anti-3-hydroxy-3-methylglutaryl-CoA reductase (anti-HMGCR), and seronegative IMNM (1, 2). IMNM is much less common in children than in adults and research into IMNM in children is still lacking.

Here, we report four children with IMNM. Three children were female, and one was male. The average age at onset was 9.65±2.87 years. All patients presented with severe proximal muscle weakness and markedly elevated CK, but they had no extra-muscular involvement (Table I). Two patients had anti-SRP antibodies, one had anti-HMGCR, and one was negative for MSAs. Myogenic changes were detected by electromyography in all patients. In the magnetic resonance imaging (MRI) STIR series, acute inflammation of the leg muscles was displayed in all patients (Fig. 1 and Table I). All patients underwent muscle biopsy. On haematoxylin and eosin and electron microscopy (EM), scattered necrotic and regenerating fibres with scarce lymphocyte infiltration or without lymphocyte infiltration were the predominant features. Immunohistochemical staining of muscle tissue revealed that MHC-1 was expressed in many myofibre membranes; MAC was positively expressed in some myofibre membranes (Fig. 2 and Table I).

Table I. Clinical features of four children with IMNM.

Case		1	2	3	4
Gender		F	F	F	M
Age at onset (y)		9.2	12	12.2	5.1
Myositis autoantibody		Anti-SRP	Anti-SRP	Anti-HMGCR	Negative
Muscular involvement	Weakness	Y	Y	Y	Y
	CMAS	6	12	8	9
	Initial CK (IU/L)	13150	11280	16820	8530
	Others	Myalgia	Myalgia	Myalgia	Myalgia
Other organs involvement	Skin	N	N	N	N
	Lung	N	N	N	N
	Heart	N	N	N	N
	Joint	N	N	N	N
Muscular biopsy	Necrotic fibres	Y	Y	Y	Y
	Regeneration/ degeneration	Y	Y	Y	Y
	$CD68^+$ macrophage	Y	N	N	Y
	Lymphocyte infiltration	N	N	Scarce	Scarce
Muscular MRI	Oedema	Y	Y	Y	Y
	Fatty replacement	Y	N	Y	N
	Atrophy	Y	N	Y	N
	Myofascial oedema	N	N	N	N
EMG	Myogenic changes	Y	Y	Y	Y
Diagnosis	Symptoms +Antibody + biopsy	Y	Y	Y	Symptoms + biopsy
Treatment	Medicine	IVMP/PDN, MTX, IVIG, RTX	PDN, MTX, IVIG	IVMP/ PDN, MTX, MMF, IVIG	PDN, MTX, IVIG
Prognosis	No improvement	√	-	-	-
	Mild improvement	-	-	-	-
	Moderate improvement	-	√	√	
	Marked improvement		-	-	√

CK: creatinine kinase; CMAS: Childhood Myositis Assessment Scale; EMG: electromyogram; MMF: mycophenolate mofetil; IVMP: intravenous methylprednisolone; IVIG: intravenous immunoglobulin; LDH: lactate dehydrogenase; MTX: methotrexate; PDN: prednisolone; RTX: rituximab.

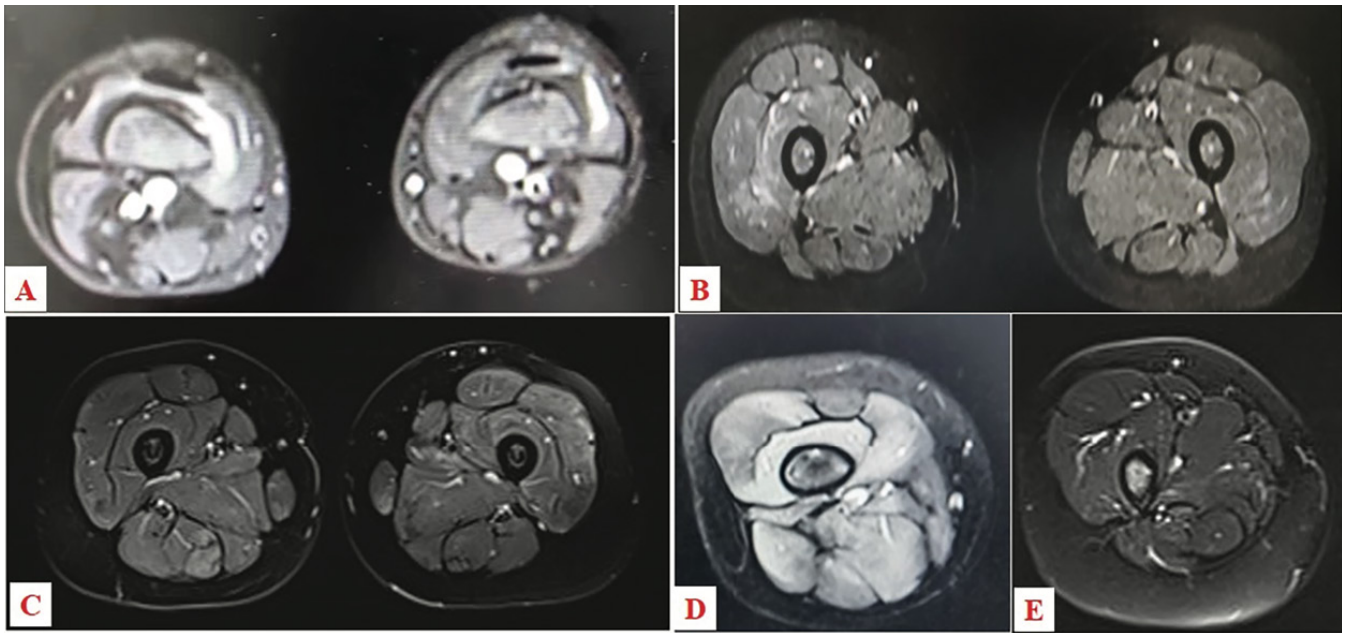

Fig. 1. MRI of lower limbs in all patients. **A**) showed severe muscle oedema in Patient 1, **B**) revealed muscle oedema in Patient 2, **C**) displayed mild muscle oedema in Patient 3, **D**) showed severe oedema of left leg in Patient 4, **E**) displayed oedema disappearing after post-treatment in Patient 4.

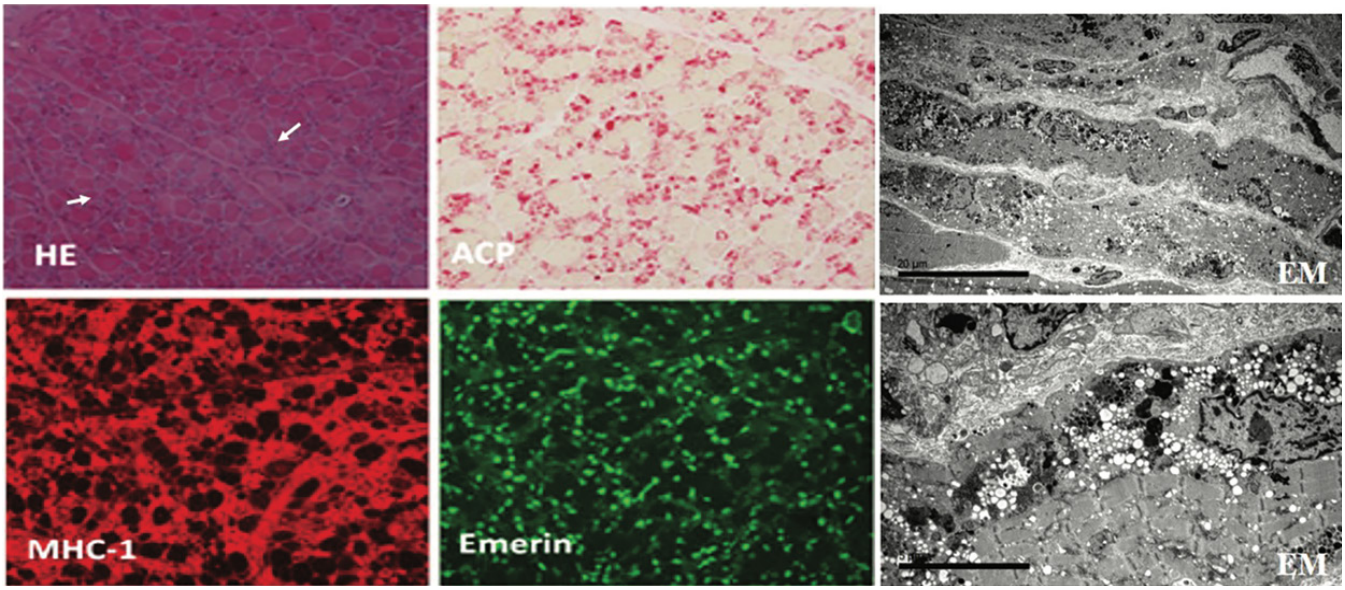

Fig. 2. Muscle biopsy of patient 4. The scattered necrotic and regenerating fibres with scarce lymphocyte infiltration were observed on H&E (white arrow: necrosis), ACP and Emerin staining showed no obvious abnormalities. On IHC, mildly positive sarcolemmal MHC-I expression in nonnecrotic or regenerating fibres. The cytoplasm was filled with varying sizes of vacuoles, autophagosomes, and glycogen autophagy under electron microscopy.
The number of mitochondria increases and the sarcoplasmic reticulum expands into large vacuoles.

Table II. Clinical features of three children with seronegative IMNM.

Case		1	2	3
Gender		M	M	M
Age at onset (y)		5.1	11	10
Muscular involvement	Weakness	Y	Y	Y
	CMAS	9		12
	Initial CK (IU/L)	8530	13006	13789
	ALT(IU/L)	328	384	509
	AST(IU/L)	638	345	664
	LDH(IU/L)	2365	1950	1700
	Aldolase (IU/L)	-	159	319
	Others	Myalgia	Myalgia	-
Other organs involvement	Skin	N	N	Cutaneous sclerosis Digital ulcers
	Lung	N	N	N
	Heart	N	N	Y
	Joint	N	N	N
	Digestive tract		N	Oesophagus
Muscular biopsy	Necrotic fibres	Y	Y	Y
	Regeneration/degeneration	Y	Y	Y
	$CD68^+$ macrophage	Y	NA	NA
	Lymphocyte infiltration	Scant	Scant	NA
Muscular MRI	Oedema	Y	Y	Y
	Fatty replacement	N	N	N
	Atrophy	N	N	N
	Fascial oedema	N	N	N
EMG	Myogenic changes	Y	Y	Y
Genetic testing	Trio-based WES	Y	N	N
Diagnosis	Symptoms + biopsy	Y	Y	Y
Treatment	Medicine	PDN, MTX, IVIG	MP/PDN IVIG	PDN, MTX*, IVIG
Prognosis	No improvement	-	-	-
	Mild improvement	-	-	-
	Moderate improvement	-	-	-
	Marked improvement	√	√	√

ALT: alanine transaminase; AST: aspartate transaminase; CK: creatinine kinase; CMAS: Childhood Myositis Assessment Scale; EMG: electromyogram; IVIG: intravenous immunoglobulin; LDH: lactate dehydrogenase; NA: not available; MTX: methotrexate; PDN: prednisolone.
*subcutaneous methotrexate.

Autophagosome accumulation was detected via EM in Patient 4 (Fig. 2).

All patients met the ENMC International Workshop on Idiopathic Inflammatory Myopathies for diagnostic criteria of IMNM (3). They all received immunotherapy, in which initial therapy included high-dose glucocorticoid treatment (intravenous methylprednisolone 500 mg/day in Patient 1 and 750 mg/day in Patient 3 for 3-5 days, followed by tapering oral prednisone), methotrexate (MTX) and intravenous immunoglobulin (IVIG). Patient 4 achieved complete remission after three months of initial therapy. MTX was replaced with mycophenolate mofetil in Patient 3, and rituximab was added to Patient 1's treatment plan due to a poor response to initial therapy. Moderate improvement was obtained in Patients 2 and 3. Despite the combination of rituximab and subsequent replacement of methotrexate with tacrolimus, Patient 1 developed muscular atrophy a permanent reduction in muscle strength. The median follow-up duration was 28.21±12.75 months after the diagnosis of IMNM.

To date, fewer than 100 children (n=90) with IMNM have been reported in PubMed (4-7), including our four patients. Therefore, paediatric IMNM is very rare. Anti-SRP-positive IMNM (n=43) and anti-HMGCR-positive IMNM (n=44) each account for approximately half of the total IMNM (4-7). Compared with the other two autoantibody groups, seronegative IMNM remains poorly described. Only three patients with seronegative IMNM have been reported (8, 9), including Patient 4. One of the three patients with seronegative IMNM had scleroderma (8). This patient should be diagnosed with connective tissue disease-related IMNM.

Our Patient 4 presented with bilateral proximal symmetric weakness and markedly elevated levels of CK. Not only were scattered necrotic and regenerating fibres without lymphocyte infiltration found in Patient 4, but autophagosome accumulation was also found under an EM, which is a nonimmune-mediated muscle injury commonly seen in adult IMNMs (10, 11). Patient 4 achieved complete remission after three months of initial therapy, including high-dose prednisone, IVIG, and MTX. Two other patients with seronegative IMNM also showed marked improvement after treatment (Table II) (8, 9). It seems that seronegative paediatric IMNM patients had a better prognosis. However, the rate of survival was lower in seronegative IMNM compared to seropositive IMNM in adults, duo to an increased risk of malignancy (12, 13).

Paediatric IMNM is very rare, especially seronegative IMNM. More studies with large-sample are needed to confirm that seropositive paediatric IMNM patients may have a better prognosis.

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Competing interests: none declared.

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