Acute myopathy of intensive care in a child after heart transplantation

Philippe Chetaille MD,* Olivier Paut MD,†
Alain Fraisse MD,* Bernard Kreitmann MD,‡
Jean Camboulives MD,† Jean-François Pellissier MD§

Purpose: Acute myopathy of intensive care has been described infrequently in children and never after organ transplantation. We report a case of acute myopathy of intensive care in a child after heart transplantation.

Clinical features: An 11-yr-old girl, with no previous medical history, developed acute cardiomyopathy leading to cardiac shock. Family history revealed four cases of unidentified myopathy and/or cardiomyopathy. Preoperatively, while muscle biopsy was near normal, myocardial biopsy revealed non specific mitochondrial disorders. A few days after heart transplantation, she developed acute hypotonia and flaccid quadriplegia, consistent with the diagnosis of acute myopathy of intensive care. Nerve conduction studies were normal, electromyography showed myopathic changes and a new muscle biopsy from quadriceps femoris showed severe loss of myosin filaments and ATPase activity in type 2 fibres. A large laboratory screening failed to demonstrate a metabolic disease or a known myopathy. Muscle strength recovered progressively in three weeks allowing home discharge. A few months later, she was free of symptoms and muscle biopsy showed full histopathological recovery.

Conclusion: Acute myopathy of intensive care can occur in children after heart transplantation. It should be suspected in the presence of muscle weakness and difficulty in weaning from ventilatory support. Electromyography confirmed a myogenic process and muscle biopsy allowed diagnosis. Full clinical and histopathological recovery usually occur within three weeks.

Objectif : La myopathie aiguë de réanimation a été rarement décrite en pédiatrie, et jamais après transplantation d'organe chez l'enfant. Nous rapportons un cas pédiatrique de myopathie aiguë de réanimation après transplantation cardiaque.

Éléments cliniques : Une enfant de 11 ans, sans antécédent, est hospitalisée pour choc cardiogénique sur cardiomyopathie aiguë. Dans sa fratrie, on note l'existence de myopathies et de cardiomyopathies non déterminées. La biopsie musculaire préopératoire est normale et la biopsie myocardique montre des anomalies mitochondriales non spécifiques. Quelques jours après une transplantation cardiaque, elle présente une hypotonie globale avec tétraplégie flasque. Une myopathie aiguë de réanimation, évoquée devant des vitesses de conduction nerveuses normales et un tracé électromyographique montrant une atteinte musculaire, est confirmée par une biopsie musculaire montrant une perte des fibres de myosine par dépolymérisation, avec perte de l'activité ATPasique dans les fibres de type 2. La recherche élargie d'une myopathie chronique ou d'une maladie métabolique est négative. En quelques semaines, l'enfant a progressivement récupéré sa force musculaire. Une biopsie musculaire, réalisée à distance, montre une architecture musculaire et une activité enzymatique normales.

Conclusion : Une myopathie aiguë de réanimation peut se développer chez le transplanté pédiatrique, puisque des facteurs favorisants sont utilisés pour l'immunosuppression. Elle doit être évoquée devant une faiblesse musculaire et des difficultés de sevrage de la ventilation artificielle. L'électromyogramme objective un processus myogénique et c'est la biopsie musculaire qui permet le diagnostic. La récupération de la force musculaire et histopathologique est obtenue en quelques semaines.

From the Departments of Pediatric Cardiology,* Pediatric Anesthesiology and Intensive Care,† Pediatric Cardio- Thoracic Surgery,‡ and Pathology and Neuropathology,§ La Timone Children's Hospital, Marseille, France.

Address correspondence to: Dr. Olivier Paut, Département d'Anesthésie-Réanimation Pédiatrique, CHU Timone- enfants, Boulevard Jean Moulin, 13385 Marseille cedex 5, France.Phone: 33-4-91-38-68-37; Fax: 33-4-91-47-81-70; E-mail: opaut@ap-hm.fr

Accepted for publication December 11, 1999.

ACUTE Myopathy of Intensive Care (AMIC) has been documented in patients treated for status asthmaticus[1,2] and other severe pulmonary disorders, sepsis and burns.[3] It is usually associated with the use of intravenous corticosteroids (CS) and non depolarizing neuromuscular blocking agents.[4,5] It has been reported rarely in transplant recipients[3,5,6] and only one case, formally documented with muscle biopsy, has been reported in children.[7] No pediatric cases have been reported after cardiac surgery or organ transplantation.

Case report

An 11-yr-old girl, with no previous medical history, was admitted in cardiac failure. She was born from related parents (first cousins) and two of her brothers died from non documented cardiomyopathy. Two others have advanced myopathy and cardiomyopathy, but their muscle biopsies did not reveal any structural or metabolic abnormality. She had a severe hypokinetic and dilated cardiomyopathy with normal coronary anatomy. Muscle biopsy (MB) showed subtle abnormalities and there was no degenerative or metabolic abnormality (Tables I,II). Myocardial biopsy showed mitochondrial disorders and slight interstitial fibrosis without myocarditis. Details of laboratory screening for muscle and heart disease are reported in Table II.

She developed refractory heart failure despite furosemide, dobutamine and enoximone, leading to biventricular circulatory assistance for 82 hr, until orthotopic heart transplantation was performed. She developed transient acute renal failure (creatinine 142 $\mu mol \cdot l^{-1}$, BUN 22 $mg \cdot l^{-1}$), liver function was slightly impaired (PT 49%, Factor V 49%). Rocuronium was given in ICU (0.7 $mg \cdot kg^{-1}$, followed by a continuous infusion 0.5 $mg \cdot kg^{-1} \cdot hr^{-1}$ over 18 hr), while cistracurium (0.17 $mg \cdot kg^{-1} \cdot hr^{-1}$ over seven hours) was given during transplantation. Postoperatively, she received methylprednisolone, rabbit antithymocyte globulin, cyclosporine A, and was sedated with fentanyl and midazolam. Renal and liver functions recovered rapidly. Weaning from ventilator was performed on second postoperative day (D2) but the trachea was rapidly reintubated for respiratory fatigue (with respiratory rate at 70 bpm). There was no signs of rejection on myocardial biopsy and echocardiography. On D7 muscle weakness was present with poor motion and rare eyelid blinking. Successful weaning from mechanical ventilation was possible on D14. Clinical examination showed diffuse, proximal and distal muscle weakness, amyotrophy with no deep tendon reflexes leading to flaccid quadriplegia and facial diplegia with poor swallowing. No fasciculation was noted. Laboratory screening was negative (Table II). Sensory and motor nerve conduction studies were normal, while detection electromyography showed rich and reduced amplitude of nerve action potentials during voluntary contraction with no sponta-

TABLE II Etiologic muscle and laboratory studies. All following studies were normal. (on the three muscle biopsies for pathology screenings).

Immunohistochemical studies (muscle specimen)	- Dystrophin 1, 2, 3 - Sarcoglycans α, ß, γ, δ - ß dystroglycan - Utrophin - Merosin - Fast and slow myosin heavy chain
Immunoblotting studies (muscle specimen)	- Dystrophin 1, 2 - Sarcoglycans α, ß, γ - Calpain - Fast and slow myosin heavy chain
Mitochondrial DNA study (muscle specimen)	- No deletion - No 3243 tRNA leu mutation
Laboratory screenings (Blood / or urine)	- CPK - LDH - Aldolase - Phosphorus - Pyruvate - Lactate - Free Carnitine - Acylcarnitine - Amino acids chromatogram - Organic acids - Long chain fatty acids chromatogram

TABLE I Time course of main pathological findings seen on the three consecutive muscle biopsies. AMIC: Acute Myopathy of Intensive Care

	Before transplantation	*Three weeks after transplantation: AMIC*	*Six months after transplantation: recovery*
Muscle Biopsy site	Right deltoid biopsy	Right quadriceps femoris biopsy	Left quadriceps femoris biopsy
Light microscopy	Discreet type 2 fibres predominance	Normal mosaic pattern	Normal mosaic pattern
	Normal myofibrillar network	Normal myofibrillar network	Normal myofibrillar network
	Slight heterogenity in fibres size	Loss of myosin ATPase in type 2 fibres	Normal myosin ATPase activity
	No necrosis		Rare lobulated type 1 fibres
Electron microscopy	Normal ultrastructure	Selective loss of myosin filament	Normal ultrastructure

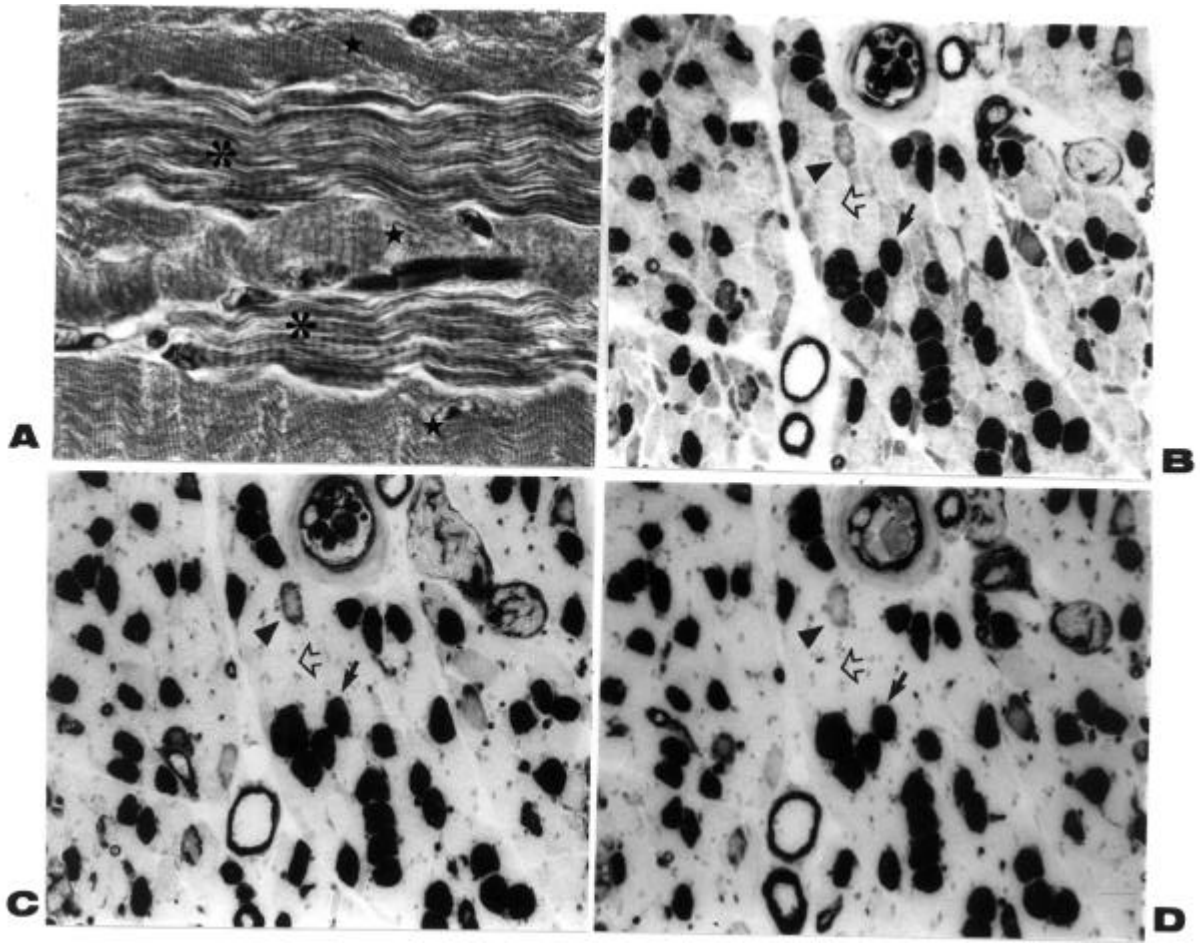

FIGURE 1 Right quadriceps femoris biopsy after cardiac transplantation showing acute myopathy of intensive care.
FIGURE 1 A Paraffin sections: presence of two types of fibres: normal fibres with normal striation (✻) and abnormal fibres with loss of myosin in which only Z lines are seen (★). (Gomori trichrome stain ; X = 100)
FIGURES 1 B,C,D Serial frozen sections (X = 20) with ATPases at different pH (FIGURE 1B pH=9.4, FIGURE 1C pH=4.35, FIGURE 1D pH=4.63). Type 2 fibres lost their myosin ATPase activity (⇒ type 2B fibre; ▸ type 2C fibre) while ATPase activity is normal in type 1 fibres and intrafusal fibres (➜).

neous activity suggesting a myogenic process. On D21, a second MB showed severe abnormalities consistent with the diagnosis of AMIC (Figures 1,2, Table I).

Prednisolone was progressively tapered to a maintenance regimen (8 mg·day^{-1}). Muscle weakness improved and she was discharged from ICU on D19 and home on D33. Muscle biopsy performed six months after transplantation, showed recovery of muscle architecture and enzymatic activity (Table I). The child at this time was free of symptoms, until now, more than two years after.

Discussion

This child, formerly free of cardiac symptoms, developed a severe cardiomyopathy. Screening for muscle disease was performed before transplantation: muscle specimen showed only slight heterogenity in fibres size. After transplantation, she developed a severe muscle fatigue related to a myogenic process. Diagnosis of AMIC was confirmed by histopathology and electron microscopy showing loss of myosin ATPase activity of type 2 fibres, secondary to myosin loss, while fast and slow myosin heavy chain (MHC)

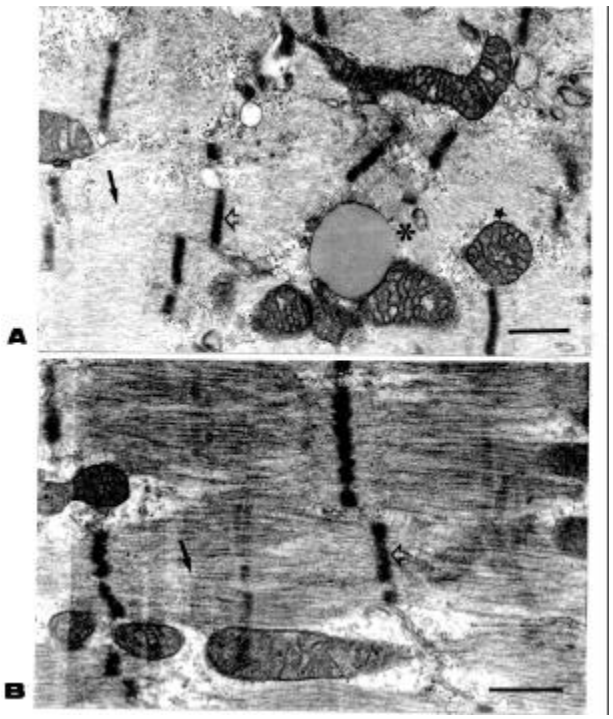

FIGURE 2 Electron microscopy aspect: Acute Myopathy of Intensive Care.
FIGURE 2A Abnormal fibres with loss of myosin filaments (➜). Only normal Z lines are seen (⇒). Normal appearence of mitochondria (★) and lipid droplets (✻) (bar = 500 nm)
FIGURE 2B Normal fibres with respect of myosin filaments (➜). Normal Z lines are also present (⇒). (bar = 400 nm)

showed a normal immunoreactivity. At recovery, MB showed repolymerisation of myosin, with normal enzymatic activities and rearrangement of thick filaments of myosin in the sarcomeres. However, while this patient developed typical AMIC, her history may also suggest an underlying muscle disorder but, despite complete muscular and metabolic screenings no diagnosis has been made..

Acute Myopathy of Intensive Care must be differentiated from other causes of muscle weakness occurring in ICU. Electrodiagnosis is essential since it permits distinction of myopathy from critical illness polyneuropathy.[5] The diagnosis of AMIC is made by histopathology. Different types of lesions are described. Non specific modifications are a selective atrophy of type 2 fibres or necrotizing and vacuolar lesions. The most specific lesions consist in a loss of thick filaments of myosin without necrosis or fibres vacuolisation: type 2 fibres lose their myosin ATPase activity because of myosin depolymerisation, supported by a normal immunoreactivity of MHC. Muscle usually recovers its normal function as its ultrastructure and enzymatic activities normalize within a few weeks.[5,6]

Non depolarizing muscle relaxants, corticosteroids and sepsis are thought to be the main etiopathogenic factors associated with AMIC.[8] Administration of high doses of CS to a vulnerable patient is the main precipitating factor. Non depolarizing muscle relaxants produce biochemical modifications of acetylcholine receptors followed by a denervation amyotrophy,[9] but no correlation exists between the outbreak of myopathy and non depolarizing muscle relaxant administration.[10] With the loss of thick filaments, AMIC seems to be a particular entity even if its etiology is not well known.[5] In animals, disassembly of myosin monomers is thought to lead to loss of thick filaments, presumably due to an effect at the level of cellular protein regulation.[5] These models give the predominant role in pathogenesis to CS. Other factors such as terminal motoneurone axonopathy could act as potentiating factors. A causal relationship between cumulating doses, length of administration of CS and non depolarizing muscle relaxants and development of AMIC has been demonstrated.[5] However, predicting factors of AMIC for an individual are lacking.[4]

Rare pediatric cases of AMIC, and none of them after organ transplantation have been previously reported. The only pediatric case documented with biopsy occurred in a 13-yr-old girl suffering from myasthenia gravis, treated with CS, who developed a myopathy with loss of myosin.[7] It is noteworthy that both cases of pediatric AMIC, occurred in children having a known or suspected neuromuscular disorder. The precipitating role of an underlying muscle disease and its incidence in pediatric intensive care need to be addressed by further studies.

We conclude that AMIC can occur in the postransplantation period in children since predisposing factors such high dose of CS for immunosuppression and muscle relaxants can be given. AMIC must be suspected in a child presenting hypotonia and muscle weakness, with myopathic changes on electromyography. The diagnosis is then confirmed by muscle biopsy. Recovery occurs within weeks, with full histopathologic restitution.

Acknowledgments
The authors thank Dr, F. Wernert for patient referral, Dr. J.P. Azoulay for electrophysiologic exploration and Dr. V. Pakis for muscle DNA studies.

References

1 *Danon MJ, Carpenter S.* Myopathy with thick filament (myosin) loss following prolonged paralysis with vecuronium during steroid treatment. Muscle Nerve 1991; 14: 1131–9.
2 *Griffin D, Fairman N, Coursin D, Rawsthorne L, Grossman JE.* Acute myopathy during treatment of status asthmaticus with corticosteroids and steroidal muscle relaxants. Chest 1992; 102: 510–4.
3 *Faragher MW, Day BJ, Dennett X* Critical care myopathy: an electrophysiological and histopathological study. Muscle Nerve 1996; 19: 516–8.
4 *Gutmann L, Blumenthal D, Gutmann L, Schochet SS.* Acute type II myofiber atrophy in critical illness. Neurology 1996; 46: 819–21.
5 *Lacomis D, Giuliani MJ, Van Cott A, Kramer DJ.* Acute myopathy of intensive care: clinical, electromyographic and pathological aspects. Ann Neurol 1996; 40: 645–54.
6 *Al-Lozi MT, Pestronk A, Yee WC, Flaris N, Cooper J.* Rapidly evolving myopathy with myosin-deficient muscle fibers. Ann Neurol 1994; 35: 273–9.
7 *Panegyres PK, Squier M, Mills KR, Newsom-Davis J.* Acute myopathy associated with large parenteral dose of corticosteroid in myasthenia gravis. J Neurol Neurosurg Psychiatry 1993; 56: 702–24.
8 *Ruff RL.* Acute illness myopathy. Neurology 1996; 46: 600–1.
9 *Martyn JAJ, White DA, Gronert GA, Jaffe RS, Ward JM.* Up-and-down regulation of skeletal muscle acetylcholine receptors. Effects on neuromuscular blockers. Anesthesiology 1992; 76: 822–43.
10 *Coakley JH, Nagendran K, Honavar M, Hinds CJ.* Preliminary observations on the neuromuscular abnormalities in patients with organ failure and sepsis. Intensive Care Med 1993; 19: 323–8.