Critical illness neuromuscular disease: clinical, electrophysiological, and prognostic aspects

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Background: Critical illness neuromuscular disease, which has been recognised as a distinct clinical entity in adults, remains poorly described in children.

Aims: To assess retrospectively the clinical, electrophysiological, and prognostic features of the disease.

Methods: Retrospective study in a children’s university hospital.

Results: Five critically ill patients presented with generalised paralysis, associated with long lasting failure to breathe in three. The cause of the generalised paralysis was critical illness neuropathy in two, acute myopathy in two, and mixed neuromyopathy in one.

Conclusions: Neuromuscular disease should be suspected in critically ill children with muscle weakness. Because corticosteroids and muscle relaxants appear to trigger some types of intensive care unit neuromuscular disease in children, their use should be restricted or administered at the lowest doses possible.

PATIENTS AND METHODS

We retrospectively studied five children presenting with polyneuropathy or myopathy acquired in an intensive care unit (ICU) between 1990 and 1996. The diagnosis was established clinically and confirmed by electrophysiological and/or pathological studies. Patients with aetiologically characterised chronic or acute neuromuscular conditions—such as Guillain-Barré syndrome, electrolyte imbalance, porphyria, or vitamin deficiency—were excluded. Organ failure was defined using the classical criteria. The following clinical features were registered: delay of motor recovery, duration of mechanical ventilation, and hospitalisation in the ICU. Longitudinal electrophysiological studies were conducted using standardised techniques in all patients: electromyography (EMG; resting and, if possible, voluntary contraction state), and motor and sensory conduction velocities, amplitudes, and distal latencies. A muscular biopsy was performed in patient 3. Cerebrospinal fluid (CSF) analysis and serum creatine kinase titres (CK) were also recorded. Tables 1 and 2 summarise the clinical and paraclinical data. Day 0 corresponds to day of admission in the ICU. All five children received parenteral nutritional support with glucose serum containing amino acids, electrolytes, oligoelements, vitamins (daily standard polyvitamin administration and weekly supplements of vitamins B₆, K, E, and H), and fat emulsion.

CASE REPORTS

Patient 1

An 8 year old girl underwent two bone marrow transplants for acute idiopathic marrow aplasia. Hepatic and cutaneous graft versus host reactions were treated with cyclosporin, prednisone, and azathioprine. During treatment she developed septic shock with multiple organ failure and required fluid resuscitation and ventilatory support. She received midazolam, fentanyl, dopamine, cefazidime, vancomycin, amikacin, and amoxicillin. On day 12, a flaccid paralysis predominating at the distal part of the lower limbs was observed. Deep tendon reflexes were absent. Serum CK was raised (1465 IU/L). Electrophysiological investigation on day 14 showed an axonal neuropathy (compound motor and sensory potential amplitudes were reduced, conduction velocities were normal). EMG showed fibrillation potentials and positive sharp waves in the examined muscles in a predominantly distal distribution. CSF analysis revealed meningitis: 280 cells/mm³ (90% lymphocytes), protein 2.36 g/l, glucose 1.7 mmol/l. Bacteriological and virological tests were negative. She recovered on day 15 and regained normal strength over the following two months.

Conclusion: critical illness neuropathy.

Patient 2

A 14 year old boy had a two year history of acute lymphatic leukemia B. Two months after finishing standard chemotherapy, he was admitted to the ICU with septic shock caused by Pseudomonas aeruginosa infection complicated by marrow aplasia and multiple organ failure requiring ventilatory support. He received cefazidime, vancomycin, cillox, ornidazole, dopamine, and steroids (dexamethasone 1 mg/kg/day on days 0–4, followed by methylprednisolone 2 mg/kg/day on days 5–11). Intermittent doses of fentanyl and narcozep, followed by a combination of fentanyl, chlorpromazine, promazine, and vecuronium (0.1 mg/kg/h on days 8–15) were given. On day 15, he became quadriplegic. Deep tendon reflexes were absent. He did not undergo extubation until six months later. CK and CSF were normal. Electrophysiological studies on day 21 showed severe sensorimotor axonal degeneration: low motor and sensory amplitudes, normal motor and sensory latencies, and absent motor and sensory conduction velocities.
nerve conduction, and complete lack of voluntary activity with needle examination. Recovery was slow and incomplete. At three months, he was only able to move his toes. Additional EMG examinations on days 43 and 81 showed initial signs of reinnervation in the upper limbs, although this was still incomplete at six months. A gradual return to normal muscle strength occurred over the next nine months in the upper limbs. In the lower limbs, muscle strength remained abnormal as a result of combined residual neuropathy and anoxic lesions of the central nervous system.

Conclusion: critical illness neuropathy.

Patient 3

An 8 year old boy was admitted to the ICU with convulsions. On examination, he was comatose, had an enlarged liver, and a temperature of 40°C. He responded with unlocalised limb flexion to pain. Vecuronium 0.05–2 mg/kg/h was started on day 4. Life threatening hyperthermia (42°C) occurred on day 6. He received intermittent doses of hypnovel and vecuronium 0.1 mg/kg/h every six hours (on days 0–4) and intravenous salbutamol. Intermittent doses of hypnovel and vecuronium 0.1 mg/kg/h provided neuromuscular blockade on days 0–8. During the ICU stay, azathioprime, cyclosporin (from day 9), and dopamine. Vecuronium (0.05–1 mg/kg/h) was administered from day 0. Recovery of normal mental status was observed on day 8. At the same time, she displayed flaccid quadriplegia with amimia and loss of deep tendon reflexes. Extubation could not be performed on day 10 as a result of neuromuscular weakness. Electrophysiological studies on day 10 showed depressed motor and sensory nerve conduction velocities, and, on needle examination, lack of spontaneous activity with polyphasic motor unit potentials to voluntary contraction. CSF analysis on day 8 was normal. CK was high (1286 IU/L). Neuromuscular improvement was slow: distal mobility recovered on day 14, deep tendon reflexes on day 30. She was extubated on day 55. Two months after the transplantation, at the end of intensive care management, muscle strength was scored at 2 in the lower limbs and 3 in the upper limbs. Recovery was complete after six months. EMG (days 21 and 40) revealed brief, small amplitude, polyphasic motor unit action potentials with early recruitment.

Conclusion: critical illness myopathy.

Patient 5

This 8 year old boy presented with severe bronchopulmonary dysplasia (ventilation via tracheostomy up to the age of 4.5 years), Little’s syndrome, and moderate mental retardation caused by premature birth (31st week). He was admitted to the ICU with status asthmaticus. He required assisted ventilation and was treated with methylprednisolone 2 mg/kg every six hours (on days 0–4) and intravenous salbutamol. Intermittent doses of hypnovel and vecuronium 0.1 mg/kg/h provided neuromuscular blockade on days 0–8. During the neurological recovery, he developed peritonitis caused by Klebsiella pneumoniae infection secondary to perforation of a duodenal ulceration. On withdrawal of the sedative (day 3) and myorelaxant (day 8), flaccid quadriplegia was observed, associated with myalgia and loss of deep tendon reflexes. Electrophysiological studies on day 13 showed normal motor and sensory nerve conduction velocities and amplitudes; needle examination identified polyphasic responses with no spontaneous activity. CK was raised (990 IU/L) and CSF analysis was normal. Ventilation was stopped on day 20. The patient’s strength returned to normal in three weeks.

Conclusion: critical illness myopathy.
DISCUSSION

A spectrum of neuromuscular disease with flaccid weakness in critically ill adults is now recognised. Three distinct entities have been identified: critical illness polyneuropathy, acute myopathy (acute necrotising myopathy or myopathy associated with the use of corticosteroids and muscle relaxants), or both. These entities are poorly described in children.

Critical illness polyneuropathy

This is characterised by development of neuropathy during a severe illness requiring intensive care. Twenty per cent of adult cases occur during severe infection, and 70% during multiple organ failure.1,2 Only eight children with critical illness polyneuropathy, aged 2–17 years (four were adolescents), have been described in the literature.20–22 In adults, severe loss of motor function is observed: typically flaccid quadriplegia, preceding motor function impairment occurring after two to four weeks of ICU management.23 Our results show a similar pattern in children.

The pathophysiology remains unknown. Our observations led us to consider a toxic mechanism. Cyclosporin and vincristine, administered in two patients, might be involved but do not explain the full extent of the disease in view of its severity, its rapid onset, and the delay between this treatment and the first neurological symptoms. The hypothesis of a neuropathy resulting from graft versus host reaction suggested in one of our cases cannot be sustained. Such neuropathies are demyelinating as a result of an inflammatory mechanism leading to high protein concentrations in the CSF (more than 1 g/l).24

Other physiopathological mechanisms have been proposed, namely drug toxicity (aminoglycosides and curare), nutritional insufficiencies, and hypoxaemia.24–26 Several mediators of the systemic inflammatory response, especially tumour necrosis factor α, which can damage myelin and oligodendrocytes in vitro, may also play an important role in the pathogenesis of critical illness polyneuropathy.27

Acute myopathy in intensive care unit patients

Two kinds exist. Acute necrotising myopathy of intensive care occurs in the context of sepsis or trauma. Features include sudden onset of generalised muscle weakness, high blood CK and, in some patients, myoglobinuria. EMG reveals myogenic signs. Muscle biopsy specimens show panfascicular necrosis.28 The muscular recovery is usually rapid. This myopathy seems to be the muscular counterpart of critical illness polyneuropathy and could explain the mixed signs observed in patients 1 and 3.

The second kind of myopathy is myopathy associated with corticosteroids and curare, which was first described in 1977; a few anecdotal cases have been reported in the literature in children.29–33 In adulthood, it occurs in 18–36% of patients admitted to ICU with severe asthma and 29% of patients receiving corticosteroids and curare to treat this condition.30 Patients with status asthmaticus who developed myopathy usually receive at least the cumulative equivalent dose of 1000 g methylprednisolone. Most of these patients receive steroids in association with neuromuscular blocking agents. The problems occur when curare is withdrawn, on average on day 14.
The clinical picture for children is similar to that of adults: diffuse muscle weakness (80–90% of patients), reaching the respiratory muscles in approximately 25% of cases, and amyotrophy (50% of patients). In newborn infants treated with curare or infants of mothers receiving this treatment, limited joint mobility has also been described, sometimes lasting for several months. Electrodiagnostic studies show reduction of compound motor action potential amplitude. Nerve conduction is normal. Serum CK is mildly increased in about 50% of patients. Muscle biopsies have shown a large variety of anomalies, ranging from isolated type II fibre atrophy to a severe necrosis involving all fibre types.

Ultrastructural studies have shown a selective loss of myosin filaments in some patients. The prognosis is generally good in adults and children. The recovery period ranges from a few days to several months and is probably linked to the extent of the muscle lesions combined with the junction blockage, which, on its own, could account for the forms of shortest duration. Sequelae are rare but can be disabling. The evolution is very similar in childhood, except in neonates, who sometimes exhibit weakness and consequent muscle contracture. There may be several factors involved in the development of this condition. Prolonged immobilisation, which did not occur in one patient, may cause atrophy as a result of non-use, although immobilisation was not associated with the high CK or electrophysiological abnormalities, as we observed. Muscular denervation after the use of non-depolarising blocking agents may persist for several weeks after their use is discontinued. This syndrome occurs in the context of renal or hepatic failure (patient 4), and metabolic acidosis (patients 4 and 5); it can also be caused by toxic effects (aminoglycosides). Development of muscular weakness after the use of curare appears to depend on the dose and usually occurs after prolonged treatment over several days or even weeks. Long term steroid treatment may cause chronic steroid myopathy with an indolent course, and often type II fibre atrophy without regeneration or vacuolation. These characteristics differ from those of myopathy associated with corticosteroids and muscle relaxants administered concurrently (patients 4 and 5).

The toxicity of these drugs can be explained, at least in part, by the increased number of cytoplasmic receptors for corticosteroids in the muscle cells as a result of immobilisation and denervation. There is no specific treatment. The severity of the problem suggests that precautions should be taken when administering muscle relaxants and highlights the need for further research to determine concentrations of curare in the muscle, particularly in infants, as at this age the drug is eliminated very slowly.”

The extent of neuromuscular blockage can be evaluated clinically (adaptation to the respiratory insufflation pressure) or by using a peripheral nerve stimulator.

**Conclusion**

In order to evaluate the extent of neuromuscular disease in the ICU, we propose careful neurological assessment of critically ill children, particularly if there is prolonged sepsis or signs of organ failure. Normal brain stem reflexes contrasting with the absence of deep tendon reflexes may suggest the diagnosis early, which should be confirmed by measurement of CK and EMG investigation. Serial CK monitoring should be performed early after exposure to steroids or neuromuscular blocking agents. A rising CK concentration could alert the clinician to an evolving myopathy. Nerve–muscle biopsy is useful when the physician is interested in seeking a classification of neuromuscular disease. Finally, patients with these diseases usually spend prolonged periods of time in the ICU. They are therefore exposed to complications (nosocomial infections), and are more expensive to treat. Specific paediatric TICUs offer the best environment for the prevention and the early detection of critical illness neuromuscular disease.
Postcard from Down Under

The wide blue yonder

I once met someone in Wolverhampton who had never travelled as far as Birmingham, a journey I made daily—sometimes by bicycle. In addition to amazement and fascination at the different way in which people live their lives, I felt a certain smugness about my own worldliness and modern tolerance for distance, it is political suicide to be seen to be separated by less than twenty kilometres. It is interesting to explain to the public the wisdom of specialisation and centralisation of services, especially in the emotive world of children's hospitals (or hospitals with tertiary children's services) or even the consultant paediatrician and I shared on-call duties over a health district covering 209 000 square kilometers. For comparison, mainland UK is 218 476 square kilometers. How-ever, the UK does have a few more bodies than Mt Isa District's 25 000 people. Mt Isa is about 500 km inland of Townsville which is where, some weekends, the next paediatrician after me could be found.

The paediatric grand round is teleconferenced across Queensland, sometimes with the presenter here in Brisbane, sometimes in the other centres. Cairns is the current Northern limit, which at 1600 km away is about as far as London is from Warsaw or Seville. From Cairns north to Cape York, Australia's most northern mainland point, is another 500 km.

In telephone conversations with people back in the UK I'm asked if I've seen Uluru (Ayer's Rock) or the Sydney Opera House yet. In my mind's eye I see the road sign a couple of kilometers from our apartment which states that Sydney is 996 km away.

I went to do an outreach clinic at the next town. I borrowed a hospital car, filled it with petrol, bought a couple of litres of water and some freshly baked bread (the latter a mandatory gift) and set off. I arrived a little over two hours later, 195 km through sun-parched outback. I'd seen no one in between, except the occasional car heading in the opposite direction. No houses, no shops, just the road and the outback for mile after hypnotic mile.

By an odd contrast, however, Australia is one of the most urban countries in the world, surpassed only by city states like Hong Kong and Singapore. Most of the population lives in the big, sprawling cities, with the vast majority of the rest clinging to the coast, from Adelaide, south via Melbourne, and then north via Sydney and Brisbane to Cairns.

Many of my colleagues here find it even stranger than I do that one of the few seats which changed hands in the 2001 British general election was on the basis of a campaign to keep open one hospital in order to prevent folk from needing to travel ten miles to another one. Of interest, though, is that of the five largest cities in Australia, three have two or more children's hospitals (or hospitals with tertiary children's services) separated by less than twenty kilometres. It is interesting to speculate—but impossible to prove—that whatever people's tolerance for distance, it is political suicide to be seen to be closing a children's hospital. It is perhaps impossible to explain to the public the wisdom of specialisation and centralisation of services, especially in the emotive world of children's illness.

Now, if you'll excuse me I'm just going for a quick bike ride to Uluru...

I D Wacogne
Chief Resident, Royal Children's Hospital, Brisbane

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