

Successful Management of Critical Illness Polyneuropathy and Myopathy in Renal Transplant Recipients

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Abstract

Critical illness polyneuropathy and myopathy commonly occur in patients with multiorgan failure and sepsis. Distal muscle weakness and loss of deep tendon reflexes are usually found, with sparing of the cranial nerve musculature. Many risk factors have been identified, specifically hypoxia, hypotension, hyperpyrexia, and age. Other independent risk factors include female sex, severity of illness, duration of organ dysfunction, renal failure and renal replacement therapy, hyperosmolality, parenteral nutrition, low serum albumin level, duration of intensive care unit stay, vasopressor and catecholamine support, and central neurologic failure. Hyperglycemia also has been identified as an independent risk factor, with important potential affect in terms of prevention. Herein, we report the development of critical illness polyneuropathy and myopathy in 7 of 22 renal transplant recipients who underwent successful ventilator weaning during treatment for bronchopneumonia. This is the first report of critical illness polyneuropathy and myopathy among renal transplant recipients. Clinical suspicion and electrophysiologic studies are tools for early diagnosis. Proper management, including correction of risk factors (especially diabetes) and long-term rehabilitation measures might be beneficial.

Key words: Renal transplant, Critical illness, Polyneuropathy

Introduction

The neuromuscular syndrome of acute limb and respiratory weakness that commonly occurs in patients with multiorgan failure and sepsis constitutes critical illness axonal motor-sensory polyneuropathy. It is a major cause of difficulty in weaning patients from the ventilator because of phrenic nerve involvement, after exclusion of respiratory and cardiac causes. Distal muscle weakness and loss of deep tendon reflexes are usually found, with sparing of the cranial nerve musculature.^{1,2,3} Critical illness polyneuropathy and myopathy (CIP/CIM) represent the response of the peripheral nervous system to critical illness, but the central nervous system is also frequently affected by critical illness, and this is manifested as diffuse encephalopathy that occurs very early in the process.⁴

Prospective and retrospective trials have identified sepsis, systemic inflammatory response syndrome, and multiorgan failure syndrome as crucial risk factors. Other less consistent risk factors include hypoxia,⁵ hypotension,⁶ hyperpyrexia, and age.⁷ Independent risk factors that have been reported in prospective studies include female sex, severity of illness,⁸ duration of organ dysfunction, renal failure and renal replacement therapy, hyperosmolality, parenteral nutrition,⁹ low serum albumin level, duration of intensive care unit (ICU) stay, vasopressor and catecholamine support,¹⁰ and central neurologic failure.⁹ Hyperglycemia also has been identified as an independent risk factor,¹⁰ with important potential affect in terms of prevention. Elevated serum glucose level and reduced serum

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albumin level are associated with nerve dysfunction and prolonged ICU stay.^{11, 8} Corticosteroids and neuromuscular blockers are not recognized as risk factors. However, many reports have found CIM, specifically thick-filament myopathy, to occur in patients treated with a combination of both agents.⁹ The potential role of antibiotics remains unresolved.

Patients admitted for treatment of sepsis show early reduced nerve conduction amplitudes, which are predictive for the development of acquired neuromuscular dysfunction.¹² Therefore, electrophysiologic screening accurately identifies patients with CIP/CIM.¹³ However, muscle biopsy remains the criterion standard for diagnosis, if it can be performed.¹⁴ In sepsis or systemic inflammatory response syndrome, 70% of patients develop CIP. However, the incidence tends to correlate with the duration of the underlying systemic inflammatory response syndrome.¹¹

Bolton and associates proposed a disturbance in the microvascular function of peripheral nerves as being responsible for this neuropathy.⁸ Several mediators of the septic syndrome are known to have histaminelike action. Circulating toxins could potentially gain access to the endoneural space and directly damage the axon.¹⁵ To our knowledge, no cases of CIP/CIM have been reported among the renal transplant population. Herein, we report the development of such syndrome in 7 of 22 renal transplant recipients who were successfully weaned from the ventilator during treatment for bronchopneumonia.

Cases

Of 45 renal allotransplant recipients who developed persistent bronchopneumonia during the period August 2009 through March 2010, 22 necessitated mechanical ventilation after diagnostic bronchoscopic aspiration and lavage. All patients presented with cough, dyspnea, and low-grade fever. On examination, tachypnea, central cyanosis, and bilateral crepitations were observed. After treatment in the ICU, 7 patients failed weaning from mechanical ventilation. All but 2 were men (aged 29 to 68 y). Five patients received basiliximab (Simulect; Novartis Pharma) and 2 received thymo (thymoglobulin) for induction of immunosuppression. Five were maintained on steroids, cyclosporine, and mycophenolate mofetil, and 2 were

maintained on steroids, tacrolimus, and mycophenolate mofetil. In addition, 4 were treated recently for acute antibody-mediated rejection according to our specific antirejection protocol (plasma exchange, intravenous immunoglobulins, and a single dose of rituximab). While they were supported by mechanical ventilation in the ICU, they developed flaccid tetraparesis with deep hyporeflexia. The flaccid paralysis occurred predominantly at the proximal portions of the limbs. Deep tendon reflexes disappeared, and central nervous system dysfunction was absent. Results of blood tests (hepatic function and electrolytes), brain computerized tomography, and electroencephalography also were normal.

Results of electromyography tests performed after weaning from the ventilator revealed reduction of the compound muscle action potential amplitudes, whereas motor and sensory conduction velocities and distal latencies were normal. These findings suggest primary degeneration of the axons that supply the limbs. Hence, the diagnosis of CIP/CIM was suggested. The plan for management was to withhold antiproliferative agents from immunosuppressive therapy and to resume them later. The patients were maintained on a small dose of steroid (5 mg per day) and low calcineurin inhibitor (CNI) trough levels (cyclosporine level near 50 and tacrolimus level near 5 ng/dL). Each patient was then treated empirically with broad-spectrum nonnephrotoxic antibiotics until laboratory test results showed pure bacterial infections (*Legionella pneumophila* in 3 cases, *Acinetobacter* in 1 case, and *Klebsiella* in 1 case), and mixed *Cytomegalovirus* (CMV) and bacterial infections (*Klebsiella* and *Legionella pneumophila*) in 2 cases. In addition, we attempted to keep electrolyte and blood glucose levels within normal ranges (mean, 135.5 ± 37.8 mmol/L). The patients received intravenous immunoglobulin and albumin infusion during the early stage (mean albumin level, 29 ± 2 g/L). Six patients required supportive continuous hemofiltration for a few days, but all required ventilator support for a mean duration of 20 ± 3 days, with the smallest possible dosage of neuromuscular blocker (Table 1). Within 3 weeks, their clinical status, including renal function, was improving, and we resumed maintenance immunosuppression. An early physical rehabilitation program was started, which included passive and active exercises, so that most of

Table 1. Summary of data for each patient.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age (y)	54	68	42	47	29	57	47
Sex	Female	Male	Female	Male	Male	Male	Male
Original renal disease	FSGS	Idiopathic	APCKD	Vasculitis	FSGS	DM	Idiopathic
HLA mismatches	3	3	0	3	4	3	2
Date of transplant	10/8/02	4/4/04	4/8/03	7/18/04	5/10/05	1/21/08	11/28/97
Date of ICU admission posttransplantation (mo)	98	80	92	77	42	23	156
Immunosuppression							
*Induction	Simulect	Simulect	Thymo	Simulect	Thymo	Simulect	Simulect
**maintenance	S/CsA/MMF	S/CsA/MMF	S/TaC/MMF	S/CsA/MMF	S/CsA/MMF	S/CsA/MMF	S/CsA/MMF
***during ICU stay	S/CsA	S/CsA	S/TaC	S/CsA/MMF	S/CsA	S/CsA	S/CsA
Recent rejections	No	Mixed rejection	AMR	Chronic changes	No	No	AMR
Clinical findings	Cough, dyspnea, hypoxia, low-grade fever, acute tetraparesis						
Final diagnosis	CMV + Legionella	Legionella	Acinetobacter	Legionella	CMV + Legionella	Legionella	Klebsiella
Plasma sugar/ albumin (mean ± SD) during ICU stay	7 ± 2/	9 ± 2.1/	8 ± 3.1/	6.5 ± 1.1/	6 ± 1.2/	7 ± 2.3/	6.4 ± 1.1/
Intervention	+	+	+	+	+	+	+
Antibacterial	+				+		
Antiviral	+	+	+	+	+	+	-
CVVHDF							
Prognosis	Good	Good	Good	Good	Good	Good	Good
Basal creatinine	150	110	82	196	251	105	120
Last creatinine	165	56	100	200	220	150	122

Abbreviations: AMR, acute antibody mediated rejection; APCKD, polycystic kidney disease; CMV, Cytomegalovirus; CsA, cyclosporine; CVVHDF, continuous veno-venous hemodiafiltration; DM, diabetes mellitus; FSGS, focal segmental glomerulosclerosis; HLA, human leukocyte antigen; ICU, intensive care unit; MMF, mycophenolate mofetil; S, sirolimus; Tac, tacrolimus

the patients were able to stand after 10 days, walk with support after 4 weeks, and walk unsupported after 3 to 4 months.

Electrophysiologic reassessment was performed after clinical recovery and revealed improvements in compound muscle action potential amplitudes; this allowed exclusion of drug-induced neuromyopathy, in particular that induced by immunosuppressants. Although we were unable to prevent development of CIP/CIM, our patients recovered fully. Possibly, because of careful neurologic evaluation and early electrophysiologic assessment, we could establish diagnosis early and accurately estimate neurologic prognosis. This allowed us to deal with possible risk factors and to initiate early rehabilitation, which might prevent disuse muscle atrophy and enable complete recovery.

Discussion

Critical illness polyneuropathy is a sensory-motor axonal polyneuropathy that is recognized as a complication of sepsis, systemic inflammatory response syndrome, and multiple organ system failure in critically ill adults.⁸ It generally shows

spontaneous improvement within weeks to months, but recovery may be limited when the neuropathy is severe. No specific therapies are available.

We managed sepsis aggressively in all of the present cases, in agreement with most authors who believe that this is the most important measure to reduce the incidence of CIP/CIM. Additional major issues include managing the difficulty of weaning from mechanical ventilation,¹⁶ initiating a rehabilitation program,¹⁷ and avoiding additional pressure neuropathies by careful positioning.

Nutritional interventions were started early, with supportive albumin infusion and intravenous immunoglobulin for all patients, which are reported to benefit such cases, especially those involving gram-negative sepsis. However, widespread acceptance of this treatment awaits further supportive data.^{18, 19} All of these measures were consistent with those of previous reports.^{15, 8, 20} It should be noted, however, that none of these measure have been shown to have actual beneficial effects on muscle function in patients in the ICU.²¹

We attempted to avoid hyperglycemia by maintaining strict glycemic control with insulin therapy because it was recently reported that this

might be beneficial in preventing CIP/CIM.⁸ Insulin itself has some potential beneficial effects, including anti-inflammatory effects,²² endothelial protection,²³ improvement of dyslipidemia, and neuroprotective effects in animals,²⁴ and it is also an anabolic hormone. In addition, multivariate analysis has attributed a beneficial effect of glycemic control on CIP/CIM.¹⁰

Our management strategy was supportive, consisting initially of aggressive pulmonary hygiene in addition to preventing secondary complications of immobility such as bed sores, deep venous thrombosis, and superimposed compressive neuropathies. All of the present patients received steroids and neuromuscular blockers, being transplant recipients on ventilator support, without significant deterioration in recovery. This was consistent with results of Hermans and associates,²¹ who concluded that these drugs are not critical or essential for the development of CIP/CIM because CIM has been reported in patients receiving only 1 of these agents or receiving neither. However, hypoalbuminemia and the use of neuromuscular blocking agents and steroids have been reported to be risk factors for the development of CIP.^{11, 25}

It is well known that CNI-associated neurotoxicity may be reversed in most patients by substantially reducing the dosage or discontinuing these drugs. However, some patients experience permanent or even fatal neurologic damage even after dose reduction or discontinuation.^{26, 27} Regimens sparing CNIs and that use the immunosuppressant mycophenolate mofetil, which has no neurotoxic effects, may reduce the incidence and severity of neurotoxic adverse events while maintaining an adequate level of immunosuppression. In the present cases, we successfully optimized immunosuppressive agents so that we kept CNI at low levels and used a small dosage of mycophenolate mofetil. The acute, transient course of events and their reversibility might exclude a possible role of CNI in the pathogenesis of such this syndrome.

With respect to long-term management, a rehabilitation program involving active and passive exercises was started along with the use of assistive devices, and medication was prescribed for neuropathic pain, if present. All patients, with the exception of 1, recovered within 4 to 8 weeks, which is earlier than that reported for nontransplant populations, which usually takes months to years to

recover, often incompletely. Clinical deficits are present in 59% of survivors, and electrophysiologic abnormalities are present in 95% of survivors followed up to 5 years.¹⁹ This difference might owe to earlier and appropriate management of our cases.

In conclusion, CIP/CIM is a rare complication, and this is the first report of this syndrome among renal transplant recipients. Clinical suspicion and electrophysiologic studies are the tools for early diagnosis. Proper management, including controlling for risk factors, especially diabetes, and initiating long-term rehabilitation measures, might be beneficial.

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