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LETTER TO THE EDITORS

Calcineurin inhibitor encephalopathy can develop years post lung transplantation

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Sirs,

Calcineurin inhibitor (CNI) encephalopathy is well described post transplantation. The classical presentation is within days or months of the transplant in the setting of large doses and elevated drug levels. We report a case of a 55-year-old female that developed a rapidly fatal neurodegenerative disease 4 years post lung transplantation. We suggest CNI encephalopathy as the diagnosis and consider the wide spectrum of CNI toxicity.

Our patient underwent bilateral sequential lung transplantation for bronchiectasis and advanced emphysema secondary to cigarette smoking and alpha-1 antitrypsin deficiency. Post-transplantation, complications included sternal non-union and reactive pleuritis with a pleural effusion. Her renal, hepatic, magnesium and cyclosporine levels, lipids and blood pressure, were regularly monitored by her respiratory physician and were within normal ranges. Medications included cyclosporine 100 mg BD, azathioprine 50 mg OD, prednisolone 7.5 mg OD with valganciclovir and cotrimoxazole prophylaxis. Co-morbidities included osteoporosis (calcium, cholecalciferol, zolendronate) and controlled hypercholesterolaemia (ezetemibe 10 mg OD). There was no history of alcohol abuse, but a family history of Parkinson's.

One year prior to death, she suffered a fall with head laceration, then over months developed fluctuating memory disturbance, headaches, clumsiness and tremor unresponsive to the addition of carbidopa/levodopa 100/25 mg OD, propranolol 10 mg BD and pizotifene 0.5 mg OD.

She presented to a secondary regional hospital in 2011 with a sudden onset headache, generalized seizure and low glasgow coma score requiring brief intubation. Post extubation she developed worsening ataxia and tremor, with new visual hallucinations. Lumbar puncture, CT brain and basic bloods were unremarkable and cyclosporine level was low–normal.

On day 16 of her admission, she was transferred to our tertiary hospital for respiratory, infectious disease and neurological opinions. Examination revealed delirium, a fine bilateral resting tremor, diffuse hyperreflexia and plantar withdrawal. Her observations remained within the normal range, but on day 18, her neurology worsened. Levodopa/carbidopa and pizotifene were ceased. Cyclosporine was changed to everolimus 2 mg BD though CNI toxicity was considered of low likelihood given low serum levels. Quetiapine 12.5 mg BD and midazolam PRN (when necessary) were used for delirium. On day 21, she developed status epilepticus requiring sedation and brief mechanical ventilation. Post extubation she had a few days of stability before deteriorating further. On day 30, all rejection medications were ceased. Despite this, her neurological status continued to worsen and she passed away on day 37.

Extensive testing (see Table 1) was undertaken to help exclude the following: Progressive multifocal leukoencephalopathy, Creutzfeldt–Jakob disease, status epilepticus, venous sinus thrombosis, vasculitis, Lewy body dementia, infectious encephalitis, graft versus host disease and rejection. A metabolic or toxic differential remained, though at the time, no reversible cause was found. Autopsy report ultimately revealed posterior encephalopathic changes consistent with the missed diagnosis of CNI encephalopathy.

Post organ transplantation, neurological side effects associated with the prescription of the CNIs cyclosporine and tacrolimus are well described. Mild side effects of headache, tremor and peripheral neuropathy occur in 10–40% of patients [1–4]. Severe side effects are less common occurring in up to 5% of patients [1,2]. Symptoms include delirium, psychosis, ataxia, blindness, seizures and paresis.

The aetiology of CNI encephalopathy is not fully understood and likely to be multifactorial [1–4]. Toxicity usually occurs within days to months of transplantation when large CNI doses and high serum levels can lead to direct neuronal toxicity, though there are case reports with therapeutic or sub-therapeutic CNI levels [1,5–8]. Given encephalopathy can occur without high levels, other factors have been suggested as mechanisms. Hypocholesterolaemia,

Table 1. Summary of investigations

Timeline	Investigation
Day 16 (available at transfer to our hospital)	Electrolytes: Cr 110 mmol/l, Mg: 0.78 mmol/l (0.7–1.05)
	Full blood count: Hb 135 g/l, MCV 102 fl, WCC 9 × 10^9/l, Plt 284 × 10^9/l
	Full blood examination: Neutrophil segmentation, macrocytes
	CRP: 4 mg/l
	Thyroid function, B12, folate, ferritin, thiamine: normal
	Cyclosporine level (trough): 121 μgm/l (low end of therapeutic range)
	Blood cultures and urine: normal
	CT Brain: normal
	CXR: normal
	ECG: Sinus tachycardia
Day 17	Lumbar puncture: negative for white and red cells, bilirubin and microscopy. Protein elevated: 0.68 g/l (0.15–0.45), no oligoclonal bands. PCR for HSV, CMV, VZV all negative. Atypical CJD bands seen 14-3-3 considered to be nonspecific
Day 21	MRI brain and MRA: normal
Day 22	EEG: 2–4 Hz delta waves: generalized slowing consistent with an encephalopathy
Day 22	Syphilis EIA: negative
Day 23	MRI brain: T2 hyperintensity in hippocampal body and tail: possibly consistent with postictal changes
	EEG: generalized bilateral slowing, no evidence of status epilepticus
	Lumbar puncture: Negative for white and red cells. PCR for HSV, CMV, EBV, enterovirus, picornovirus, polyomavirus (JC, BK), 14-3-3 were all negative
Day 23	Ammonia: normal
	Anti TPO antibodies, thyroglobulin: normal
	Cortisol, caeruloplasmin: normal
	ANA, ANCA: negative
	Serum protein electrophoresis: normal
	Hepatitis B surface antigen: negative, HCV antibody: negative
	HIV: negative
	CRP: 120 mg/L
Day 25	MRI Lumbar spine: Osteoporotic compression fracture.
	Everolimus level: 8.7 mcg/L (6–13)
Day 32	EEG: generalized slowing, no EEG correlation with twitches/myoclonus
Post day 37	Postmortem brain histopathology: Marked and diffuse white matter oedema in the brain, brainstem and cerebellum, most marked in the occipital lobe. Hypoxic changes in the hippocampus. No evidence of CJD, infection or vasculitis. Conclusion: The changes of this nature are not specific and could be multifactorial, including toxicities and metabolic defects. It is possible the morphology is in keeping with a "reversible" leucoencephalopathy. No other significant aetiology for the clinical manifestations has been found.

methylprednisolone and hepatic failure may change calcineurin binding or metabolism. Active drug metabolites may inhibit nitric oxide and lead to inflammation, disruption of the blood brain barrier and axonal injury. Hypertension and hypomagnesaemia may worsen inflammation and endothelial damage through vasoactive peptides. Cerebrovascular accidents or previous seizures have also been documented as possible risk factors, which leads us to suggest that previous head injury also could lower the threshold for CNI encephalopathy. Controlling risk factors can improve CNI toxicity symptoms and CNI reduction or withdrawal usually, but not universally result in neurological recovery [1,2,6–9]. Although rejection can occur in up to 30% of patients, introduction of a different CNI is often tolerated without neurological relapse [2–4].

Magnetic resonance imaging (MRI) brain changes are uncommon in CNI encephalopathy, even in those with significant clinical signs [1,2]. However, posterior reversible encephalopathy syndrome (PRES) can be considered at the severe end of the CNI encephalopathy spectrum and has MRI changes of vasogenic oedema in the parieto-occipital lobes and cerebellum [6,8]. As with CNI encephalopathy, PRES does not always correlate to high CNI levels and again, usually reverses with CNI withdrawal [6,9].

Autopsy findings of CNI encephalopathy were found in our patient, though are nonspecific for a toxic or metabolic encephalopathy. Posterior encephalopathic changes include oedema, infarction, reactive astrocytosis, neuronal loss, haemorrhagic foci, diffuse neuronal damage and demyelinization [3,8].

In retrospect, the clinical features and autopsy suggest the diagnosis of a fatal CNI encephalopathy given the extensive investigations and absence of other metabolic or toxic causes of white matter oedema. This cannot be proven as the most diagnostic feature is neurological improvement following drug withdrawal [4]. Unfortunately our patient passed away without improvement.

This case is unique, in that CNI encephalopathy years post transplant has not been published in a transplant patient. There are "late" accounts of CNI neurotoxicity in the months following transplantation, but not years [7,9]. Although outside of high serum drug levels, current theories do not suggest clear reasons why late CNI toxicity could not occur. Some risk factors were present at the patient's admission, including mild hypomagnesaemia, controlled hypercholesterolemia and her previous head injury, which could have lowered the threshold for CNI encephalopathy. In retrospect, symptoms of memory disturbance, tremor and clumsiness may have signalled CNI toxicity up to 12 months preceding her admission, but were missed as toxicity due to her low-normal CNI levels and lateness of onset post-transplant.

Our recommendation is that development of even mild neurological symptoms months–years post-transplantation should prompt consideration of CNI encephalopathy and an immediate review of CNI prescription.

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