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The Case | Altered mental status in a transplant patient

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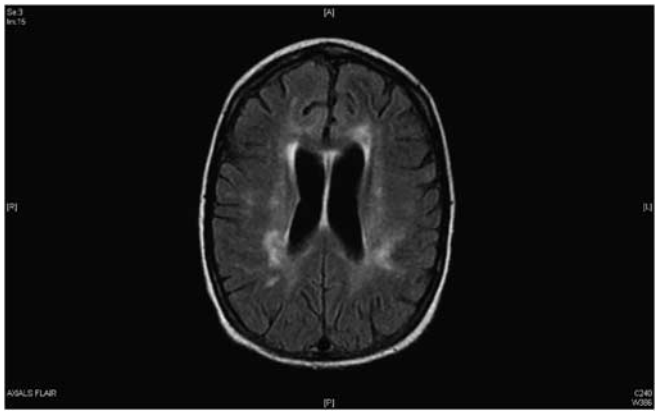

Figure 1 | Magnetic resonance imaging of the brain.

A 27-year-old woman with end-stage renal disease secondary to type I diabetes received a living-related renal transplant in December 2000. The kidney function immediately improved and serum creatinine during the first month was between 106 and 124 μmol/l. In September 2001, her serum creatinine increased to 292 μmol/l. In November 2001, she underwent a renal biopsy, which showed no evidence of acute cellular rejection.

One week later, she presented to the emergency room with confusion and falls. The patient's husband stated that she had tremors over the previous 4 months, but they had worsened over the past week. The patient also reported visual hallucinations beginning 1 day before admission. Her home medications were acyclovir, amantadine, aspirin, bupropion, cyclosporine, fluconazole, insulin, isosorbide dinitrate, metoclopramide, metoprolol, mycophenolate mofetil, pantoprazole, prednisone, sulfamethoxazole/trimethoprim, and warfarin. Additional symptoms of ataxia, agitation, and aggressive behavior were also present. On examination, the patient was alert, oriented, and in no apparent distress, but extremely tremulous. Her blood pressure was 164/90 mm Hg; however, the remaining physical exam was unremarkable. On admission, blood urea nitrogen and serum creatinine were 17.1 and 327 μmol/l (estimated creatinine clearance of 0.33 ml/s), respectively. Laboratory results that were remarkable were the following: serum sodium 125 μmol/l, chloride 90 μmol/l, glucose 15.9 μmol/l, and hemoglobin 102 g/l. Cyclosporine level was 195 nmol/l. A computed tomography scan of the head, magnetic resonance imaging of the brain (Figure 1), electroencephalogram, and electrocardiogram were performed.

What is the cause of this patient's altered mental status?

SEE NEXT PAGE FOR ANSWERS

The Diagnosis | Amantadine toxicity

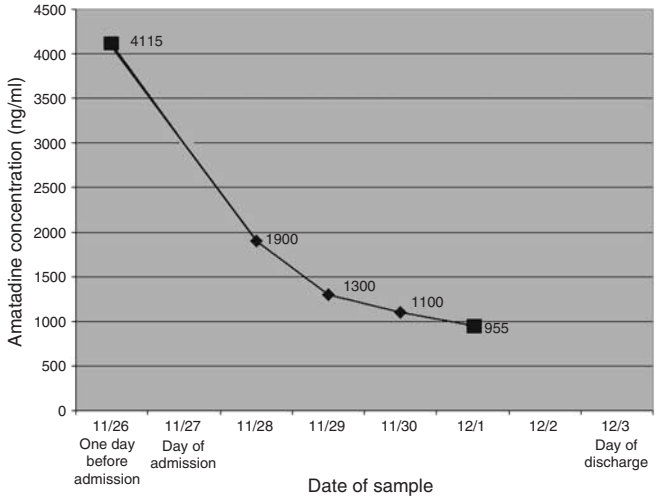

Figure 2 | Amanadine measured and estimated serum levels vs. day of stay. —◆— Measured amantadine level (ng/mL); ■ Esimated amantadine level (ng/mL)
*Estimated serum amantadine levels were calculated using the patient's estimated half-life, which was calculated from the true measured amantadine levels.

As the patient's amantadine dosage was increased 5 days before admission, amantadine toxicity was suspected and the drug was discontinued. The patient's computed tomography and electrocardiogram were unremarkable. Magnetic resonance imaging of the brain demonstrated chronic ischemic changes. Electroencephalogram did not show diffuse slowing. Both serotonin syndrome and neuroleptic malignant syndrome were ruled out. Bupropion, sulfamethoxazole/trimethoprim, acyclovir, and metoclopramide were also discontinued. High-dose benzodiazepines were used to control the patient's agitation and hallucinations over the next 7 days. Serial amantadine levels were obtained (Figure 2). Clinical evidence of amantadine toxicity was resolved on day 5 of hospitalization. She was restarted on bupropion, sulfamethoxazole/trimethoprim, and metoclopramide at the same doses without recurrent symptoms. Methylphenidate was added for the treatment of her depression and cognitive deficit. She was discharged 7 days after admission with an improved serum creatinine of 221 μmol/l (estimated creatinine clearance of 0.48 ml/s).

Amantadine serum concentrations of greater than 1000 ng/ml have been associated with toxicity.[1] Amantadine toxicity is associated with central nervous system findings more commonly in chronic toxicity and with cardiovascular effects more commonly in acute toxicity.[2] Cardiovascular effects that have been reported with acute amantadine toxicity are bradycardia, congestive heart failure, hypotension, torsades de pointes, and ventricular arrhythmias.[2] In addition, coma, seizures, and death have been reported with acute toxicity.[2] Central nervous system effects such as agitation, altered mental status, ataxia, delirium, hallucinations (auditory and visual), hypersomnia, impaired concentration, insomnia, nightmares, psychosis, and tremor have been more evident with chronic toxicity; however, they can occur with acute toxicity.[1–3] Risk factors for chronic amantadine toxicity are concurrent anticholinergic medications, renal impairment, and advanced age.[1–3]

The care of renal transplant recipients requires the use of many drugs with potential interactions, and renal function in such patients frequently changes. Because 90% of amantadine is excreted in the urine, it is important to adjust the dose for renal function in patients with renal impairment to avoid the accumulation of amantadine and drug toxicity.[3] The reason for this patient's acute renal insufficiency was not clear. Her renal biopsy was normal and her cyclosporine concentrations were not elevated. The increase in her serum creatinine level began while she was being treated with intravenous acyclovir, and this is the presumed etiology of her renal insufficiency. There is no known nephrotoxicity from amantadine, although it might aggravate renal insufficiency by causing urinary retention. This case highlights the importance of adjusting amantadine dose when renal function changes and monitoring for potential medication interaction in renal transplant recipients.

REFERENCES

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