Tacrolimus-associated mania with psychotic symptoms in a child after renal transplant

PRASHANT GUPTA, JAWAHAR SINGH,
ANANYA MAHAPATRA, PRATAP SHARAN

ABSTRACT

Tacrolimus is one of the mainstays for post-transplant immunosuppression. A variety of neuropsychiatric adverse effects have been reported above the levels of its therapeutic use. Manic symptoms associated with its use have been rarely reported. We report possibly the first such case in a child post-renal transplantation and discuss the potential neuro-immunological basis of these symptoms.

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INTRODUCTION

Tacrolimus (FK-506) is one of the mainstays for post-transplant immunosuppression and finds some use in autoimmune diseases (Crohn disease, psoriasis and rheumatoid arthritis). It is a narrow therapeutic index drug.[1] A variety of neuropsychiatric adverse effects have been reported beyond the therapeutic levels.[1] We found only 2 published reports of manic symptoms associated with tacrolimus use.[2,3] We report possibly the first such instance in a child and discuss the potential neuro-immunological basis of these symptoms.

THE CASE

An 8-year-old boy underwent renal transplant for stage IV chronic kidney disease in 2013. Post-transplant, he was started on mycophenolate mofetil (500 mg/day), tacrolimus (6 mg/day) and prednisolone (5 mg/day); and an antihypertensive, amlodipine (5 mg/day) was administered regularly at the paediatric nephrology clinic. Serum tacrolimus concentration was regularly monitored and maintained within the normal maintenance range of 5–10 ng/ml. He also received valproate 400 mg/day, for generalized tonic–clonic seizures, which predated his renal transplant, and for which no specific cause could be detected. He was seizure-free since 2013 when valproate was started.

He was well till October 2016 when his parents noticed that he was not sleeping properly; he was more active than usual and did not seem to get tired. He would move around incessantly, frequently shifting tasks without completing them. He became irritable if someone interrupted his activities. He started ordering around his parents authoritatively, often shouting at them and threatening them with dire consequences, and sometimes hitting them, which was very unlike him. He appeared to be talking excessively, even with strangers, and interrupting him was difficult. He started telling people that he is 'Lord Hanuman', is very powerful and that he can do anything. While saying so, he would make gestures like Gods in Hindu mythology, as if to give a boon or a curse. This belief was held at a delusional intensity. All through this time, he did not have fever and his sensorium was clear. Within 2 weeks of onset, his condition warranted inpatient psychiatric management. Neither he nor his family had any history of psychiatric illness.

At the time of admission, he was receiving the above-mentioned drugs in usual doses. His weight was 24 kg and height 123 cm. His blood pressure was 120/70 mmHg and pulse rate 87/minute. There were no apparent signs of encephalitis. His haemoglobin, blood counts, serum electrolytes, urea and creatinine, liver functions and CT scan of the head were normal. Serum valproate levels were in the normal range for seizure control (55 µg/ml), but tacrolimus levels were elevated (17.8 ng/ml). The dose of tacrolimus was then reduced to 4 mg/day. In the next 4 days, serum tacrolimus levels decreased to 8.4 ng/ml, and some improvement in the manic symptoms was also noticed. Since the improvement was slow and the symptoms were severe, quetiapine was started. There was progressive improvement in the psychiatric condition, temporally correlated with a gradual reduction in tacrolimus levels from 8.8 ng/ml to 7.1 ng/ml and a gradual increase in the dose of quetiapine from 50 to 450 mg/day over a period of 7 weeks during the inpatient stay. Symptoms had resolved completely at the time of discharge. One week into the treatment, he also developed hyponatraemia and pancytopenia which improved on replacing valproate with levetiracetam.

Two months later, he had similar manic and psychotic symptoms despite continuing with quetiapine (450 mg/day) and reduced dose of tacrolimus (3.5 mg/day). The dose of quetiapine was further increased to 500 mg, which led to sedation but inadequate control of symptoms in the next 1 month. Tacrolimus levels were again found to be elevated (13.4 ng/ml). Vital parameters were normal. The patient was not on any drugs whose interaction with tacrolimus could explain the rise in its levels. Although, the laboratory parameters showed pancytopenia, no abnormalities were noticed in liver functions ruling out any problems in hepatic metabolism of the drug. Blood urea nitrogen was also within normal limits. However, there was vomiting and weight loss (2 kg), which may have contributed to the rise in tacrolimus levels. He was admitted under the paediatric nephrology unit. Tacrolimus was stopped and cyclosporine started. Supportive treatment was given for his medical condition. Quetiapine was continued in a reduced dose (400 mg/day). The mental and physical status improved over the next 2 weeks. The patient maintained well even after 3 months of replacing tacrolimus with cyclosporine (dose 150 mg/day, serum levels 1330 ng/ml). At the time of writing this report, it was decided to gradually reduce the dose of quetiapine during follow-up if the patient continues to remain asymptomatic.

DISCUSSION

The clear temporal association of psychiatric symptoms with elevated serum tacrolimus levels on 2 occasions, and their resolution with reduction of levels or removal of the drug on both occasions confirmed a diagnosis of 'tacrolimus-associated mania with psychotic symptoms' in this patient. Although he was also receiving prednisolone, it was in a low dose, and there had been no recent change in the dose. Moreover, his renal transplant was working well as was evident by laboratory parameters, and there was no evidence of recent seizures, ruling out other potential causes of psychiatric symptoms.

Bersani *et al*.[2] reported a 'manic-like psychosis' associated

All India Institute of Medical Sciences, New Delhi, India
PRASHANT GUPTA, JAWAHAR SINGH, ANANYA MAHAPATRA, PRATAP SHARAN Department of Psychiatry

Correspondence to PRASHANT GUPTA; *pg_aiims@yahoo.co.in; drpgaiims@gmail.com*

with elevated blood concentrations (13.8 ng/ml) of tacrolimus in a 40-year-old man following renal transplant, and Jain *et al*.[3] reported a 68-year-old woman who received tacrolimus for acute lymphoblastic leukaemia and developed 'mania with psychosis' even with subtherapeutic levels of tacrolimus (1.6 ng/ml). Our patient also had both manic and psychotic symptoms. A few case reports of tacrolimus-associated psychotic symptoms (without manic symptoms) have also been published,[4–6] though in only 1 of them did the patient have a clear sensorium.[4] A retrospective study on adverse effects of tacrolimus in liver transplant recipients mentioned 2 patients developing psychosis and confusion, though the details were not provided.[7] All these reports are of adults, while ours is possibly the first such instance in a child. Previous reports have shown improvement in symptoms with antipsychotic drugs such as haloperidol[3,6] or olanzapine,[2,4] or with a reduction in the dose of tacrolimus,[2,4] or its replacement with alternative immunosuppressant therapies (mostly change to cyclosporine).[3,5,6] Some have used a combination of these 2 approaches.

There has been limited research into the neurobiological basis of such adverse effects. Tacrolimus exerts its immunosuppressive effects by binding to a family of immunophilins called FK506-binding protein 12 (FKBP12).[8] The high molecular weight congener of this protein FK506-binding protein 51 (FKBP5) is a co-chaperon of glucocorticoid receptors (GR), and overexpression of FKBP5, as seen in some polymorphisms, has been shown to reduce binding of cortisol with GR as well as the nuclear translocation of GR.[9] Through this mechanism, FKBP5 has been thought to affect the stress response system and thus has been implicated in the pathogenesis of anxiety, depression, post-traumatic stress disorder and psychosis.[9–14] We speculate that the interaction of tacrolimus with FKBP5 may have a role in the emergence of psychiatric symptoms, though the available literature is silent on this. A scientific enquiry may provide valuable insights into the neuro-immunological mechanisms of these psychiatric conditions. This case highlights the need to closely monitor patients receiving tacrolimus for the emergence of such psychiatric adverse effects.

Conflicts of interest. None declared

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