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Case report

Tacrolimus-related polyneuropathy: Case report and review of the literature

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Abstract

Patients, in particular recipients of orthotopic liver transplants, receiving the immunosuppressant tacrolimus (FK-506), are at risk for developing central neurotoxic adverse events. We report the occurrence of a tacrolimus-induced peripheral neurotoxic event, i.e. pure motor axonal polyneuropathy of the lower limbs in a 44-year-old woman, 9 days after combined orthotopic liver and pancreas transplantation. She was treated for 5 days with intravenous immunoglobulins. Partial recovery followed over months to years. An overview of all 11 reported FK506-associated polyneuropathies is given.

Keywords: Tacrolimus; Liver transplantation; Neurotoxicity; Polyneuropathy; Immunoglobulins

1. Introduction

Tacrolimus (or FK-506), is a calcineurin inhibitor, increasingly used as an immunosuppressive agent in transplant patients. Some reports have described toxicity of this agent to the central nervous system and only occasionally to the peripheral nervous system, i.e. polyneuropathy mainly resembling chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) [1,2]. We describe a patient who developed an acute and severe pure motor polyneuropathy of the lower limbs in the early postoperative period after liver and pancreas transplantation and early after initiation of treatment with tacrolimus.

2. Case report

A 44-year-old woman with multiple endocrine neoplasia type 1 (MEN 1), and related history of pancreatectomy giving rise to secondary diabetes mellitus, parathyroidectomy and left hemithyroidectomy, was admitted to the intensive care unit (ICU) after a combined orthotopic liver and pancreas transplantation. Immunosuppressive treatment consisted of orally administered tacrolimus (Prograft, Fujisawa, Brussels) (a dose between 0.04 and 0.08 mg/kg body weight/day), intravenously administered glucocorticoids (methylprednisolone (Pfizer, Brussels) 125 mg/day on day 1, with subsequent tapering of the dosage) and intravenous antithymocyte globulin (2 mg/kg/day) during the first 5 days after transplantation.

During the acute phase after transplantation an upper gastro-intestinal hemorrhage, a transient mild increase in serum creatinine (1.8 mg/dl, normal values <0.9 mg/dl) and urea (163 mg/dl, normal value 17–45 mg/dl) without a necessity for dialysis, recurrent pleural effusions and atrial fibrillation occurred. Prolonged hospitalisation in the ICU was therefore necessary. Nine days after transplantation the patient developed a rapidly progressive paraparesis in both proximal and distal muscles and areflexia in the lower limbs. The weakness was slightly more pronounced in the right leg. She had no weakness in the upper limbs, no sensory deficit, no breathing difficulties, normal cranial nerve and bulbar function, and normal cognitive functions. Routine laboratory results (including electrolytes) were within the normal

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Table 1
Initial and follow-up nerve conduction studies

Time	R/L	Peroneal motor		Tibial motor		Sural sensory	
		Amp > 3.0	CV > 41.0	Amp > 3.0	CV > 41.0	Amp > 12.0	CV > 44.0*
32 d post-TX (23 d after onset symptoms) symptoms	R	**NR**	**NR**	**0.1**	**NR**	15.3	$40.9_{(28.3)}$
	L	–	–	**0.1**	**40.5**	20.8	47.6
5 months post-TX	R	**1.5**	**33.5**	**0.1**	**35.9**	–	–
	L	**2.1**	**39.3**	–	–	–	–
17 months post-TX	R	**0.1**	**39.2**	**0.3**	45.9	20.4	$42.1_{(29.7)}$
	L	4.1	42.0	–	–	–	45.0

Amp: amplitude (motor: in mV; sensory: in μV); CV: conduction velocity (in m/s); NR: no response; –: not measured; d: days, TX: transplantation. Bold = abnormal values. R/L = right/left. *, normal value of CV when skin temperature is 32 °C. (*x*), decreased skin temperature at distal leg in degrees Celsius (normal = 32 °C).

range. The tacrolimus serum level was 12 ng/ml (normal 8–20 ng/ml).

Transverse myelitis, acute polyneuropathy and cauda equina syndrome were withheld as possible diagnoses. Magnetic resonance imaging (MRI) of the thoraco-lumbo-sacral spine showed no signs of myelopathy or disturbances of the cauda equina. Electromyographic examination revealed an asymmetric (slightly more pronounced at the right side) pure motor axonal polyneuropathy with signs of massive denervation in the distal muscles of the lower limbs (Table 1). Sensory nerve conduction velocities (NCV) in the lower limbs were normal, as well as motor and sensory NCV in the upper limbs. An immunologic and extensive serologic screening for more than 35 infectious causes (both early and 4 weeks later, i.e. during the reconvalescence period) could not denote an immunological nor infectious etiology. Thyroid function tests were normal and a tight control of the serum glycemia was achieved by the administration of continuous intravenous insulin.

A lumbar puncture showed a slightly elevated total protein without a marked albumino-cytologic dissociation (protein level 59.2 mg/dl, white blood cells <2 mm^{-3}).

We concluded that the polyneuropathy was caused by or related to the use of tacrolimus. Interestingly, the tacrolimus serum level had never been within the toxic range, i.e. higher than 20.0 ng/ml. Subsequently, we reduced the daily tacrolimus dose, we started mycophenolate-mofetil and initiated a 5 day course of intravenous immunoglobulins (0.4 g/kg/day) and intensive revalidation. The patient was discharged to the internal ward on day 15 after transplantation. Neurological follow-up revealed a slow partial recovery of muscle strength and deep tendon reflexes in the lower limbs. At 4 months post-transplantation the patient was able to stand supported by a bar at both sides. At 8 months she walked by means of two crutches, and at 13 months she could walk up the stairs with bilateral support. Two years after her transplantation, she was able to walk indoors supported by one person or by means of a rollator, and outdoors using a wheelchair. Follow-up nerve conduction velocities at 5 and 17 months post-transplantation showed recovery of the motor nerve responses in the lower limbs with an increase of amplitudes and conduction velocities (Table 1).

3. Discussion

Neuromuscular complications following liver transplantation are less common (4%) than central nervous system symptoms (26%). Peripheral complications consist mainly of a mononeuropathy or acute myopathy [3]. Immunosuppressive therapy is generally not a recognised risk factor for the development of peripheral neuropathy, as opposed to toxicity to the central nervous system.

In most patients, tacrolimus-related polyneuropathy resembles chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) with primarily demyelinating changes on nerve conduction studies. Most patients presented with marked weakness within weeks after receiving the first dose of FK-506. Table 2 gives an overview of the 11 patients reported with tacrolimus-associated polyneuropathy, including their predisposing factors [4–10]. In our patient diabetes mellitus was the only (other) recognised predisposing factor for a peripheral neuropathy [11]. She was 44 years old, correlating with the mean age (46 years) of other patients (Table 2) with FK506 related polyneuropathy previously described. The time between initiation of tacrolimus and onset of symptoms was 9 days in our patient, compatible with the other reports where this delay varied between 8 days and 3 weeks (Table 2).

In our patient besides tacrolimus associated neuropathy, several other differential diagnoses were considered: Guillain-Barré syndrome, critical illness polyneuropathy, liver allograft failure associated neuropathy and diabetes related acute neuropathies. Although acute Guillain-Barré syndrome can present as an acute pure motor axonal neuropathy we felt this diagnosis was less likely. Acute pure motor axonal Guillain-Barré syndrome has mainly been described in Asia after episodes of diarrhoea or upper respiratory tract infections. This neuropathy predominates in the distal parts of the lower limbs and cranial nerve involvement is frequent. In our patient proximal muscles were more severely affected than distal muscles and cranial nerves remained spared. The observation of a slight increase in protein level in the cerebrospinal fluid (59.2 mg/dl, normal <49 m/s) was considered of uncertain significance especially in a patient with diabetes mellitus. We also did not withhold the diagnosis of criti-