Original Article

Autonomic Neuropathy In Acute Ciclosporin Toxicity

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Abstract

Cyclosporine is associated with several well-known adverse effects; however, autonomic insufficiency related to the drug is rarely described in the literature. We report the case of a 72-year-old male paediatrician from Karachi, Pakistan, who was receiving cyclosporine for pure red-cell aplasia. He presented with dizziness, recurrent falls, tremulousness, and urinary incontinence. Examination revealed a significant postural drop in systolic blood pressure and fine resting tremors. Although specific autonomic testing was unavailable, the clinical picture and supporting investigations strongly suggested the presence of autonomic dysfunction. His cyclosporine level was markedly elevated (947.1 ng/mL). Discontinuation of cyclosporine, along with supportive management, led to rapid improvement in blood pressure, tremors, and urinary symptoms. The medication was later restarted at a lower dose with close therapeutic drug monitoring. This case highlights a rare presentation of autonomic neuropathy secondary to acute cyclosporine toxicity and underscores the need for vigilant monitoring, prompt recognition, and further research into this uncommon complication.
Keywords: Cyclosporine; Drug Toxicity; Autonomic Nervous System Diseases; Orthostatic Hypotension; Tremor; Urinary Incontinence; Pure Red-Cell Aplasia.

Introduction

Cyclosporin A (CsA) is an immunosuppressive agent that has been used for decades to prevent transplant rejection and to treat autoimmune disorders. It is a calcineurin inhibitor (CNI) and a cyclic undecapeptide. It was initially introduced in the mid-1980s and has proven efficacy in the survival of grafts in organ transplants.[1,2]

Pure red cell aplasia (PRCA) is a medical condition characterised by normocytic, normochromic anaemia, low levels of reticulocytes, and a decrease or absence of erythroid precursors in the bone marrow. PRCA can be congenital or acquired later in life. Red cell aplasia is mainly treated with immunosuppressive therapy and supportive treatment, such as blood transfusions.[3]

Literature reports serious side effects of cyclosporine use owing to its high toxicity, including nephrotoxic, hepatotoxic, neurotoxic, and cardiotoxic effects.[1]

We report a case of a patient who developed postural hypotension, a characteristic of autonomic neuropathy (AN), while receiving treatment for pure red cell aplasia (PRCA). To the best of our knowledge, this is the first documented case report to specifically demonstrate cyclosporine-related autonomic neuropathy.

Case Presentation

We present the case of a 72-year-old male patient, a pediatrician by profession, residing in Karachi, Pakistan. He has had a confirmed diagnosis of Pure Red Cell Aplasia since December 2022. Additionally, the patient has a medical history of Bronchial Asthma, single-vessel coronary artery disease (underwent Percutaneous Coronary Intervention in 2004), Unstable Angina, and Hypertension.

On March 28, 2023, the patient presented to us with dizziness, frequent falls, trouble walking, and shaky hands that had been occurring for two months. He experienced dizziness upon standing, leading to three falls at home, where he needed help getting up. He also had episodes of urine incontinence, which significantly impacted his quality of life. The patient did not have a history of headaches, fainting, seizures, hearing problems, memory issues, or trouble concentrating. He had no addictions or allergies. His medications included cyclosporine 125 mg twice daily since January 2023, valsartan, salmeterol, fluticasone inhaler, theophylline, and antiplatelets.

At the time of presentation, the patient's examination revealed the following findings: he appeared pale and experienced a drop in systolic blood pressure of more than 30 mmHg every time he stood up from a sitting position, while his blood pressure remained normal (approximately 120–130 mmHg systolic) when lying down or sitting. He exhibited fine resting tremors, required assistance while walking, and had no signs of Parkinsonism or hyperthyroidism. The remainder of the systemic examination did not reveal any significant abnormalities.

During the patient's hospital stay, comprehensive laboratory tests were conducted to further evaluate his condition (Table 1).

Magnetic Resonance Imaging (MRI) of the brain was done to rule out a central cause of these symptoms and revealed mild cerebral atrophy with age-related microangiopathic ischemic changes. Nerve conduction study (NCS) and electromyography (EMG) revealed acute-on-chronic sensory motor generalised polyneuropathy with ongoing denervation in a few muscles (axonal neuropathy). The 2D-echo was normal, with a preserved ejection fraction. Cyclosporine levels were markedly elevated (947.1ng/mL (< 200 ng/mL)). No specific test is available in our setup to confirm autonomic neuropathy. It was concluded from the history, examination, laboratory results, and imaging that cyclosporine might be the culprit of this patient's autonomic insufficiency.

Contributions:
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Table 1: Labs at time of admission

LABS	RESULT	NORMAL RANGE	LABS	RESULT	NORMAL RANGE
Hemoglobin	11.2g/dL	(12.3-16.6)	**Glycosylated Hemoglobin**	5.7%	(<6.0)
Leukocyte count	$9.6x10^9$/L	(4.8-11.3)	**Antinuclear Antibody (ANA)**	positive	Negative
Platelets	$357x10^9$/L	(150-400)	**Adrenocorticotropic hormone(ACTH)**	Not detected	(0-46)
Reticulocytes	3 %	(0.6-2.4)	**Acetylcholine Receptor antibodies**	<0.25nmol/L	(<0.40)
Bilirubin	0.6 mg/dL	(0.1-1.2)	**Serum Aldolase**	8 U/L	(2.5-10)
Gamma-Glutamyl Transferase(GGT)	26 IU/L	(<35)	**Creatine phosphokinase (CPK)**	43 IU/L	(4.6-171)
Alanine transaminase (ALT)	35 IU/L	(<45)	**Anti-smooth muscle antibodies (ASMA)**	Negative	'-'
Aspartate aminotransferase (AST)	24 IU/L	(<35)	**Thyroid stimulating hormone(TSH)**	3.40 µIU/mL	(0.5-8.9)
Alkaline phosphatase (ALP)	49 IU/L	(45-129)	**Cortisol**	20.20 µg/dL	(4.82-19.5)
Creatinine	1.0 mg/dL	(0.8-1.3)	**Urine for Albumin Creatinine Ratio (ACR)**	51.0mg/g	(<30)
Sodium(Na)	138 mmol/L	(136-145)	**Cyclosporin levels**	947.1ng/mL	(100-200)
Potassium (K)	4.3 mmol/L	(3.5-5.1)	'-'	'-'	'-'

In addition to discontinuing cyclosporine, the patient received intravenous (IV) fluids, fludrocortisone, thromboembolic deterrent (TED) stockings, and mirabegron, in addition to his regular medications for ischaemic heart disease and asthma. This led to an improvement in his postural drop in blood pressure within a few days. Supportive medications like Fludrocortisone and Mirabegron were stopped. Cyclosporine was then restarted at a lower dose of 50 mg twice daily, as the patient did not wish to permanently stop or switch to another drug for his aplasia. Routine monitoring of cyclosporine levels was conducted, and subsequent levels were found to be within the desired range, that is, between 100 and 200 ng/mL. The patient reported improvements in tremors, dizziness, and urinary symptoms; however, he still experienced difficulty with walking. However, even this difficulty gradually improved over a period of six weeks. Currently, the patient can move around without support and without experiencing any postural drop in blood pressure.

Discussion

Cyclosporine is a lipophilic compound that relies on biological carriers, such as erythrocytes and lipoproteins, for its distribution.[4] Despite its lipophilic nature, CsA typically does not penetrate the blood-brain barrier (BBB) under normal physiological conditions. However, CsA, along with other similar calcineurin inhibitors, can damage capillary endothelial cells of the BBB, particularly in the presence of factors contributing to alterations in BBB permeability, such as inflammation.[2] Oligodendrocytes, which are rich in calcineurin, are particularly susceptible to CNIs, which can also impact glial cells, alter neurotransmitter receptor activity, and potentially harm astrocytes.[2]

Neurotoxic effects of CNIs extend to the peripheral nervous system (PNS), encompassing dose-dependent and dose-independent phenomena, including fine, resting, and action tremors, toxic neuropathy, myopathy, and autonomic neuropathy (AN). The primary approach to treating tremors involves dose reduction and the use of beta blockers.[2] In one study, the incidence of drug-related neurological side effects was reported to be 40%,[5] while another study reported neurotoxicity in 25% of patients receiving immunosuppressive therapy; autonomic neuropathy was not specifically addressed in either study.[6]

Autonomic neuropathies, whether inherited or acquired, often result in selective or disproportionate damage to autonomic fibres. Both sympathetic and parasympathetic fibres are typically affected, although there are certain exceptions.[7] In addition to drug side effects, conditions such as multisystem atrophy, polyneuropathy (e.g., Guillain-Barré Syndrome and Chronic Inflammatory Demyelinating Polyneuropathy), diabetes mellitus, amyloid deposition, paraneoplastic syndromes, and inherited neuropathies can contribute to the development of AN.[8] Common manifestations include blood pressure disorders (e.g., orthostatic hypotension, increased peripheral vascular resistance, and diminished diurnal variations), gastrointestinal issues (gastroparesis, alternating constipation and diarrhoea), and genitourinary complications (incontinence and erectile dysfunction).[2]

Notably, an article suggested that autonomic function may improve in some transplant recipients but persist or worsen in others, potentially due to immunosuppressive drugs. However, the impact of specific immunosuppressants has not been investigated or reported in the literature.[2] In an exploration of drug-related neurotoxicity in transplant recipients, it was found that one-third of renal transplant recipients developed tremors related to CNIs, typically responsive to dose reduction, as observed in our patient.[2]

Our patient presented with orthostatic or postural hypotension, a significant indicator of severe autonomic neuropathy. Intriguingly, in the absence of autonomic neuropathy, cyclosporine usually induces hypertension.[9] The patient was successfully managed by discontinuing the offending drug, providing supportive care, and counselling him appropriately.

Conclusions

Although cyclosporine-related autonomic insufficiency is rarely reported in the literature. But this case of a 72-year-old patient with Pure Red Cell Aplasia exhibiting autonomic insufficiency was linked to Cyclosporine therapy. Lab investigations, prompted by his symptoms and signs, revealed Cyclosporine as the likely cause. He was managed with discontinuation of the drug for the time being, supportive measures, and then dose adjustment. This case highlights the rare occurrence of autonomic neuropathy in acute Cyclosporine toxicity, stressing the importance of vigilant monitoring, prompt intervention, and further research on this topic. We were able to find very limited data in the literature on this specific topic, and more studies are required to demonstrate the mentioned side effect of the drug, along with its dose dependency and specific management.

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