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Acute Pisa syndrome secondary to betahistine treatment in a patient with mild cognitive impairment ☆☆☆



Síndrome de Pisa agudo tras tratamiento con betahistina en un paciente con deterioro cognitivo leve

Dear Editor:

Betahistine is an oral histamine analogue which, due to its vasodilatory properties, is used habitually to treat episodic vertigo and other inner ear disorders.¹ Adverse effects include headache, confusion, nausea, dyspepsia, and hypotension. The literature describes only one case of acute dystonia² and one of delayed-onset dystonia³ associated with the drug; no paper published to date describes Pisa syndrome (PS).

PS is characterised by an abnormal, dystonic posture of the trunk, causing a lateral inclination with some degree of axial rotation. The condition was originally described in 1972 by Ekbohm et al.,⁴ in patients receiving antipsychotic drugs. Since then, researchers have pointed to other drugs, including antiemetics, antidepressants, benzodiazepines, cholinesterase inhibitors, and almost all dopaminergic drugs, as potential causes of PS.^{5,6} The condition has been described in patients with various neurodegenerative

diseases and with normal pressure hydrocephalus (NPH); other cases are idiopathic.^{5,7,8}

We present the case of a 76-year-old woman, with a history of episodes of vertigo and a one-year history of mild cognitive impairment, for which she was under follow-up at another hospital. Neuroimaging findings were suggestive of NPH. The patient attended the emergency department due to acute-onset lateral deviation of the trunk following a single 16 mg dose of betahistine to treat a vertigo episode similar to those she had previously experienced. She had no further symptoms and was taking no other drugs. The general physical examination revealed no other abnormalities. In the neurological examination, we observed a leftward inclination of the trunk and normal vestibular manoeuvres. A cranial CT scan displayed mild cortical atrophy and increased ventricular volume, with no signs of transudate. Within 24 hours of betahistine withdrawal, the patient's posture returned to normal and she remained completely asymptomatic. The patient was lost to follow-up following discharge.

Past drug exposure is a highly valuable criterion for demonstrating the cause of potential adverse drug reactions; however, we must also consider biological plausibility, consistency, and the statistical strength of the association.⁹ The reproduction of symptoms supports a proposed association; however, given the paramount importance of ethics in the field of medicine, this was not considered in the present case. Clinical suspicion and communication are therefore crucial in these cases, despite the evidential limitations of reporting isolated clinical cases. It is also necessary to verify causality.

This is the first published case of PS occurring subsequently to a single 16 mg dose of betahistine, in a patient with several noteworthy characteristics. Firstly, the patient was under follow-up for mild cognitive impairment at another centre; this may be related to Alzheimer disease or to NPH, given the clinical and neuroimaging findings. Both Alzheimer disease and NPH have been described as potential causes of PS; there is also a possibility of patients being

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affected by both conditions.^{8,10} Secondly, the acute onset and subsequent complete recovery following withdrawal of the drug is suggestive of a connection. Thirdly, the patient reported several previous episodes of vertigo with similar characteristics; these were treated with betahistine, with no trunk deviation.

The pathophysiology of PS is not fully understood. It has been suggested that the acute or subacute onset of PS following ingestion of specific drugs may be similar to the case of dystonia, given the good response to anticholinergics or reducing the dosage of the drug involved. This may point to an imbalance between dopamine and choline levels.⁵ Drugs acting on such neurotransmitters as norepinephrine and serotonin may also have a role; however, the mechanism involved is unknown.⁶ Chronic forms of PS have been described in patients with such neurodegenerative conditions as Parkinson's disease. The suggested mechanisms include alteration of proprioceptive sensory feedback, peripheral vestibular hypofunction, impaired subjective visual vertical, and even musculoskeletal disorders.⁵

In patients with Alzheimer disease, only one case of PS has been confirmed by an anatomical pathology study in a patient who had not been exposed to any drug; the underlying mechanisms are unknown.⁸ It has been suggested that in patients with NPH, PS symptoms may be related to compromised periventricular blood flow, decreased dopamine levels in the substantia nigra, or damage to the striatal GABAergic neurons.⁷ This mechanism may be involved in the present case; however, the acute onset of the condition after the dose of betahistine and the complete recovery following withdrawal would appear to suggest the involvement of multiple mechanisms. The histaminergic system could, therefore, be an additional factor, with betahistine being the trigger for PS in this patient. We should also note that in the previous episodes of vertigo, the patient took betahistine and did not experience PS.

We would therefore suggest that the onset of mild cognitive impairment may affect the action of betahistine by causing imbalances in the neurotransmission systems involved in postural control, triggering PS.

In animal models, betahistine acts as a partial histamine H₁ receptor agonist, increasing vestibular blood flow and histamine turnover, and as an H₃ receptor antagonist, promoting histamine release in the central nervous system.¹¹ The rat striatum contains a high concentration of H₃ receptors, and reactions have been described between H₃ receptors and the D₁ and D₂ dopamine receptors. Some studies have described betahistine acting as a postsynaptic antagonist, with H₃ agonism resulting in motor inhibition and H₃ antagonism increasing motor activity through coactivation of the D₁ and D₂ receptors.¹² In the context of these observations, the antidystonic effects of such H₁ receptor antagonists as diphenhydramine suggest that histamine may be involved in dystonia. However, the literature includes very few reports of dystonia secondary to betahistine use, despite the frequent use of the drug to treat vertigo in our setting.^{2,3}

In conclusion, we suspect that in this patient with amnesiac mild cognitive impairment, betahistine may have caused an imbalance in the vestibular pathways, the striatal circuitry, or both, causing a deviation of the trunk and triggering PS.

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