CASE REPORT

First line antiepileptics and their hidden risks - a unique case report on diffuse calvarial thickening and twisted tongue linked to the use of phenytoin and sodium valproate

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Abstract

Introduction: Phenytoin and sodium valproate are widely used antiepileptics with well documented side effects profile. However diffuse calvarial thickening and lingual dystonia with the use of phenytoin and sodium valproate respectively is extremely rare. This case underscores the importance of recognizing rare side effects in patients on long term anticonvulsant therapy.
Case presentation: We present two cases of seizure disorder patients who were on first line antiepileptics phenytoin and sodium valproate developed uncommon side effects of diffuse calvarial thickening and lingual dystonia respectively during their follow up. CASE 1: 15 year old boy a case of refractory epilepsy with global developmental delay who was on multiple antiepileptics including phenytoin was admitted with breakthrough seizures. Patient had gum hypertrophy and serum phenytoin level was elevated and CT brain showed diffuse calvarial thickening, the offending drug was stopped. CASE 2: 45 year old female a case of idiopathic generalised epilepsy was started on sodium valproate for seizure control and she developed lingual dystonia during follow up. Having ruled out the secondary causes of dystonia the possible temporal association between the use of sodium valproate and lingual dystonia. Patient improved after stopping the use of sodium valproate.
Discussion: This case report highlights two rare adverse effects associated with commonly used anticonvulsants emphasizing the need for heightened clinical vigilance.Early identification is essential for better clinical outcome.
Conclusion: Long term use of phenytoin and sodium valproate can lead to rare but significant adverse effects such as calvarial thickening and lingual dystonia.

Keywords: Adverse effects, Phenytoin, Sodium valproate, Diffuse calvarial thickening, Lingual dystonia

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INTRODUCTION

Phenytoin and sodium valproate are commonly used antiepileptics that are extremely effective in the management of epileptic convulsions. Phenytoin can cause localized and systemic adverse effects, including gingival, neurological, hematological, reticuloendothelial, cardiac and dermatological reactions, due to elevated serum levels of the drug. One of the rare but notable side effects is diffuse calvarial thickening characterized by widening of the diploic space. The prevalence of this condition remains poorly defined because of its infrequent case reports, but it is considered an uncommon finding after prolonged phenytoin therapy. Sodium valproate is generally well tolerated but can occasionally cause side effects, including nausea, vomiting, hair loss, weight gain and, rarely, movement disorders. Lingual dystonia is an uncommon but potentially disabling side effect of sodium valproate characterized by abnormal involuntary sustained or intermittent contractions of the tongue muscles, which can significantly impair speech, swallowing and patient quality of life. Drug-induced dystonia accounts for 2–5% of all cases, with sodium valproate being a rare but recognizable culprit. Here, we present two unique side effects, diffuse calvarial thickening [1] and lingual dystonia [2], with the use of phenytoin and sodium valproate, respectively, in two different patients. The aim of this study was to highlight the rarity and significance of diffuse calvarial thickening and lingual dystonia with the use of phenytoin and sodium valproate, respectively.

CASE REPORT

CASE 1: A 15-year-old boy with two siblings born out of a nonconsanguineous marriage delivered at term with a history of global developmental delay and refractory epilepsy of multiple semiology since 1 year of age. The patient was on multiple chronic anticonvulsants, including T. phenytoin, T. sodium valproate, T. levetriacetam, T. Clobazam for seizure control. The patient had been on T. phenytoin since the age of 8 years and had been adjusted over time to a maintenance dose of 100 mg 1-0-1 for seizure

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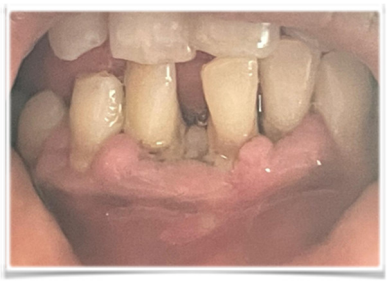
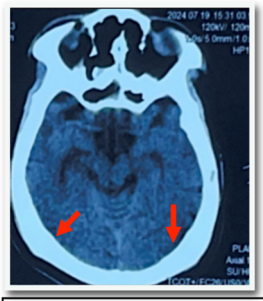
control at another facility. The patient was admitted to our facility with breakthrough seizures. Upon examination, gingival hypertrophy (Figure 1.a) was noted, and noncontrast CT revealed diffuse calvarial thickening with cerebellar atrophy (Figures 1.b and 1.c). Further investigations were performed to exclude secondary causes of hyperostosis, including serum parathyroid level, a hematological workup for thalassemia and other metabolic workups that did not contribute. Having excluded secondary causes, the serum phenytoin level was greater than 20 mcg/ml (10–20 mcg/ml - normal range). The chronological sequence revealed diffuse calvarial thickening and cerebellar atrophy linked to chronic phenytoin toxicity as a more likely etiology in our patient, and the patient was switched over to alternate antiepileptics; however, the calvarial thickening remained stable, and the patient was followed up for any progression.

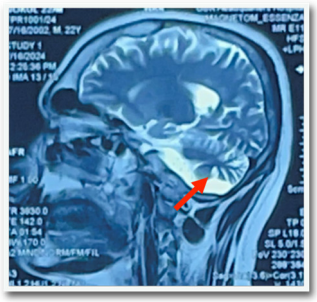
CASE 2: A 45-year-old female with a known case of Idipathic generalized epilepsy for 2 years presented with a 1-month history of progressive abnormal persistent twisting movement of the tongue associated with difficulty in speech, chewing and swallowing. The patient was on T. Sodium valproate 200 mg 2-1-2 optimized for seizure control during follow-up at an outside clinic. Her past medical history was unremarkable for intake of any other drugs, including antipsychotics, metaclopramide, and any psychiatric or metabolic illness. The O/E patient had isolated lingual dystonia (Figure 2.a) with no other involuntary movements involving her face, limbs or any other part of her body, with normal sensory, motor, or cerebellar function and fundus examination. All routine investigations to exclude secondary causes of dystonia, including complete hemogram, peripheral smear for acanthocytes, iron study, B12 assay, thyroid profile, LFT, copper study, slit lamp examination for the KF ring, CSF analysis and neoplastic workup, were negative. MRI of the brain was unremarkable (Figure 2.b). The temporal association between sodium valpraote use and symptom onset favors the diagnosis of sodium valproate-induced lingual dystonia. The offending drug was tapered and switched to T. levetriacetam 500 mg 1-1-1, and the patient was treated with T. trihexyphenidyl 2 mg 2-2-1, T. clonazepam 0.5 mg 1-0-1 and speech therapy. The patient improved symptomatically, and her dystonia resolved during follow-up (Figure 2.c).



a. Gum hypertrophy

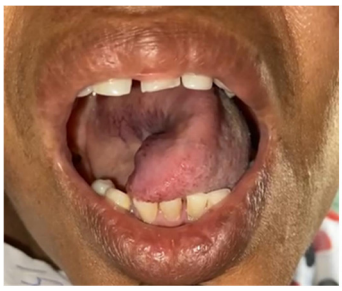


b. NCCT brain axial-diffuse calvarial

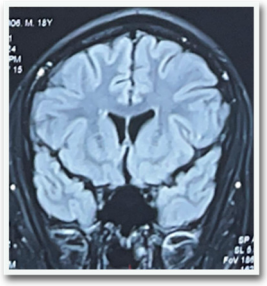


c. MRI T2 sagittal brain-cerebellar atrophy

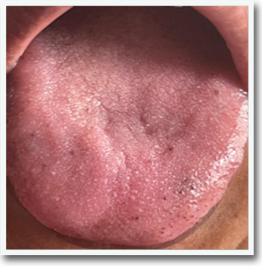
Figure 1. Examinations related to case 1.



a. Lingual Dystonia



b. MRI T2 flair coronal-normal



c. Follow up after 4 months

Figure 2. Examinations related to case 2.

DISCUSSION

Phenytoin and sodium valproate are widely used anticonvulsants known for their efficacy with well-documented side effects. However, diffuse calvarial thickening and lingual dystonia following prolonged phenytoin and sodium valproate use, respectively, require meticulous clinical evaluation. Diffuse calvarial thickening with the use of chronic phenytoin therapy has long been noted; however, the exact incidence is not known [1,3]. The proposed pathophysiology involves stimulation of osteoblast activity and inhibition of bone resorption by transforming growth factor beta 1 and morphogenetic proteins [1,3,4]. Sodium valproate is also known to alter calcium and vitamin D metabolism [5]. The combined use of phenytoin and sodium valproate could have contributed to the accelerated development of diffuse calvarial hyperostosis, with phenytoin being the primary agent responsible [3]. A study by Milhaud et al. (1982) and Malaviya et al. described cranial hyperostosis in long-term users of phenytoin, emphasizing the rare occurrence in chronic users. Although diffuse calvarial thickening is often asymptomatic, it may serve as a marker for chronic phenytoin exposure and should prompt the treating physician to assess its clinical significance. Sodium valproate is generally well tolerated but rarely causes movement disorders, including parkinsonism, tremors and dystonia [6]. Lingual dystonia, a focal form of dystonia involving the tongue, is an extremely rare adverse effect of sodium valproate, with very few cases reported in the literature. The exact pathophysiology remains unclear but is believed to involve GABAergic and dopaminergic pathways. Sodium valproate increases the availability of GABA, an inhibitory neurotransmitter that alters the balance of neurotransmitters in the basal ganglia, leading to dystonic movements [6]. Fatima et al reported lingual dystonia in a young adult with traumatic brain injury treated with sodium valproate. Similarly, another case of lingual dystonia as a part of broader spectrum tardive syndromes induced by long-term use of sodium valproate has been reported. The prognosis depends on the withdrawal of the offending drug. However, delayed recognition may lead to refractory symptoms. This rare manifestation of valproate-induced lingual dystonia highlights the need for increased awareness of such side effects. Clinicians should be highly vigilant in monitoring such adverse effects when patients are receiving long-term anticonvulsant therapy to mitigate further complications.

CONCLUSION

Our case underscores the link of rare adverse effects, such as diffuse calvarial thickening and lingual dystonia, with the use of commonly used antiepileptic drugs, such as phenytoin and sodium valproate, respectively. Recognizing these side effects is crucial for timely intervention, preventing further complications and guiding treatment adjustments to ensure patient safety.

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Conflict of Interest: None

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