

Atypical Absence Epilepsy and Migraines in Mosaic Trisomy 14 Treated with Topiramate: A Case of FOXP1 Overexpression?

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Abstract

Mosaic trisomy 14 is a rare chromosomal anomaly with less than 30 cases reported. Neurological manifestations include developmental delay and seizures. To date there is no data on how these cases were managed clinically or any hypotheses on the underlying pathophysiology. We report a 9-year-old girl who presented with developmental delay, learning difficulties, migraines, and seizures. She was diagnosed with de novo mosaic trisomy 14. Her EEG demonstrated generalized 4.5Hz spike-polyspike slow waves. She was successfully treated with high-dose topiramate, which resulted in improvement of her migraines as well as normalization of her EEG. Mosaic trisomy 14 can present with migraines and atypical absence epilepsy, and topiramate, which is FDA-approved for both conditions, was effective at higher doses. Overexpression of the Forkhead Box G1(FOXP1) gene, which resides on chromosome 14, may explain why epilepsy occurs in this condition.

Keywords: Mosaic trisomy 14; Blaschko's lines; Atypical absence epilepsy, FOXP1 gene, GABA

Introduction

Trisomy 14 was first described by Murken., *et al.* [1] with approximately 30 cases reported to date. Neurological manifestations include developmental delay and seizures [2], however, currently there are no reports on the clinical management or any hypotheses on the underlying pathophysiology. Here we highlight the clinical neurological features of mosaic trisomy 14 with unprecedented EEG data and a plausible hypothesis of the underlying mechanism of this disorder.

Case Report

A 9-year-old Hispanic female was referred to our clinic for headaches and seizures. She was born to non-consanguineous parents. Her perinatal course was unremarkable, but her mother reported birthmarks on her extremities and trunk.

She was developmentally delayed since infancy and had been in special education since kindergarten and at the time of her initial visit she was 2 years behind her grade level. She also has had seizures since infancy, consisting of 1-minute staring spells with urinary incontinence, with occasional truncal jerking. At age 7 she was first treated with liquid valproic acid (VPA) 250mg three times daily, to which her seizures did not respond, hence switched to carbamazepine, which did not improve her seizures either. Her initial EEG at age 8 with her previous neurologist showed 2 secs of 5Hz generalized spike-slow waves during sleep while on extended release VPA 250mg twice daily. She continued to have seizures even on 750mg daily.

In addition, she has had vertex, near-daily migraines since age 3, radiating posteriorly, with nausea and photophobia, lasting 30 - 40 min only to recur 3 - 4 hours later, which did not respond to ibuprofen or VPA.

There was no family history of developmental delay, seizures or migraines.



Figure 1: Digital photos of our patient with mosaic trisomy 14. Note facial asymmetry (top left), anteverted nares, micrognathia (top right), a short neck, a prominent forehead, broad fingers (bottom left), and Blaschko's lines (bottom right).

On exam she demonstrated psychomotor retardation, facial asymmetry, anteverted nares, micrognathia, a short neck, a prominent forehead, and Blaschko's lines.

Clinical features	Present	Absent
Growth retardation		X
Psychomotor retardation	X	
Broad upturned nose	X	
Dysplastic and/or apparently low set ears		X
Micrognathia	X	
Short neck	X	
Congenital heart disease: atrial septal defect(ASD)	X	
Prominent forehead	X	
Hypertelorism		X
Narrow palpebral fissures		X
Epicanthal folds		X
Small chin/lower jaw set backwards	X	
Large mouth		X
Cleft or highly arched palate		X
Body/facial asymmetry	X	
Pectus carinatum		X
Narrow chest		X
Abnormal skin-pigmentation (Blaschko's lines)	X	
Genitourinary abnormalities		X

Table 1: Our patient's morphology, compared with findings described by Shinawi.

There were no abnormal involuntary movements such as chorea. Her head circumference was normal for her age. Her brain MRI was normal. Chromosomal microarray detected increased levels of DNA in chromosome 14, at a copy number dosage of 27.0% being positive for trisomy 14, hence she was diagnosed with mosaic trisomy 14. As congenital heart defects have known to be associated with this condition she was referred to Cardiology, and she was found to have a small secundum atrial septal defect (ASD) on transthoracic echocardiography, which did not warrant any intervention.

Her anti-seizure regimen was switched from VPA to topiramate (TPM) sprinkles. Her initial EEG on TPM 50mg twice daily showed 8 secs of generalized, 4.5Hz spike-polyspike slow waves during wakefulness and Stage II sleep.

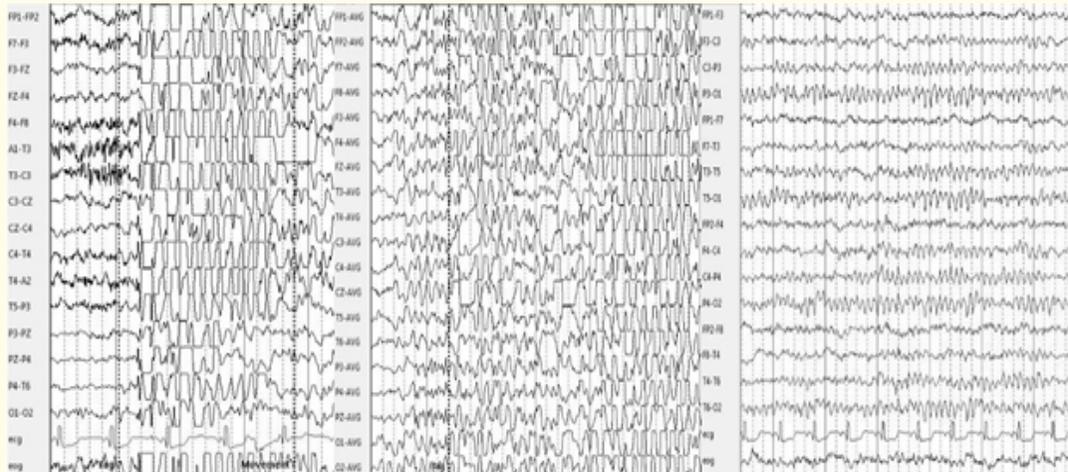


Figure 2: EEG findings of our patient with mosaic trisomy 14 characteristic of atypical absence epilepsy. Left: transverse montage, showing generalized, high amplitude 4.5Hz spike-polyspike slow waves during drowsiness while on TPM 50mg twice daily.

Middle: average montage, showing same findings during Stage II sleep while on TPM 50mg twice daily

Right: bipolar montage, showing normalization of EEG with TPM 125mg twice daily (5.7mg/kg).

And she continued to have seizures, therefore this was increased to 75mg twice daily. She was still having seizures twice a week on this dose, hence we increased her dose to 100mg twice daily, and at 125mg twice daily (5.7 mg/kg) her EEG normalized and her seizures resolved. Her migraines had also significantly improved, and sumatriptan 50mg as needed was effective for abortive therapy.

Discussion

Clinical features of mosaic trisomy 14

Mosaic trisomy 14 is an extremely rare condition; complete trisomy 14 is incompatible with life, therefore the cases observed in daily clinical practice are mosaics [3]. There was no ring chromosome 14 detected in our case [2]. The natural course of mosaic trisomy 14 has been described by Fujimoto, *et al.* [4] Common characteristic features of mosaic trisomy 14 include growth retardation, developmental delay, and dysmorphism [5], which was consistent with previous literature. The craniofacial features of this condition are listed in Table 1. Overall our patient had a milder phenotype than previous reports [6-8], which could be explained on the basis of her lower degree of mosaicism at 27%. This was higher than the levels reported by Shinawi, *et al.* [9], where findings such as her facial asymmetry were previously described. Blaschko's lines, which are characteristic for mosaicism, are not specific for partial trisomy 14 and can be seen in other disorders [9].

Epilepsy has been reported in mosaic trisomy 14 [2]. Based on the clinical presentation and EEG findings, our patient had atypical (with polyspikes and occurring at a rate of 4.5Hz) absence epilepsy. Despite her epilepsy her MRI was normal; Dandy-Walker malforma-

tion [3] and corpus callosal abnormalities [10] have been reported in mosaic trisomy 14. Epilepsy in mosaic trisomy 14 will be discussed in detail in the following sections.

EEG findings of mosaic trisomy 14

This is the first report documenting the EEG findings of a patient with mosaic trisomy 14. Clinically our patient presented with an atypical absence phenotype. Her EEG clearly suggested a form of generalized epilepsy, with generalized, 4Hz spike-polyspike and slow wave complexes. These findings are helpful for the neurologist, as carbamazepine (which was initially used in this case) is less effective in primary generalized epilepsy. The presence of such epileptic discharges even in Stage II sleep is intriguing; there is a compelling body of evidence that the function of the sleep spindle is related to intellectual ability and memory consolidation, [11] which might explain in part why the child had learning disabilities.

Overexpression of the transcription factor FOXG1, which resides on chromosome 14, has also been shown to lead to overproduction of GABAergic neurons [12]. GABAergic reticular neurons are crucial in generating sleep rhythms and inhibiting external signals through thalamocortical neurons, which leads to unconsciousness during absence epilepsy [13].

Why does mosaic trisomy 14 cause atypical absence epilepsy and migraines?

It is unknown why mosaic trisomy 14 causes epilepsy. Polvi, *et al.* [14] reported a common susceptibility haplotype D14S70 for both epilepsy and migraine on 14q12-q23; unfortunately, we were unable to verify if our patient had this haplotype or not due to insurance restrictions. Interestingly, the Forkhead Box G1(FOXG1) gene resides on chromosome 14, inhibits gliogenesis, and promotes neuron genesis and neurite outgrowth [15]. FOXG1 is a nuclear-cytosolic transcription factor essential for the forebrain development and involved in neurodevelopmental and cancer pathologies. Different subcellular localizations of FOXG1 control the machinery that leads to cell differentiation, replication, and bioenergetics, possibly linking mitochondrial functions to embryonic development and pathological conditions [16].

The dynamic expression of FoxG1 during migration within the intermediate zone is essential for the proper assembly of the murine cerebral cortex [17]. It functions as a critical initiator of neocortico-genesis through spatiotemporal repression, which balances the production of non-radially and radially migrating glutamatergic subtypes of neurons during mammalian cortical expansion [18]. FoxG1 is also expressed continuously in the postnatal and adult murine hippocampal dentate gyrus(DG), which is a major source of epileptogenic, and is critical for DG formation, especially during early postnatal stage [19].

Overexpression of the transcription factor FOXG1 has also been shown to lead to overproduction of GABAergic neurons [12]. Overexpression of GABA(B)R1a receptors in mice (R1a (+)) manifests as an atypical absence seizure phenotype characterized by 3 - 6Hz slow spike-and-wave discharges, reduced synaptic plasticity, and cognitive impairment, which is consistent with our EEG findings [20].

Cases of FOXG1 duplications with epilepsy and developmental delay have been reported [21], and animal studies have shown that overexpression of the FOXG1 gene resulted in thickening of the neuro epithelium and telen- and mesencephalic outgrowth, as a result of reduced cell apoptosis. Such structural aberration may induce persistent network disturbances, leading to epilepsy.

FOXG1 has recently been suggested as a dosage-sensitive gene, and not only duplication but even a small increase in the dosage of FOXG1 can cause severe epilepsy and developmental delay, including infantile spasms in humans [22,23].

The form of epilepsy seems to be more severe in cases of FOXG1 duplications (with infantile spasms and dysrhythmia) than mosaic trisomy 14 [10] most likely due to the fact that not all the cells (in our case 27%) have FOXG1 duplications. The underlying mechanism as to why migraines occur in mosaic trisomy 14 remains unclear.

How does TPM control epilepsy and migraines in mosaic trisomy 14?

Here we have clearly demonstrated that high-dose TPM resolves epileptiform discharges on the patient's EEG; lower doses did not control the discharges on her EEG. How TPM controls seizures in mosaic trisomy 14 seems less clear. One of the several anti-seizure

mechanisms of TPM is GABA A receptor modulation, perhaps by controlling overexpression of GABA B R1a receptors, which is seen in overexpression of FOXP1.

VPA, on the other hand, seems act on GABA-ergic pathways through multiple indirect pathways, somewhat different from TPM, which might explain why the seizures were resistant to VPA. In conclusion, mosaic trisomy 14 can present with migraines and generalized epilepsy, where TPM, which is FDA-approved for both conditions, can be effective, especially at higher doses. Overexpression of the FOXP1 gene (and GABA) may explain why epilepsy occurs in this condition. TPM modulates GABA A receptors, which may suppress seizures in mosaic trisomy 14 by controlling overexpression of GABA B R1a receptors.

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