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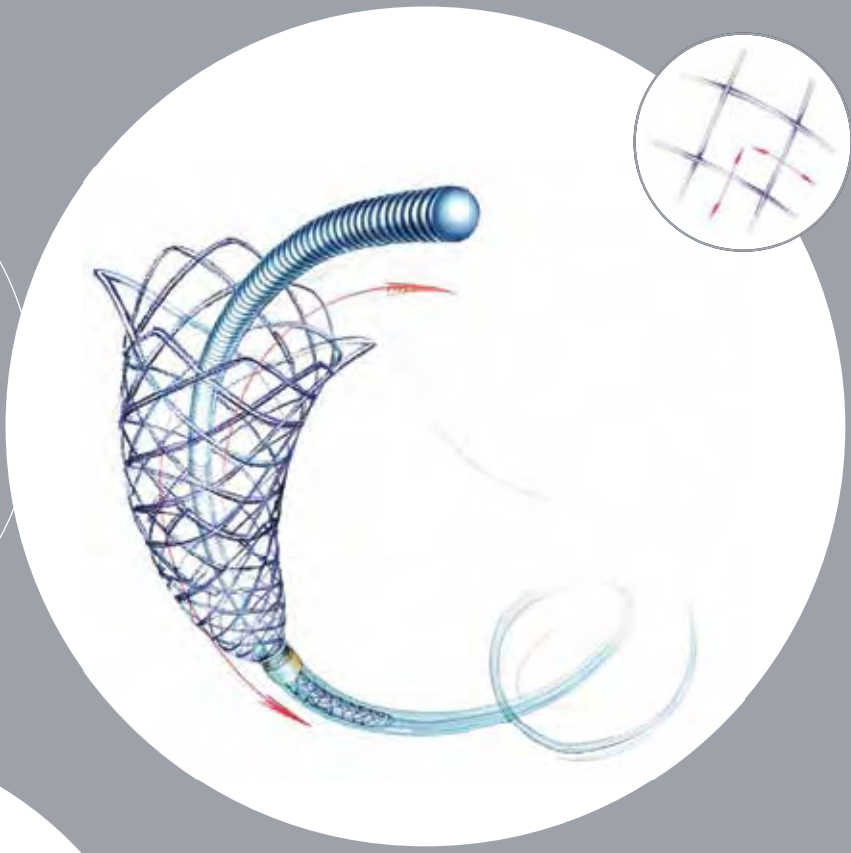

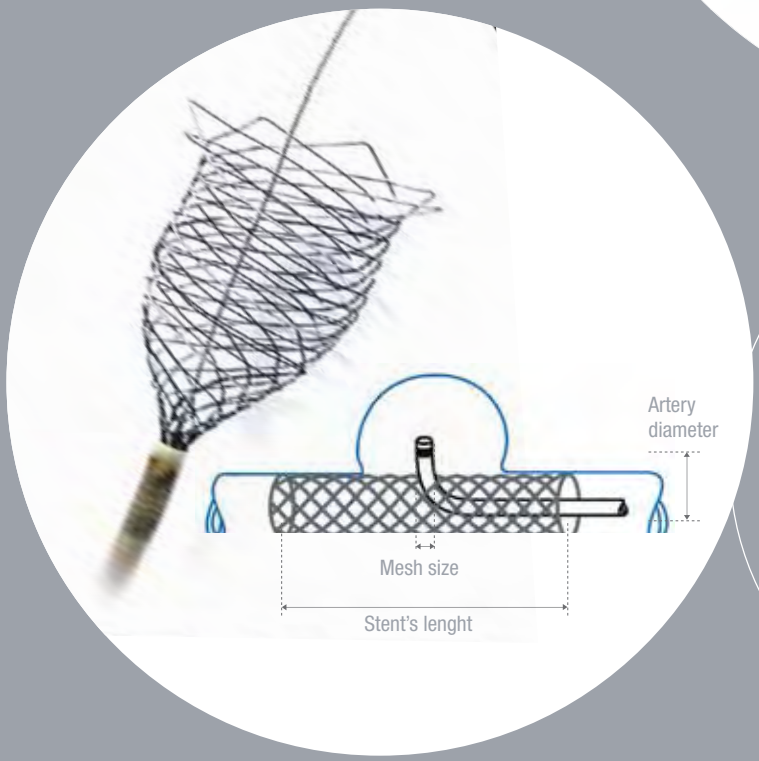

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Case report

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Vigabatrin-induced MRI changes associated with extrapyramidal symptoms in a child with infantile spasms

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Abstract

Vigabatrin is an antiepileptic drug used for treatment of infantile spasms. We present a female patient with infantile spasms in treatment with vigabatrin who developed ataxic movements. MRI demonstrated a symmetrical pattern of thalamic and globi pallidi diffusion restriction. While these image features have been widely described to be related to the use of vigabatrin, this case highlights the development of movement disorders in association with MRI signal changes. Awareness of the reversible nature of this condition is reassuring for the treating team and avoids unjustified studies.

Keywords

Vigabatrin, infantile spasms, ataxic movements, magnetic resonance imaging

Introduction

Infantile spasms are among the most recognized types of epileptic encephalopathy of the early infancy. This disorder presents with a classic triad of epileptic spasms, a characteristic electroencephalographic pattern known as hypsarrhythmia, and psychomotor delay or arrest. In 25–32% of patients no underlying cause is detected.[1,2] If the treatment has been started early and the cessation of spasms and resolution of hypsarrhythmia on electroencephalography (EEG) has been reached, the cryptogenic group has a more favorable neurodevelopmental outcome when compared to those with an identifiable cause.

Vigabatrin (VGB) is a gamma-aminobutyric (GABA) analog that irreversibly inhibits the enzyme GABA-transaminase, the major inhibitory neurotransmitter in the central nervous system. It is the first-line therapy for infantile spasms in tuberous sclerosis and the second-line therapy for other etiologies. While hormonal therapies such as corticosteroid and adrenocorticotropic hormone (ACTH) seem to be more efficacious than VGB, they are associated with some important collateral effects, such as arterial hypertension.[3]

Reported side effects of VGB include permanent peripheral visual field defects, seen as soon as two to three months following its initiation, headache, drowsiness, fatigue and dizziness.[4]

Recently, magnetic resonance imaging (MRI) structural abnormalities that include reversible symmetrical involvement of the basal ganglia, thalamus and brainstem have been reported related to the use of this drug.[4–6]

We present a case of an infant suffering infantile spasms treated with VGB and ACTH who developed characteristic MRI alterations and extrapyramidal movements.

Case report

A healthy full-term infant was born following an unremarkable pregnancy. She presented with normal psychomotor development without any symptoms until the sixth month of life, when she developed characteristic infantile spasm that raised concern for West syndrome. This was confirmed by EEG, which demonstrated a hypsarrhythmic pattern. Concurrently she initiated a global arrest in development. An MRI was performed that showed moderate global atrophy. VGB treatment was initiated with progressive doses reaching 150 mg/kg/day, with no response after one month; therefore, ACTH was added in a dose of 0.5 mg intramuscularly every other day, for two weeks. After two doses she

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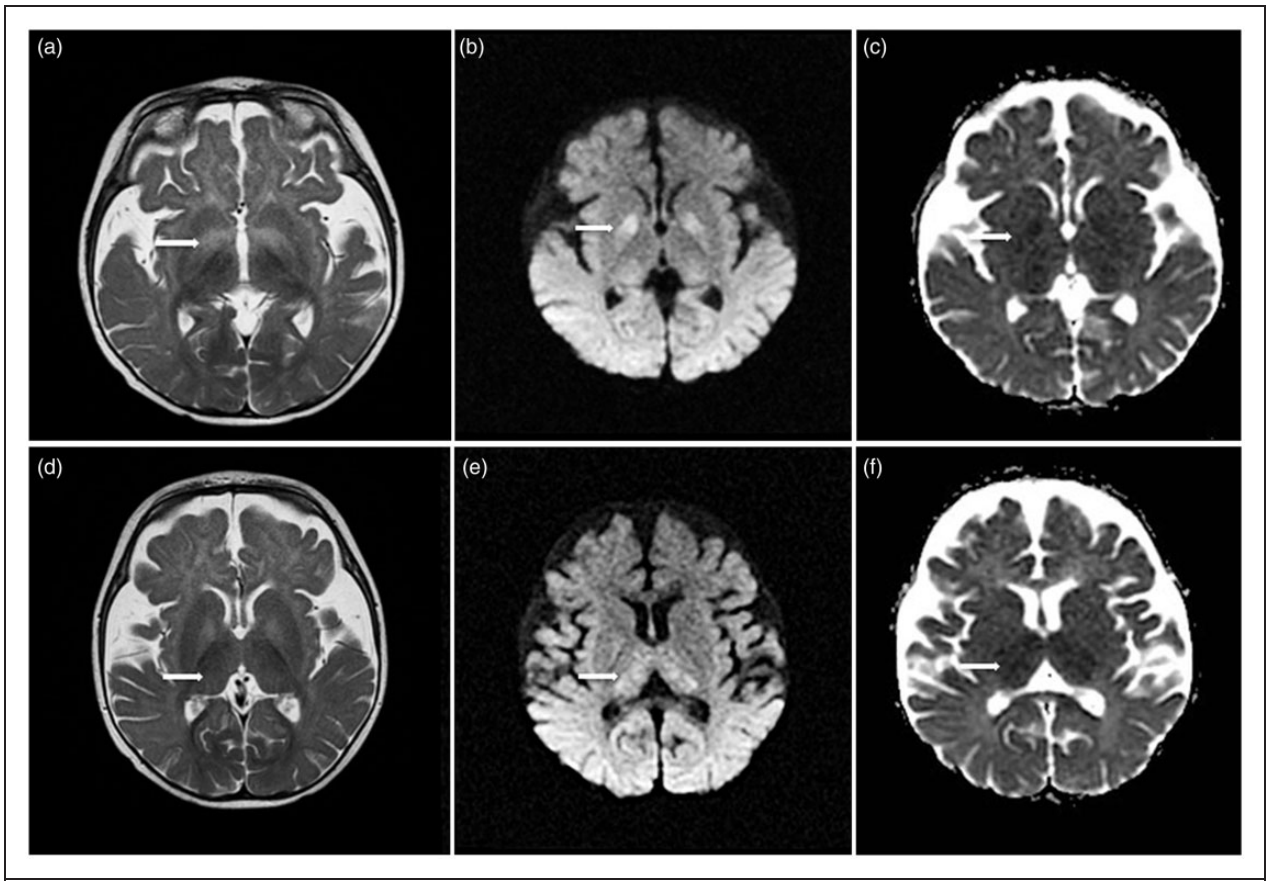

Figure 1. MRI after one month of vigabatrin therapy. The patient developed extrapyramidal movements. Axial T2-weighted images demonstrate subtle signal increase in the globi pallidi (a) (arrow) and thalami (d) (arrow). DWI (b), (e) and ADC maps (c), (f) show diffusion restriction in the corresponding sites, more evident than the T2-weighted images. Generalized brain atrophy is observed. MRI: magnetic resonance imaging; DWI: diffusion-weighted imaging; ADC: apparent diffusion coefficient.

reduced spasm frequency and the EEG alterations. By that time, she attended our institution and at the initial evaluation, ataxic movements, consisting in lingual stereotyped movement and choreiform movement of the arms, were detected. The laboratory workup, including genetic evaluation, was negative for metabolic disease.

A new MRI was performed that exhibited a symmetrical pattern of thalamic and globi pallidi restriction. T1- and T2-weighted images revealed no abnormalities (Figure 1).

VGB-associated MRI signal changes were suspected. The VGB dose was reduced gradually with regression of the extrapyramidal symptoms. After two months, when she was still receiving 58 mg/kg/day, the symptoms finally disappeared.

A control MRI was performed six months later that showed no alteration in the previously affected deep gray matter (Figure 2).

Discussion

VGB is an irreversible inhibitor of GABA-transaminase, which increases the concentration of GABA, an inhibitor neurotransmitter that decreases epileptogenic circuits and seizure frequency in patients with infantile spasms.[1]

Several reports in animals revealed that high doses of VGB produce reversible intramyelinic edema (vacuolization) in tracts such as the visual pathways, fornix column and white matter of the cerebellum.[4]

There is no evidence of VGB-associated intramyelinic edema and MRI changes in adults.[5,7] This suggests either vulnerability of immature myelin to the toxicity of VGB itself or an indirect effect related to elevated GABA levels,[5] but the mechanism leading to vacuolization and why the deep encephalic structures are more affected are still unclear.

Asymptomatic and reversible MRI anomalies related to the use of VGB have been described.[4–6] These may affect 22–32% of patients with infantile spasms and are described as reversible T2-hyperintensity and/or restricted diffusion-weighted imaging (DWI) in globi pallidi, nuclei dentate, thalami, corpus callosum, midbrain and brainstem,[4,6] globi pallidi being the more frequently involved. These anomalies have been described to affect patients younger than 2 years and more likely children younger than 12 months. MRI changes appeared after five weeks to six months[5] and

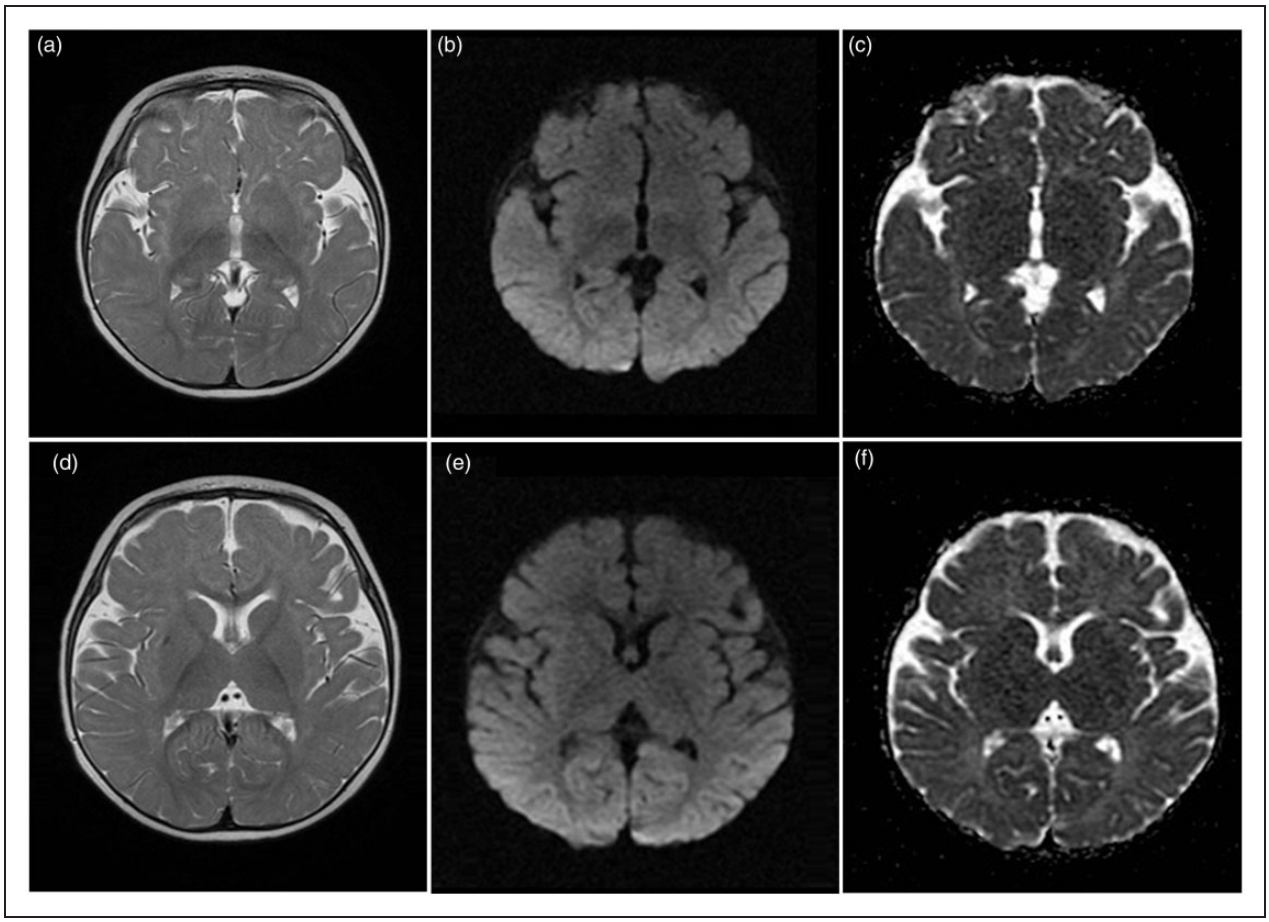

Figure 2. Follow-up MRI six months later shows no alteration in the previously affected deep gray matter. Cerebral atrophy is less pronounced than at the initial scanning. MRI: magnetic resonance imaging.

remitted completely after three months, even without discontinuation of VGB.[4]

The alterations are dose dependent but they do not have a relation to the duration of the VGB treatment. Patients with infantile spasms, treated with other drugs like ACTH or prednisone, do not exhibit MRI signal changes.[4]

Recently Dill et al.[5] described two patients with infantile spasms who developed neurological symptoms related to VGB treatment. In those cases the affected areas correlated with the patients' symptoms: Dystonia, athetoid movements and tremor imply an affliction of the extrapyramidal system; alteration of vigilance stands for affliction of the thalamus; hypotonia and bradycardia reflect midbrain/brainstem functions. In both cases, clinical and radiological manifestations were completely reversible after the cessation of the VGB.

In a study population that included 124 children with infantile spasms in treatment with VGB, extrapyramidal symptoms were described in eight cases.[6] MRI was performed in seven of these patients and in just two VGB-induced changes were demonstrated. Although these results do not provide enough evidence to link MRI changes to the movement disorders, unlike those cases described by Dill and our case, none of the patients were cryptogenic, and the etiologies of their infantile spasms included chromosomal abnormalities, metabolic diseases and focal cortical scarring.

In our case, there is a clear temporal concomitance between the start of the drug treatment and the development of extrapyramidal symptoms and MRI signal changes that resolved after withdrawal/dose reduction of VGB. This, in addition to a non-underlying cause that explained these anomalies, like metabolic diseases or genetic alterations, suggests a correlation between extrapyramidal symptoms and MRI changes with the use of VGB in patients with infantile spasms.

In summary, T2-hyperintensities on brain MRI have been widely associated with the use of VGB for the treatment of infantile spasms. These alterations have been observed to be asymptomatic and reversible. There are few publications describing cases treated with VGB that, as in our case, developed movement disorder associated with MRI signal changes. Prospective studies are required to better understand these associations.

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Conflict of interest

None declared.

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