Clinical Radiology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Clinical Radiology

journal homepage: www.clinicalradiologyonline.net

Review

The vigabatrin-associated brain abnormalities on MRI and their differential diagnosis

D.G. Corrêa [a,b,*], B. Telles [c,d], T. de A.L. Freddi [e]

[a] *Department of Radiology, Clínica de Diagnóstico por Imagem (CDPI)/DASA, Avenida das Américas, 4666, 302A, 303, 307, 325, 326, Barra da Tijuca, Rio de Janeiro, RJ 2640-102, Brazil*

[b] *Department of Radiology, Rio de Janeiro State University, Boulevard 28 de Setembro, 77, Vila Isabel, Rio de Janeiro, RJ 20551-030, Brazil*

[c] *Department of Radiology, Curitiba Institute of Neurology, Rua Jeremias Maciel Perretto, 300, Campo Comprido, Curitiba, PR 81210-310, Brazil*

[d] *Department of Radiology, Hospital Pequeno Príncipe, Rua Desembargador Motta, 1070, Água Verde, Curitiba, PR 80250-060, Brazil*

[e] *Department of Radiology, Hcor, Rua Desembargador Eliseu Guilherme, 147, Paraíso, São Paulo, SP 04004-030, Brazil*

ARTICLE INFORMATION

Article history:
Received 18 August 2023
Received in revised form
12 October 2023
Accepted 14 November 2023

Vigabatrin is an anti-epileptic drug that inhibits the enzyme γ-aminobutyric acid (GABA)-transaminase. The anticonvulsant effect of vigabatrin involves increasing GABA levels and attenuating glutamate–glutamine cycling. Vigabatrin indications include infantile spasms and refractory focal seizures. Despite having a significant role in paediatric epileptology, vigabatrin has adverse effects, such as retinal toxicity, in up to 30% of patients after 1 year of use and brain abnormalities on magnetic resonance imaging (MRI). The percentage of patients with brain abnormalities on MRI varies between 22–32% of children using vigabatrin to treat infantile spasms. Risk factors for presenting these imaging abnormalities are cryptogenic infantile spasms, age <12 months old, high dosage, and possible concomitant hormonal therapy. Clinically, these abnormalities are usually asymptomatic. Histopathological analysis reveals white matter vacuolation and intramyelinic oedema. The typical findings of vigabatrin-associated brain abnormalities on MRI are bilateral and have a symmetrical hyperintense signal on T2-weighted imaging, with diffusion restriction, that often compromise the globi pallidi, thalami, subthalamic nuclei, cerebral peduncles, midbrain, dorsal brainstem, including the medial longitudinal fasciculi, and dentate nuclei of the cerebellum. In this article, the authors intend to review the clinical manifestations, histopathological features, imaging aspects, and differential diagnosis of vigabatrin-associated brain abnormalities on MRI.

* Guarantor and correspondent: D.G. Corrêa, Clínica de Diagnóstico por Imagem (CDPI)/DASA, Avenida das Américas, 4666, 302A, 303, 307, 325, 326, Barra da Tijuca, Rio de Janeiro, RJ 2640-102, Brazil. Tel.: +55 21 993843617.
E-mail address: diogogoulartcorrea@yahoo.com.br (D.G. Corrêa).

https://doi.org/10.1016/j.crad.2023.11.010
0009-9260/

Introduction

Vigabatrin (4-aminohex-5-enoic acid) is a selective and irreversible inhibitor of γ-aminobutyric acid (GABA)-transaminase, used as an anti-epileptic drug. This enzyme catalyses the inactivation of GABA.[1] Thus, vigabatrin increases the level of GABA in presynaptic terminals within the central nervous system. Initially, it was thought that its effects occurred only because of the increased levels of GABA, the main inhibitory neurotransmitter in the central nervous system, reducing or eliminating seizures[2]; however, recent studies found that the anticonvulsant effect of vigabatrin also occurs due to attenuation in glutamate–glutamine (the main excitatory neurotransmitter in the central nervous system) cycling between neurons and astroglia.[3,4]

The initial enthusiasm for vigabatrin, because of its good tolerability and lack of drug–drug interactions (the only known drug interaction is a decrease in phenytoin concentration of 25–40%, in about one-third of patients),[5] was reduced by cases of retinal toxicity, with visual field defects in up to 30% of patients after one year of use.[6] Furthermore, this medication has been associated with reversible, symptomatic and asymptomatic brain abnormalities on magnetic resonance imaging (MRI).[7]

Despite these adverse effects, vigabatrin has a significant role in paediatric epileptology.[8] It is an anti-epileptic drug with proven efficacy in treating infantile spasms, including those with West syndrome, especially in patients with tuberous sclerosis complex, in monotherapy or combination with other treatments, and refractory focal-onset seizures.[9] Then, distinguishing between brain MRI abnormalities related to vigabatrin and other aetiologies, such as metabolic, infectious, and ischaemic, is of utmost importance.[8]

This article reviews the significance, clinical manifestations, histopathological features, imaging aspects, and differential diagnosis of vigabatrin-associated brain abnormalities on MRI (Tables 1 and 2).

Table 2
Main differential diagnosis of vigabatrin-associated brain abnormalities on magnetic resonance imaging (MRI).

Differential diagnosis	Main imaging features
Acute severe hypoxic–ischaemic encephalopathy in term neonate	Restricted diffusion affecting the cerebral cortex, bilateral putamen, caudate nucleus, globus pallidus and thalamus, brainstem tegmentum
Leigh's disease	Bilateral and often symmetrical restricted diffusion in the putamen, caudate, globus pallidus, thalamus and cerebellar dentate nucleus
Kernicterus (chronic stage)	Bilateral hyperintense signal on T2-weighted images in the globus pallidum, without diffusion restriction

Infantile spasms and west syndrome

Traditionally, West syndrome, infantile spasms, and infantile spasms syndrome were used interchangeably as synonyms[10]; however, more recently, infantile spasms have been used to refer only to the ictal phenomenon, while infantile spasms syndrome is a group of disorders characterised by severe, drug-resistant early epileptic encephalopathies, associated with infantile spasms, with onset in early life, related to persistent electroencephalographic abnormalities and progressive cerebral dysfunction. In contrast, West syndrome is a subtype of infantile spasms syndrome, corresponding to approximately 90% of this syndrome.[11] The association of infantile spasms, neurodevelopmental regression and hypsarrhythmia on the electroencephalogram defines West syndrome.[10] Therefore, some patients may present with the ictal phenomenon with infantile spams without associated hypsarrhythmia.[12]

Infantile spasms are classified as cryptogenic, in which the patients have a normal brain imaging, or as

Table 1
Summary of brain magnetic resonance imaging (MRI) findings, most common affected regions, clinical manifestations, and histopathological features of vigabatrin-associated brain abnormalities.

MRI appearance	Most commonly affected regions in descending order of frequency	Clinical manifestations	Histopathological findings
- Symmetrical hyperintense signal on T2-weighted imaging, with restricted diffusion - Isointense signal on T1-weighted imaging, with no gadolinium enhancement - Short echo time spectroscopy demonstrates reduced N-acetylaspartate peak, increased choline peak, generally with no lactate peak	- Globus pallidum - Dorsal portion of the brainstem, including the medial longitudinal fasciculus - Thalamus - Dentate nucleus - In our experience, the fornix may also be affected.	- Most patients are asymptomatic - Some patients present extrapyramidal symptoms - Very rarely, the patients present with acute encephalopathy	- White matter vacuolisation on optic microscopy - Intramyelinic oedema on electron microscopy

Please cite this article as: Corrêa DG et al., The vigabatrin-associated brain abnormalities on MRI and their differential diagnosis, Clinical Radiology, https://doi.org/10.1016/j.crad.2023.11.010

symptomatic, with a determined cause on MRI.[13] Infantile spasms can be associated with structural brain disorders, such as several cortical development malformations, complex malformation syndromes, such as Down, Pallister–Killian, and Williams–Beuren syndromes, inborn errors of metabolism, such as phenylketonuria, and neurocutaneous disorders, mainly tuberous sclerosis complex.[11,13]

Typically, infantile spasms begin during the first year of life, mostly between 4 and 9 months. Ictal phenomenon is characterised by abrupt tonic contraction lasting a few seconds (typically <3 seconds) of the axial flexors, extensors, or both muscles of the neck and trunk, with the abduction of the arms, in clusters for some minutes, that may last half an hour or even longer. During the crisis, the eyes may be fixed or deviated, associated with focal facial movements and blinking, with or without cardiac and respiratory involvement. Episodes of crying or screaming may precede or follow the ictal episode. The seizures appear mostly in rapid sequence just before falling asleep or after waking up. Severe spasms may also occur during sleep.[11,14] Hypsarrhythmia appears on an electroencephalogram as a chaotic and disorganised basal activity with asynchronous and non-rhythmic slow waves of high amplitude and focal or multifocal spikes.[10]

Although treatment should be ideally quickly initiated after identifying infantile spasms to control seizures and improve long-term outcomes rapidly, the disorder may pass unnoticed by parents and general doctors in its initial phase. Adrenocorticotropic hormone (ACTH), vigabatrin, and corticosteroid are the primary recommended drugs in these patients, which can be used in isolation or combined.[10]

Vigabatrin was the first anti-epileptic drug explicitly approved for treating infantile spasms by the American Food and Drug Administration (FDA).[15] It also has a specific license from the European Medicines Agency.[14] Vigabatrin can be used for infantile spasms, with or without West syndrome, including those with tuberous sclerosis complex and focal seizures.[8]

Vigabatrin-associated brain abnormalities on MRI

The safety of vigabatrin has been questioned since preclinical studies, which demonstrated white matter vacuolation and intramyelinic oedema in rats.[16] In humans, vigabatrin-associated brain abnormalities seen on MRI are also well-established.[17] The percentage of affected patients varies between 22–32% of the paediatric population that uses vigabatrin to treat infantile spasms.[18] Risk factors for presenting these abnormalities are cryptogenic infantile spasms, age <12 months old, high dosage, specially >125 mg/kg/day, and possibly concomitant hormonal therapy.[18–20] These vigabatrin-associated brain abnormalities are associated with the peak dosage but not with cumulative dosage.[21] Adults are usually not affected.[18] Although it is not fully understood why vigabatrin-associated brain abnormalities are seen more commonly in young children, especially those <12 month-old with infantile spasms, and not in adults and in children using vigabatrin due to other seizure types, it is hypothesised that the neuronal circuitry that underlies infantile spasms makes these patients susceptible to these alterations.[22,23] Furthermore, no evidence suggests that vigabatrin-associated brain abnormalities appear in children or adults treated with vigabatrin for focal seizures.[19]

Brain MRI demonstrates bilateral and symmetrical restricted diffusion affecting preferentially deep central structures, such as the globus pallidus, thalamus, subthalamic nucleus, cerebral peduncle, midbrain, dorsal pons, including the medial longitudinal fasciculus, and dentate nucleus of the cerebellum, with no gadolinium-enhancement (Fig 1 and Electronic Supplementary Material Fig. S1).[7,17,24–27] In some cases, hyperintense signal on T2-weighted imaging can be found in the same regions (Electronic Supplementary Material Fig. S2). Rarely, patients may present only with hyperintensity on T2-weighted images without restricted diffusion. The globus pallidum is the most commonly affected structure, followed by the dorsal surface of the brainstem. Less than 50% of the affected patients present involvement of the dentate nuclei and thalamus (Electronic Supplementary Material Fig. S3).[18]

These alterations, with or without drug withdrawal, can be reversible and not associated with clinical sequelae (Electronic Supplementary Material Figs. S4 and S5).[28] It is difficult to determine the duration of vigabatrin therapy and the onset of the MRI abnormalities because of the varying frequency of examinations in the studies. In addition, it is not possible to determine precisely the time required for these alterations to disappear; however, in a study performed by Milh *et al.*,[29] the brain MRI hyperintensities transiently increased since the end of the first month after the beginning of vigabatrin treatment, peaked about 3–6 months after vigabatrin onset, and returned to normal after 12 months of treatment. In the study performed by Wheless *et al.*,[19] the median time between the beginning of vigabatrin use and the detection of the MRI abnormalities was 11 months in patients using >125 mg/kg/day and 24 months in patients using a lower dose. In the study by Pearl *et al.*,[25] the average therapy duration in patients with these MRI abnormalities was 3 months (ranging from one to eleven months), with a median dosage of 170 mg/kg/day, and the abnormalities resolved in all patients, except for one patient who presented minimal residual abnormalities in the globus pallidus, in an MRI performed only 18 days after vigabatrin withdraw. In the study performed by Dracopoulos *et al.*,[18] the MRI abnormalities resolved in 11 of 15 patients following vigabatrin withdrawal (time between withdrawal and follow-up MRI ranged from 0.7 to 28 months; mean time 14.3 months), and in two patients while still on therapy; on the other hand, two patients continued to present imaging abnormalities, even after cessation of vigabatrin (interval of 3 weeks and 1 month); in the same study, four patients performed MRI before, during, and after vigabatrin treatment, with documentation of the appearance of these abnormalities and their resolution, after 2–8 months of drug withdrawal.

^{1}H-Magnetic resonance spectroscopy (MRS) can reveal decreased N-acetyl aspartate (NAA)/creatine ratios and

Please cite this article as: Corrêa DG et al., The vigabatrin-associated brain abnormalities on MRI and their differential diagnosis, Clinical Radiology, https://doi.org/10.1016/j.crad.2023.11.010

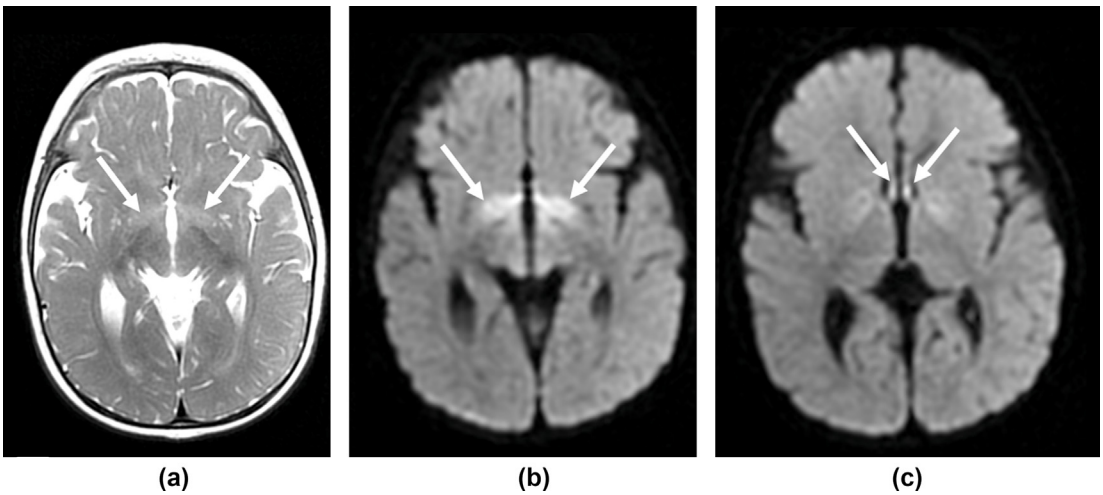

Figure 1 A 8-month-old male patient with cryptogenic West syndrome, who had been taking vigabatrin for 4 months. Brain MRI showed hyperintense signal in the globi pallidi on T2-weighted imaging (arrows in a), with restricted diffusion (arrows in b). There was also restricted diffusion in the fornices, bilaterally (arrows in c).

elevated choline peak, usually with no lactate peak (Fig 2 and Electronic Supplementary Material Fig. S5)[25,29]; however, this spectroscopy pattern is non-specific. Furthermore, Dracopoulos *et al.*[18] reported the presence of lactate peak on spectroscopy in at least two patients using vigabatrin, making these findings even more non-specific. The abnormalities seen on spectroscopy are also reversible.[25] It is important to remember that NAA peak is equivalent to the age of the newborn. The brain of the newborn is relatively immature and has much less neuronal activity in comparison to adults, which is reflected in a shorter peak of NAA.[30] NAA is a marker of neuronal density and viability, present in large quantities in the normal brain. NAA is the highest peak in normal spectroscopy. The choline peak reflects cell membrane metabolism, and its elevation is related to increased cell populations and membrane volume, associated several conditions, such as inflammation, demyelination, tumour, gliosis, and/or ischaemia. Creatine is a relatively stable peak, used as a reference marker. In the normal brain, lactate is present in small amounts and it is not seen in a normal spectroscopy. In conditions where anaerobic glycolysis takes over, such as ischaemia, hypoxia, seizures, metabolic disorders, lactate levels increase significantly and a lactate peak can be seen on spectroscopy.[31]

In the authors' experience, the fornix is commonly affected in vigabatrin-associated brain abnormalities on MRI, although rarely reported,[32] also with reversible restricted diffusion (Fig 1 and Electronic Supplementary Material Figs. S1–S5). This is in accordance with animal studies showing changes in the fornix of rats on vigabatrin.[33,34] Although not commonly described on brain MRI in humans yet, when retrospectively evaluating the images of previously

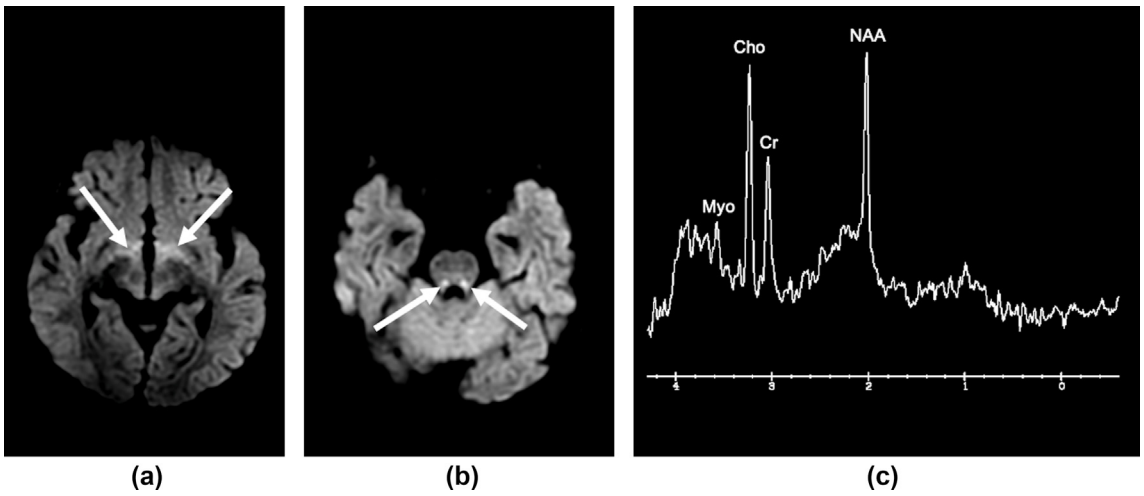

Figure 2 A 1-year-old female patient with cryptogenic West syndrome, who had been taking vigabatrin for 5 months. Brain MRI showed restricted diffusion in the globi pallidi (arrows in a), and medial longitudinal fasciculi (arrows in b). (c) Single-voxel ^{1}H-MRS with the voxel positioned in the right basal ganglia region (35 ms echo time), demonstrated elevated choline peak (3.2 ppm), with no lactate peak (1.3 ppm). Cho, choline; Myo, myo-inositol; NAA, N-acetylaspartate.

Please cite this article as: Corrêa DG et al., The vigabatrin-associated brain abnormalities on MRI and their differential diagnosis, Clinical Radiology, https://doi.org/10.1016/j.crad.2023.11.010

published studies, restricted diffusion was observed in the fornix in some human cases.[7,17,19,24,25,35] This consideration is important because the visualisation of signal abnormality in the fornix can be a supportive finding for the diagnosis of vigabatrin-associated MRI abnormalities. On the other hand, it is important to keep in mind that isolated restricted diffusion in the fornix–fimbria complex can be detected in 7.4% of children between 0 and 2 years of age, with no clear aetiology, as a probable transient phenomenon.[36] Some authors have described brain atrophy associated with these alterations[7]; however, brain atrophy is probably an effect of epileptic encephalopathy and not an effect of the medication.

In addition, reversible restricted diffusion in the splenium of the corpus callosum, recently named cytotoxic lesion of the corpus callosum, can be seen in patients using vigabatrin, usually associated with other anti-epileptic drugs[37–39]; however, in contrast to the bilateral MRI alterations in the globus pallidum, thalamus, and brainstem described above, these alterations were described in adults, treating epilepsies with focal seizures,[38] hippocampal sclerosis, and dysembryoplastic neuroepithelial tumour,[37] usually associated with other anti-epileptic drugs and/or infections.

Clinical manifestations

The majority of infants with vigabatrin-related brain abnormalities on MRI do not present coincidental symptoms[40]; however, rarely, these abnormalities have been previously associated with extrapyramidal symptoms, characterised by hyperkinetic movements, including choreoathetosis, myoclonus, tremor, dystonia, opisthotonic posturing, and ataxic movements, with stereotyped lingual movements.[7,24,40,41]

Some authors have also associated these abnormalities with life-threatening acute encephalopathy, characterised by somnolence, apathy, hypotonia, and bradycardia, usually associated with those extrapyramidal symptoms.[7,24,40] Furthermore, there is an increased risk of symptomatic vigabatrin-associated brain abnormalities on MRI, with encephalopathy, using combined vigabatrin-ACTH therapy, usually beginning within 2 months after starting combination therapy, especially in patients with symptomatic infantile spasms.[42] In one patient with vigabatrin-related encephalopathy, an electroencephalogram demonstrated generalised slow activity.[43]

Histopathological features and pathophysiology

Previous studies found intramyelinic oedema, manifesting as microvacuoles on optical microscopy, in the visual pathways, fornix columns, and white matter of the cerebellum in experimental animals.[16,44] The first studies in humans failed to find histopathological changes associated with vigabatrin[45,46]; however, this may have occurred due to the patient's age and the findings' reversibility.

Pearl *et al.*,[20] in a post-mortem study, found bilateral symmetrical vacuoles, measuring 1–100 μm in diameter (spongiosis) in white matter tracts of the central tegmental tract, optic nerves and optic chiasm, hilum and amiculum of inferior olive, hypothalamus, and medial longitudinal fasciculus, in a 27-month-old male child using vigabatrin to treat infantile spasms. The lesions were characterised by myelin splitting and round cavities without axonal spheroids, gliosis, or microglial reaction. The authors did not perform electron microscopy. Horton *et al.*[47] demonstrated vacuoles with 25–50 μm diameter in focal areas of the anterior cingulate and precuneus gyri, anterior limb of the internal capsule, globus pallidus, optic tract, cerebral peduncle, medial lemniscus and medial longitudinal fasciculus, pyramid, inferior cerebellar peduncles, dentate nucleus, and white matter of some cerebellar folia, in a 10-month-old male infant using 175 mg of vigabatrin twice daily, to treat infantile spasms. Electron microscopy demonstrated intramyelinic oedema in similar regions, characterised by adherent vacuoles to adjacent normal myelin sheaths, resulting in the separation of the outer layers of myelin at the intraperiod line.

A study evaluating the diffusion tensor imaging of patients on vigabatrin demonstrated decreased fractional anisotropy in the globus pallidum, dorsal brainstem, and the thalamus, as well as decreased axial diffusivity in these regions, with no alterations in radial diffusivity, suggesting that axonal changes play a role in the observed abnormal signal intensity. The authors suggested that axonal swelling or degeneration, reactive astrogliosis, or an as yet unknown factor may have contributed to the significantly reduced axial diffusivity.[48]

The pathophysiological mechanism leading to vigabatrin-induced intramyelinic oedema remains unknown. A possible explanation is a direct toxic effect of the medication on oligodendrocytes; however, *in vitro* studies demonstrated only very slight toxicity for oligodendrocytes, even at high concentrations of vigabatrin. Another hypothesis involves the effect of inhibition of GABA-transaminase, which results in an increase in GABA concentration in the central nervous system. This is supported by the fact that other GABA-transaminases inhibitors, such as ethanolamine-O-sulfate and γ-allenyl GABA, also produce intramyelinic oedema in similar regions compared to vigabatrin; however, these other GABA-transaminase inhibitors produce less severe intramyelinic oedema than vigabatrin, suggesting that other unreported mechanisms are also related to vigabatrin-induced abnormalities.[49] The characteristic pattern of affected centrencephalic structures of the MRI alterations may reflect the stage of myelin maturation and a regional variation of GABA metabolism in the immature brain.[18]

Clinical management

Although vigabatrin has an excellent efficacy, especially in a catastrophic epileptic disease, such as infantile spams, it has unusual and disturbing side effects, such as visual field

Please cite this article as: Corrêa DG et al., The vigabatrin-associated brain abnormalities on MRI and their differential diagnosis, Clinical Radiology, https://doi.org/10.1016/j.crad.2023.11.010

deficits and MRI abnormalities, associated or not with extrapyramidal symptoms, limiting its prescription. Patients using vigabatrin should be closely monitored, in order to follow the clinical efficacy, side effects, and MRI abnormalities.

Although there is no consensus on the management of asymptomatic patients with vigabatrin-associated MRI abnormalities, some authors recommend immediate discontinuation of the drug.[50,51] On the other hand, the Medicines and Healthcare Products Regulatory Agency (MHRA) of the United Kingdom Government do not recommend screening children taking vigabatrin with repeated MRIs; however, when the patient develops neurological deterioration, such as movement disorders, it is reasonable to perform a MRI to assess the underlying cause, and consider reducing the dose or stopping the drug, with careful consideration, due to the risk of deterioration in seizure control.[52] Therefore, the decision to withdraw the medication, abruptly or gradually, should be considered according to the clinical context of each patient, such as association with other anti-epileptic drugs and the presence of clinical manifestations resulting from the vigabatrin use.

Differential diagnosis

The differential diagnosis of bilateral and symmetrical lesions in the basal ganglia and thalamus of infants is extensive. A history of infantile spasms treatment with vigabatrin is essential and is the most important clinical feature for diagnostic confirmation. The evaluation of the differential diagnosis of bilateral and symmetric lesions in the basal ganglia and thalamus is beyond the scope of this article. Thus, we will briefly discuss how neuroimaging can contribute to the differential diagnosis of vigabatrin intoxication with other disorders that present similar and sometimes identical imaging features, in young children (Table 2).

The imaging features of hypoxic–ischaemic encephalopathy depend on the age and severity of the injury. Although the globus pallidus, thalamus, and brainstem tegmentum can be affected with restricted diffusion, injuries in the brainstem are usually more extensive, and the patients have a different clinical context, with a history of severe cardiac arrest. The caudate nucleus and the cerebral cortex are usually also involved, which may contribute to the differentiation (Fig 3 and Electronic Supplementary Material Fig. S6).[53]

Inborn errors of metabolism, especially mitochondrial diseases, urea cycle disorders, aminoacidopathies, and organic acidopathies, also have to be considered in the differential diagnosis.[54] Leigh's disease usually presents with a bilateral and symmetrical hyperintense signal on T2-weighted imaging, with restricted diffusion in the putamen, caudate nuclei and midbrain, beyond globus pallidum, thalamus and cerebellar dentate nuclei, which may aid in the differential diagnosis (Electronic Supplementary Material Fig. S7).[55] Succinic semialdehyde dehydrogenase deficiency[56] and methylmalonic acidaemia[54,57] are other inborn errors of metabolism that can present with symmetric alterations in the globus pallidum. Maple syrup urine disease is a aminoacidopathy in which the classic form affects neonates, and presents with marked restricted diffusion along myelinated white matter tracts (cerebellar white matter, dorsal brainstem, cerebral peduncles, posterior limb of the internal capsules, and peri-rolandic cerebral white matter). The thalami and globi pallidi are affected during metabolic crises in the neonatal period.[54]

Chronic abnormalities related to kernicterus can present with a hyperintense signal on T2-weighted imaging in the globus pallidum, but it does not show diffusion restriction (Electronic Supplementary Material Fig. S8).[58]

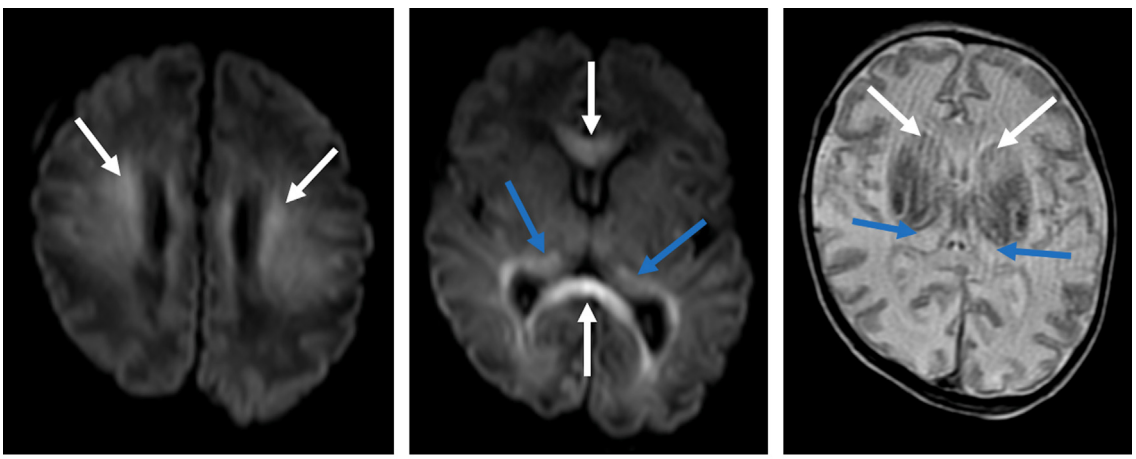

Figure 3 A 10-day-old term newborn male patient with a history of profound perinatal asphyxia. Brain MRI showed symmetrical bilateral restricted diffusion in the corona radiata (arrows is a), corpus callosum (white arrows in b), and thalami (blue arrows in b). (c) T2-weighted imaging demonstrated abnormal hyperintensity of the basal ganglia (white arrows in c) and thalami (blue arrows in c). There was no restricted diffusion in the fornix.

Please cite this article as: Corrêa DG et al., The vigabatrin-associated brain abnormalities on MRI and their differential diagnosis, Clinical Radiology, https://doi.org/10.1016/j.crad.2023.11.010

Finally, these disorders usually do not present restricted diffusion in the fornix. Therefore, visualisation of symmetrical diffusion restriction in the globus pallidum and fornix may help diagnose vigabatrin-associated brain abnormalities, especially in cases in which the clinical history is unclear.

Limitations and further research

This review has some limitations that should be explored in future studies. Children using vigabatrin usually present other comorbidities and it is difficult to evaluate if there are long-term clinical consequences (mental and/or physical) of vigabatrin-associated brain abnormalities on MRI. Furthermore, the time interval between the beginning of vigabatrin use and the appearance of MRI alterations, as well as the interval between the appearance of MRI alterations and their resolution, are not yet well determined in the literature. Therefore, a long-term prospective study, randomised, with placebo participants should be performed in the future to answer these questions.

Conclusion

A history of vigabatrin exposure is essential for the diagnosis of vigabatrin-associated brain abnormalities. Usually, MRI reveals symmetrical restricted diffusion on globus pallidum, dorsal brainstem, thalamus, and fornix, which are often asymptomatic and reversible. Typically, it occurs in infants treating infantile spasms and clinical correlation is paramount for the final diagnosis and to avoid unnecessary investigations trying to exclude other conditions that have similar MRI features.

Conflict of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.crad.2023.11.010.

References

1. Foroozan R. Vigabatrin: lessons learned from the United States experience. *J Neuroophthalmol* 2018;**38**:442–50.
2. Lewis H, Wallace SJ. Vigabatrin. *Dev Med Child Neurol* 2001;**43**:833–5.
3. Yang J, Shen J. Elevated endogenous GABA concentration attenuates glutamate-glutamine cycling between neurons and astroglia. *J Neural Transm (Vienna)* 2009;**116**:291–300.
4. Kang TC, An SJ, Park SK, *et al*. Effect of vigabatrin on glutamate dehydrogenase in the hippocampus of seizure prone gerbils. *Neurosci Lett* 2003;**340**:115–8.
5. Gidal BE, Privitera MD, Sheth RD, *et al*. Vigabatrin: a novel therapy for seizure disorders. *Ann Pharmacother* 1999;**33**:1277–86.
6. Spence SJ, Sankar R. Visual field defects and other ophthalmological disturbances associated with vigabatrin. *Drug Saf* 2001;**24**:385–404.
7. Dill P, Datta AN, Weber P, *et al*. Are vigabatrin induced T2 hyperintensities in cranial MRI associated with acute encephalopathy and extrapyramidal symptoms? *Eur J Paediatr Neurol* 2013;**17**(3):311–5.
8. Golec W, Sołowiej E, Strzelecka J, *et al*. Vigabatrin—new data on indications and safety in paediatric epilepsy. *Neurol Neurochir Pol* 2021;**55**:429–39.
9. Wheless JW, Ramsay RE, Collins SD. Vigabatrin. *Neurotherapeutics* 2007;**4**:163–72.
10. D'Alonzo R, Rigante D, Mencaroni E, *et al*. West syndrome: a review and guide for paediatricians. *Clin Drug Investig* 2018;**38**:113–24.
11. Pavone P, Polizzi A, Marino SD, *et al*. West syndrome: a comprehensive review. *Neurol Sci* 2020;**41**:3547–62.
12. Caraballo RH, Ruggieri V, Gonzalez G, *et al*. Infantile spams without hypsarrhythmia: a study of 16 cases. *Seizure* 2011;**20**:197–202.
13. Saltik S, Kocer N, Dervent A. Magnetic resonance imaging findings in infantile spasms: etiologic and pathophysiologic aspects. *J Child Neurol* 2003;**18**:241–6.
14. Lux AL. Latest American and European updates on infantile spasms. *Curr Neurol Neurosci Rep* 2013;**13**:334.
15. Tolman JA, Faulkner MA. Vigabatrin: a comprehensive review of drug properties including clinical updates following recent FDA approval. *Expert Opin Pharmacother* 2009;**10**:3077–89.
16. Butler WH, Ford GP, Newberne JW. A study of the effects of vigabatrin on the central nervous system and retina of Sprague Dawley and Listerhooded rats. *Toxicol Pathol* 1987;**15**:143–8.
17. Hussain K, Walsh TJ, Chazen JL. Brain MRI findings with vigabatrin therapy: case report and literature review. *Clin Imaging* 2016;**40**:180–2.
18. Dracopoulos A, Widjaja E, Raybaud C, *et al*. Vigabatrin-associated reversible MRI signal changes in patients with infantile spasms. *Epilepsia* 2010;**51**:1297–304.
19. Wheless JW, Carmant L, Bebin M, *et al*. Magnetic resonance imaging abnormalities associated with vigabatrin in patients with epilepsy. *Epilepsia* 2009;**50**:195–205.
20. Pearl PL, Poduri A, Prabhu SP, *et al*. White matter spongiosis with vigabatrin therapy for infantile spasms. *Epilepsia* 2018;**59**:e40–4.
21. Hussain SA, Tsao J, Li M, *et al*. Risk of vigabatrin-associated brain abnormalities on MRI in the treatment of infantile spasms is dose-dependent. *Epilepsia* 2017;**58**:674–82.
22. Siniatchkin M, van Baalen A, Jacobs J, *et al*. Different neuronal networks are associated with spikes and slow activity in hypsarrhythmia. *Epilepsia* 2007;**48**:2312–21.
23. Chugani HT, Shewmon DA, Sankar R, *et al*. Infantile spasms: II. Lenticular nuclei and brain stem activation on positron emission tomography. *Ann Neurol* 1992;**31**:212–9.
24. Hernández Vega Y, Kaliakatsos M, U-King-Im JM, *et al*. Reversible vigabatrin-induced life-threatening encephalopathy. *JAMA Neurol* 2014;**71**:108–9.
25. Pearl PL, Vezina LG, Saneto RP, *et al*. Cerebral MRI abnormalities associated with vigabatrin therapy. *Epilepsia* 2009;**50**:184–94.
26. Jain P, Alwadhi R, Kumar V. Reversible MRI changes in an infant with epileptic spasms on low dose vigabatrin. *Indian J Pediatr* 2016;**83**:1049–50.
27. Trindade RAR, Wainstein B, Campos LG, *et al*. Globus pallidus restricted diffusion associated with vigabatrin therapy. *Arq Neuropsiquiatr* 2018;**76**:127–8.
28. Desguerre I, Marti I, Valayannopoulos V, *et al*. Transient magnetic resonance diffusion abnormalities in West syndrome: the radiological expression of non-convulsive status epilepticus? *Dev Med Child Neurol* 2008;**50**:112–6.
29. Milh M, Villeneuve N, Chapon F, *et al*. Transient brain magnetic resonance imaging hyperintensity in basal ganglia and brain stem of epileptic infants treated with vigabatrin. *J Child Neurol* 2009;**24**:305–15.
30. Xu D, Vigneron D. Magnetic resonance spectroscopy imaging of the newborn brain—a technical review. *Semin Perinatol* 2010;**34**:20–7.
31. Soares DP, Law M. Magnetic resonance spectroscopy of the brain: review of metabolites and clinical applications. *Clin Radiol* 2009;**64**:12–21.
32. Iyer RS, Chaturvedi A, Pruthi S, *et al*. Medication neurotoxicity in children. *Pediatr Radiol* 2011;**41**:1455–64.
33. Jackson GD, Williams SR, Weller RO, *et al*. Vigabatrin-induced lesions in the rat brain demonstrated by quantitative magnetic resonance imaging. *Epilepsy Res* 1994;**18**:57–66.

Please cite this article as: Corrêa DG et al., The vigabatrin-associated brain abnormalities on MRI and their differential diagnosis, Clinical Radiology, https://doi.org/10.1016/j.crad.2023.11.010

34. Preece NE, Houseman J, King MD, *et al*. Development of vigabatrin-induced lesions in the rat brain studied by magnetic resonance imaging, histology, and immunocytochemistry. *Synapse* 2004;**53**:36–43.
35. Thapa M, Khanna PC. Vigabatrin-associated diffusion MRI abnormalities in tuberous sclerosis. *Pediatr Radiol* 2010;**40**(Suppl. 1):S153.
36. Rootman MS, Kornreich L, Osherov AN, *et al*. DWI hyperintensity in the fornix fimbria on MRI in children. *AJNR Am J Neuroradiol* 2022;**43**:480–5.
37. Kim SS, Chang KH, Kim ST, *et al*. Focal lesion in the splenium of the corpus callosum in epileptic patients: anti-epileptic drug toxicity? *AJNR Am J Neuroradiol* 1999;**20**:125–9.
38. Prilipko O, Delavelle J, Lazeyras F, *et al*. Reversible cytotoxic edema in the splenium of the corpus callosum related to anti-epileptic treatment: report of two cases and literature review. *Epilepsia* 2005;**46**:1633–6.
39. Starkey J, Kobayashi N, Numaguchi Y, *et al*. Cytotoxic lesions of the corpus callosum that show restricted diffusion: mechanisms, causes, and manifestations. *RadioGraphics* 2017;**37**:562–76.
40. Fong CY, Osborne JP, Edwards SW, *et al*. An investigation into the relationship between vigabatrin, movement disorders, and brain magnetic resonance imaging abnormalities in children with infantile spasms. *Dev Med Child Neurol* 2013;**55**:862–7.
41. Schonstedt V, Stecher X, Venegas V, *et al*. Vigabatrin-induced MRI changes associated with extrapyramidal symptoms in a child with infantile spasms. *Neuroradiol J* 2015;**28**:515–8.
42. Bhalla S, Skjei K. Fulminant vigabatrin toxicity during combination therapy with adrenocorticotropic hormone for infantile spasms: Three cases and review of the literature. *Epilepsia* 2020;**61**:e159–64.
43. Haas-Lude K, Wolff M, Riethmüller J, *et al*. Acute encephalopathy associated with vigabatrin in a six-month-old girl. *Epilepsia* 2000;**41**:628–30.
44. Weiss KL, Schroeder CE, Kastin SJ, *et al*. MRI monitoring of vigabatrin-induced intramyelinic edema in dogs. *Neurology* 1994;**44**:1944–9.
45. Cocito L, Maffini M, Loeb C. MRI findings in epileptic patients on vigabatrin for more than 5 years. *Seizure* 1992;**1**:163–5.
46. Agosti R, Yasargil G, Egli M, *et al*. Neuropathology of a human hippocampus following long-term treatment with vigabatrin: lack of microvacuoles. *Epilepsy Res* 1990;**6**:166–70.
47. Horton M, Rafay M, Del Bigio MR. Pathological evidence of vacuolar myelinopathy in a child following vigabatrin administration. *J Child Neurol* 2009;**24**:1543–6.
48. Simao GN, Zarei Mahmoodabadi S, Snead OC, *et al*. Abnormal axial diffusivity in the deep gray nuclei and dorsal brain stem in infantile spasm treated with vigabatrin. *AJNR Am J Neuroradiol* 2011;**32**:199–203.
49. Cohen JA, Fisher RS, Brigell MG, *et al*. The potential for vigabatrin-induced intramyelinic edema in humans. *Epilepsia* 2000;**41**:148–57.
50. Carvalho Neto Ad, Coelho LO, Ono SE, *et al*. Treatment of West syndrome with vigabatrin: reversible MRI signal changes. *Arq Neuropsiquiatr* 2011;**69**:998.
51. Ben-Menachem E. Vigabatrin's complicated journey—to be or not to be? *Epilepsy Curr* 2009;**9**:130–2.
52. Medicines and Healthcare products Regulatory Agency. MHRA public assessment report. Vigabatrin use: risk of movement disorders and brain MRI abnormalities. https://assets.publishing.service.gov.uk/media/5df7610fed915d093a15d217/Vigabatrin_brain_MRI_abnormalities_and_movement_disorders.pdf. [Accessed 17 October 2023].
53. Huang BY, Castillo M. Hypoxic–ischemic brain injury: imaging findings from birth to adulthood. *RadioGraphics* 2008;**28**:417–39.
54. Davies A, Tolliday A, Craven I, *et al*. An approach to reporting paediatric leukoencephalopathy and leukodystrophies. *Clin Radiol* 2023;**78**:401–11.
55. Senthilvelan S, Sekar SS, Kesavadas C, *et al*. Neuromitochondrial disorders: genomic basis and an algorithmic approach to imaging diagnostics. *Clin Neuroradiol* 2021;**31**:559–74.
56. Esposito S, Moscatelli M, Caccia C, *et al*. Teaching NeuroImages: symmetrical abnormalities of the globi pallidi in succinic semialdehyde dehydrogenase deficiency. *Neurology* 2020;**95**:e2316–7.
57. Bindu PS, Kovoor JM, Christopher R. Teaching NeuroImages: MRI in methylmalonic acidemia. *Neurology* 2010;**74**:e14.
58. Abeyakoon O, Batty R, Mordekar S, *et al*. The encephalopathic child. *Neuroradiol J* 2011;**24**:483–502.

Please cite this article as: Corrêa DG et al., The vigabatrin-associated brain abnormalities on MRI and their differential diagnosis, Clinical Radiology, https://doi.org/10.1016/j.crad.2023.11.010