Cerebral and cerebellar pseudoatrophy associated with valproic acid: report of three cases in children

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Introduction. Cerebral and cerebellar pseudoatrophy is a rare adverse effect of valproic acid (VPA) that we need to be aware of, due to its diagnostic and therapeutic implications.

Case report. We report three cases of children between 5 and 9 years old, with epilepsy and previous normal brain magnetic resonance imaging, who were taking the drug at correct doses. Pseudoatrophy manifests subacutely with symptoms and images of cerebral and/or cerebellar atrophy, reversible after drug withdrawal.

Discussion and conclusions. This is a type of VPA-related encephalopathy, different from dose-dependent toxic encephalopathy, hyperammonaemic encephalopathy or encephalopathy related to liver failure. In children, it causes cognitive, motor, mood and behavioral deterioration, and may be accompanied by epileptic decompensation. Withdrawing the drug leads to complete clinical-radiological recovery, and reducing the dose leads to improvement.

Key words. Anticonvulsants. Brain. Cerebellum. Child. Pseudoatrophy. Valproic acid.

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Introduction

Valproic acid (VPA) is a widely used antiepileptic drug in children with focal and generalized epilepsies and epileptic encephalopathies. Although generally well-tolerated, multiple adverse reactions have been associated with VPA [1].

Cerebral and cerebellar pseudoatrophy is one of the lesser-known side effects of VPA due to its low prevalence. However, awareness of this adverse effect is very important to avoid unnecessary further testing, and early diagnosis allows rapid drug withdrawal, resulting in improvements in clinical and imaging abnormalities [2-5].

We present the cases of three epileptic children with no previous abnormal findings on brain magnetic resonance imaging (MRI). All developed subacute symptoms of diffuse cerebral atrophy, two with cerebellar involvement. When VPA was withdrawn, complete resolution of symptoms was achieved within 1.5-4 months followed by reversal of pseudoatrophic changes on MRI in 1-3 years.

Case reports

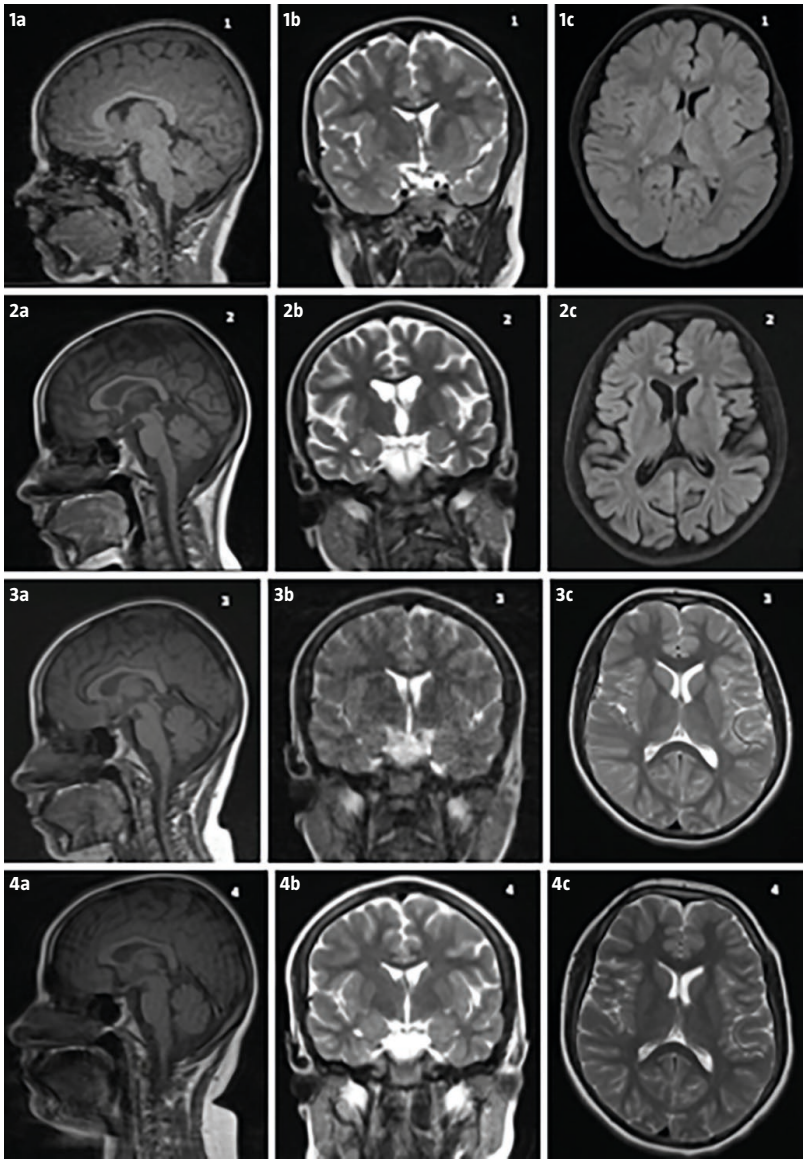
Patient 1

A 9-year-old female with no history of neurological disorders and normal psychomotor and cognitive development was diagnosed with Landau-Kleffner syndrome at 6 years of age. A high-resolution brain MRI scan performed in the initial diagnostic work-up revealed normal findings (Fig. 1: 1a, 1b, 1c); an electroencephalogram (EEG) showed electrical status epilepticus in sleep (ESES). Different therapeutic approaches failed to achieve any improvement in the electroencephalographic pattern, even for a limited time. Throughout the course of the disease, she only experienced one clinical seizure at 8 years of age, consisting of focal status epilepticus with impairment of consciousness.

After three years of treatment with VPA at a therapeutic dose (32 mg/kg/day) and serum concentration of 118 mg/L, combined with clobazam and lamotrigine, the patient presented acute intermittent left eyelid ptosis, experienced a generalized seizure, and reported excessive daytime sleepiness.

A blood test, including analyses of kidney and liver function, thyroid profile, and electrolyte levels showed no alterations. Findings from an EEG revealed evidence suggestive of continued ESES, and presence of diffuse cortical/subcortical atrophy was observed on an MRI scan, predominantly in the supratentorial gray matter and without focal lesions (Fig. 1: 2a, 2b, 2c). Magnetic resonance spectroscopy also showed a moderate decrease in the *N*-acetylaspartate peak. A study of intermediary metabolism in blood, urine, and cerebrospinal fluid was also normal, and a muscle biopsy was negative for mitochondrial disorders.

Figure 1. Magnetic resonance imaging findings for patient 1. Baseline images showing no evidence of disease. a) Images revealing pseudoatrophy. b) Images obtained five months after discontinuation of valproic acid (VPA) showing partial recovery. c) Full recovery evidenced on images obtained 16 months after withdrawal of VPA.



VPA was withdrawn due to suspected VPA-related pseudoatrophy. After 1.5 months, the patient presented normal eyelid opening, absence of seizures, and disappearance of hypersomnia.

A follow-up MRI scan performed 4.5 months after discontinuation of the drug therapy showed significant improvement in cortical/subcortical atrophy (Fig. 1: 3a, 3b, 3c), and 16 months after, the initial findings had normalized completely (Fig. 1: 4a, 4b, 4c); a spectroscopy evidenced normalization of the *N*-acetylaspartate peak.

Patient 2

A 5-year-old male patient was diagnosed with Lennox-Gastaut syndrome with non-structural etiology at age 4.5 years. After one year of treatment with VPA at a therapeutic dose (46 mg/kg/day) and blood concentration in the normal range (95 mg/L) in combination with clobazam and levetiracetam, the patient presented progressive cognitive and behavioral worsening with conspicuous irritability, motor restlessness, impulsiveness, and inattentive behavior. Regarding motor function, the patient had become increasingly slow and clumsy and had developed ataxia and dysarthria over the preceding months. In addition, he complained of hyperphagia and very marked daytime sleepiness (more than 14 hours a day). The frequency of common seizures (generalized tonic-clonic) had also worsened.

A blood test revealed slightly elevated ammonia levels (42 µmol/L). An MRI scan showed diffuse atrophy of the subthalamus and cerebral cortex, and on spectroscopy, a decrease in the *N*-acetylaspartate peak was found; these findings were not present on the previous MRI, which was normal. The electroencephalogram did not show significant changes. A neuropsychological evaluation showed cognitive decline –total intelligence quotient (IQ) 63 on Wechsler Preschool and Primary Scale of Intelligence (WPPS)-III test–. Presence of mitochondrial and lysosomal disorders was ruled out based on the findings of an etiological study using muscle and skin biopsy specimens.

After reducing the dose of VPA by 24% (to 35 mg/kg/day), significant clinical improvement was evidenced in behavior, motor function, and drowsiness, including good seizure control. A follow-up MRI scan showed very slow resolution of brain atrophy (three years after onset of symptoms, no brain involvement was in evidence), although the patient continued to show discrete cerebellar atrophy. The *N*-acetylaspartate peak was also normal at this time. Since the symptoms resolved and VPA was essential to control the epilepsy, complete withdrawal of the drug was not considered (Fig. 2).

Patient 3

A female patient, aged 5 years and 11 months, was

Table. Epidemiologic, clinical, laboratory, and imaging findings in the study patients presenting cerebral pseudoatrophy associated with valproic acid, as well as the disease course in these patients.

Case	Age (years)	Sex	Previous diagnosis	Time receiving VPA (years)	Dose (mg/kg/day)	Monotherapy/ polytherapy	VPA concentration (mg/L)	Ammonia (mg/mL)	Symptoms	Therapy reassessment	Time until resolution of symptoms (months)	Time until resolution of atrophy (months)
1	9	F	Landau-Kleffner syndrome	3	32	Polytherapy: VPA, CLB, LCM	118	38	Epileptic exacerbation. Excessive drowsiness. Ptosis of the left eye	Withdrawal of VPA	1.5	16
2	5	M	Lennox-Gastaut syndrome	1	46	Polytherapy: VPA, LEV, CLB	95	42	Epileptic exacerbation. Cognitive impairment. Impulsive, irritable, restless behavior. Inattentiveness. Excessive drowsiness. Ataxia	Reduction of dose (24% less)	4	36 (persistent mild atrophy of the cerebellum)
3	6	F	Focal epilepsy. Mutation of PCDH 19	4.5	50	Monotherapy: VPA	78	49	Epileptic exacerbation. Cognitive impairment. Ataxia. Dysarthria	Withdrawal of VPA	3	12

CLB: clobazam; LCM: lacosamide; LEV: levetiracetam; VPA: valproic acid.

diagnosed with focal epilepsy with onset at age 18 months due to a mutation in the *PCDH19* gene. At the time of presentation, she had a two-year history of delayed psychomotor development and acute disseminated encephalomyelitis secondary to the presence of anti-MOG antibodies.

After three years of treatment with VPA at recommended doses, maintaining blood concentration at the correct levels (78 mg/L), she developed progressive cognitive deterioration, instability and gait alteration, dysarthria, and episodes of absent gaze during which she showed little interaction with her surroundings.

On admission, ammonia levels in blood were slightly elevated (49 mg/dL), though there were no other relevant laboratory findings. An MRI scan showed signs of mild cortical/subcortical atrophy with prominent sulci of the bilateral cerebral convexity and of the cerebellar foliae associated with a very slight increase in the size of the lateral ventricles compared to the study from the previous year, which was normal. A video-EEG revealed no evidence of epileptic activity.

A neuropsychological evaluation revealed evident cognitive decline with a fall in total intelligence quotient (47 at the time of admission) contrasting with her early intellectual disability, which was mild (total IQ of 66 on the WPPS-V scale). An etiological study using muscle biopsy and a study of

Figure 2. Magnetic resonance imaging of patient 2. a) Findings at baseline, showing no evidence of disease. b) Images revealing presence of brain pseudoatrophy. c) Images suggesting improvement of the cerebral volume loss obtained eight years after valproic acid dose reduction.

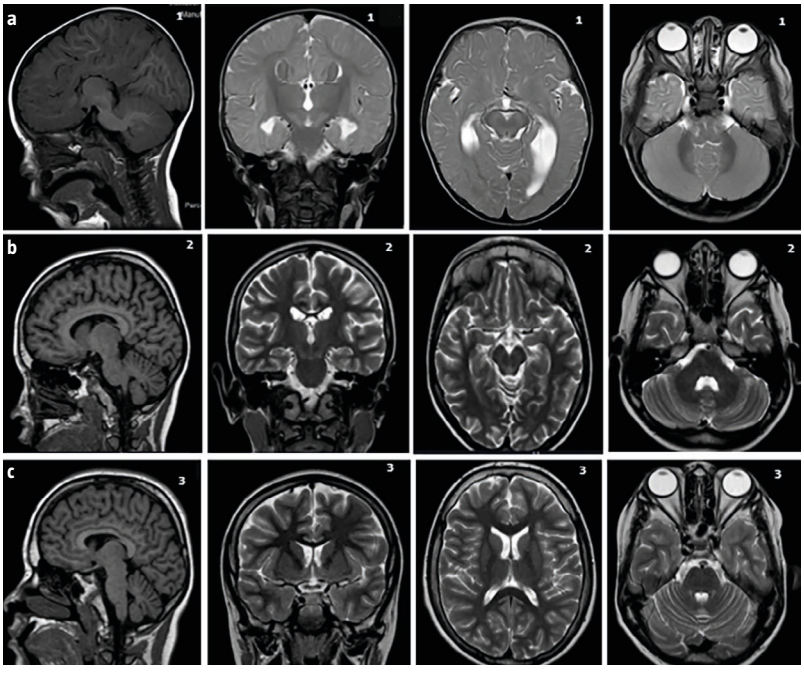
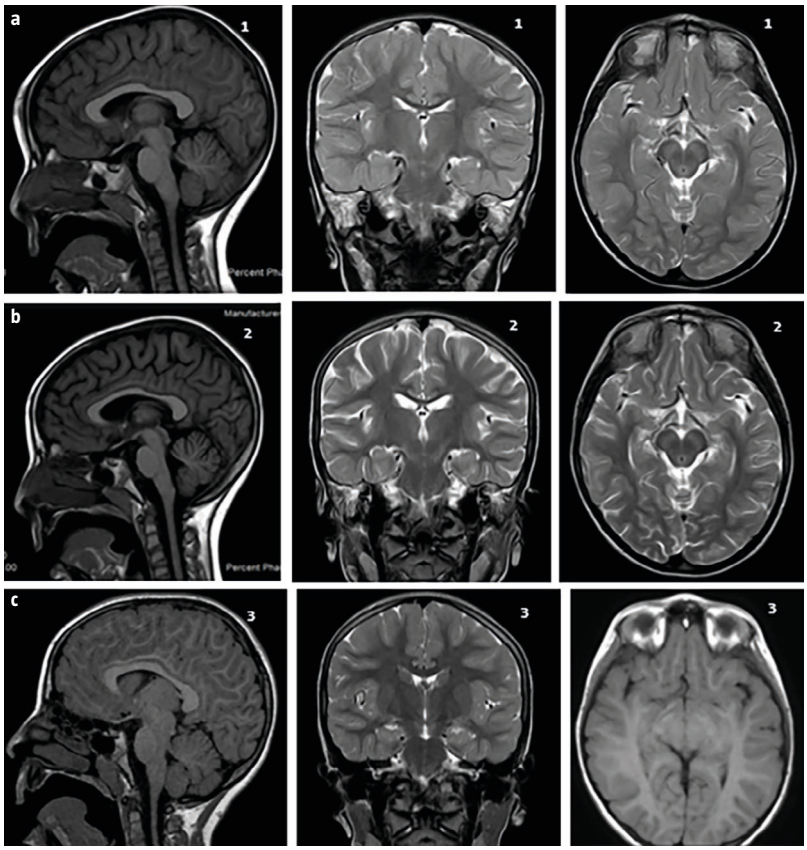


Figure 3. Findings of magnetic resonance imaging for patient 3. a) Baseline scan revealing no abnormalities. b) Scan obtained during the period of pseudoatrophy. c) Image obtained 16 months after withdrawal of valproic acid, showing complete recovery.



neurotransmitters in cerebrospinal fluid and intermediary metabolism were normal.

Given the suspicion, VPA was replaced with levetiracetam.

Five months later, the symptoms had resolved, and an MRI scan performed 1 year after the change in drug therapy was completely normal. A repeat neuropsychological assessment performed one year after the episode showed cognitive recovery, with a total IQ of 61 (WPPS-V) (Fig. 3).

The characteristics of the three reported cases are summarized in the table.

Discussion

Although VPA is generally well-tolerated, it can cause serious side effects in the nervous system, including acute or subacute encephalopathy, which may take the form of encephalopathy due to a dose-dependent toxic effect, hyperammonemic encephalopathy, or encephalopathy related to fulminant liver failure or liver dysfunction. In addition, a fourth type of VPA encephalopathy associated with cerebral and cerebellar atrophy, termed 'reversible cerebral and cerebellar pseudoatrophy', has been described in recent decades [6].

The most common symptoms of cerebral and cerebellar pseudoatrophy in adults are parkinsonism and cognitive impairment with loss of brain volume, thus resembling findings in dementia [6]. In patients with epilepsy, VPA decreases the volume of white matter and causes thinning of the parietal cortex [7]. Manifestations described in these patients include ataxia, parkinsonism, tremor, dysmetria, dysdiadochokinesia, cognitive impairment, stupor, bradylalia, slowed motor speed, decreased memory and abstract thinking, amimia and a purposeless smile, and even hallucinations and disorientation. [2,5,8,9].

In the few cases reported in children, the primary symptoms are cognitive, motor, and behavioral impairment and mood disturbances, including learning difficulties (literacy problems, language regression, inattention, memory impairment, apathy); behavior changes (irritability, impulsivity, emotional lability), and motor difficulties (clumsiness, tremor, ataxia) [3,4,6]. Our patients also presented exacerbation of their epilepsy, two had daytime drowsiness, and one presented intermittent ptosis, a symptom not previously described in the literature.

Discontinuation of treatment with VPA completely reverses the symptoms and abnormal findings of imaging studies. In the pediatric cases reported, symptoms disappeared two days to 19 months after drug withdrawal, and neuroimaging signs of brain and/or cerebellar atrophy reversed between four months and two years after discontinuation [2-6,9]. In our series, clinical normalization occurred in a matter of months, both in the two patients in whom VPA was withdrawn entirely and in the one child in whom the dose was reduced to 75% of the initial level.

Complete normalization of imaging findings occurred only with drug withdrawal. This suggests that before withdrawing the drug altogether, a dose reduction should be considered in those children in whom VPA is effective in controlling epilepsy. It can make us think of a possible dose-dependent effect effect. However, all patients were being administered the drug at doses within the recommended range.

This finding is consistent with previous descriptions in the literature, where the levels were normal in most cases [2,6] or slightly elevated [3-5,9].

We believe that a genetic predisposition may exist for this condition, likely unrelated to the underlying disease, as each patient had a different baseline condition.

Conclusion

Cerebral and cerebellar pseudoatrophy should be suspected in patients treated with VPA who present acute or subacute cognitive, motor, or/and behavioral deterioration, exacerbation of epilepsy with no clear trigger, symptoms of cerebellar involvement and/or movement disorders, even in cases of prolonged, ongoing treatment administered at dose levels within therapeutic range and in the absence of other adverse effects. In such cases, it would be advisable to withdraw or reduce the VPA dose before carrying out invasive tests.

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Pseudoatrofia cerebral y cerebelosa asociada a ácido valproico. Descripción de tres casos pediátricos

Introducción. La pseudoatrofia cerebral y cerebelosa es un efecto adverso infrecuente del ácido valproico (VPA) que debemos conocer por sus implicaciones diagnósticas y terapéuticas.

Caso clínico. Presentamos tres casos de niños de entre 5 y 9 años, con epilepsia y resonancia magnética craneal previa normal, que llevaban el fármaco con dosis correctas. La pseudoatrofia se manifiesta de forma subaguda con síntomas e imagen de atrofia cerebral y/o cerebelosa, reversible tras la retirada del fármaco.

Discusión y conclusiones. Se trata de un tipo de encefalopatía relacionada con VPA diferente a la encefalopatía tóxica dependiente de la dosis, la encefalopatía hiperamoniémica o la relacionada con fallo hepático. En niños, cursa con deterioro cognitivo, motor, anímico y conductual, y puede acompañarse de descompensación epiléptica. La retirada del fármaco conlleva una recuperación completa clinicorradiológica, y la disminución de dosis, una mejoría.

Palabras clave. Ácido valproico. Antiepiléptico. Cerebelo. Cerebro. Niño. Pseudoatrofia.