Hallucinations After Withdrawal of Valproic Acid

abstract
We report 2 children with a history of epilepsy in whom valproic acid (VPA) withdrawal was identified as a potential cause of hallucinations. After a restart of VPA, the hallucinations disappeared. We suggest mechanisms for the occurrence of the hallucinations and a possible control of a predisposition to hallucinations by VPA. Pediatrics 2012;130:e236–e238

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KEY WORDS
hallucinations, valproic acid, children

ABBREVIATIONS
GABA—γ-aminobutyric acid
VPA—valproic acid

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Valproic acid (VPA) is a first-choice antiepileptic drug, administered to children with various epilepsy syndromes. In children with long-term remission of seizures, VPA is often withdrawn. Recently, urgent consultations by a child and adolescent psychiatrist were requested for 2 patients with hallucinations after withdrawal of VPA.

PATIENT PRESENTATIONS

Case 1
A 4-year-old girl was referred to the emergency department of the University Medical Center Utrecht, The Netherlands, with visual, acoustic, and tactile hallucinations. After waking up at night, she became very anxious and complained of seeing and hearing snakes in her bed. She had had nightmares every now and then but had never experienced hallucinations before. There were no physical complaints, and she did not have a fever. The girl had previously been diagnosed with idiopathic generalized epilepsy and had been taking VPA for 2.5 years in a dose of 31 mg/kg per day (plasma level at the age of 3: 82 mg/L; therapeutic range: 40–100). One month before presentation, her treating child neurologist had started to taper VPA after a seizure-free period of 1.5 years. At the time of admission, she still used VPA in a dose of 5 mg/kg per day (plasma level: 19 mg/L). The family history was negative for hallucinations or psychosis. Her hallucinations and anxiety continued for 2 days every 2 hours with a duration of 10 to 30 minutes of each episode. An epileptic origin, e.g., complex partial seizures due to temporal lobe epilepsy, was considered but excluded with a normal EEG recorded during the hallucinations. An MRI of the brain and laboratory investigations, including analysis of cerebral spinal fluid, were all normal. Hashimoto thyroiditis, porphyria, systemic lupus erythematoses, and other causes of autoimmune encephalitis were excluded. There was no evidence of (sexual) abuse. Two days after onset of hallucinations, the dosage of VPA was increased again to 31 mg/kg per day, resulting in complete disappearance of the hallucinations and anxiety within 2 days. After another year of treatment with VPA, neither epilepsy nor hallucinations have been observed. It was decided at that time to slowly withdraw VPA again over 6 months time. Two months after complete withdrawal, she is still free of symptoms.

Case 2
A 12-year-old girl was referred to the adolescent psychiatric outpatient clinic of the University Medical Center Utrecht for a second opinion. She was diagnosed with autism and referred for neurologic evaluation because of possible epilepsy. She was diagnosed with cryptogenic focal epilepsy, and she started taking VPA up to a dose of 30 mg/kg per day, resulting in freedom from seizures. After a seizure-free period of 1 year, the child neurologist withdrew VPA over a period of 6 weeks. No plasma levels were determined in this period. Immediately after complete withdrawal of VPA, she presented with an increase of oppositional behavior with agitation and racing thoughts, and onset of psychotic symptoms. She heard voices and saw nonexistent persons. She had never experienced visual or acoustic hallucinations before. An EEG revealed no epileptiform activity, and temporal lobe epilepsy was therefore considered unlikely. Laboratory tests and MRI of the brain were all normal. Three months after onset of these symptoms, she was again referred to our outpatient clinic. VPA was restarted. The hallucinations disappeared completely, and the behavioral problems rapidly improved within 4 weeks. During the following 8 months of VPA use, the girl had progressive menorrhagia. VPA was tapered off again over a period of 8 months, without recurrence of psychiatric symptoms until today (>1.5 year).

DISCUSSION
We described 2 children with a history of epilepsy, who started hallucinating during or after withdrawal of VPA over a period of 6 weeks. Common causes of hallucinations were excluded. We suggest that VPA withdrawal was the cause of the hallucinations in these cases because restart of VPA immediately relieved symptoms. Halucinations are defined as perceptions in the absence of identifiable external stimuli. Several conditions and disorders are associated with hallucinations. In young children, hallucinations have been reported in relation to high fever, stress response, traumatic events, night terror, toxic ingestion, adverse medication effects, delirium, encephalitis, and narcolepsy. Moreover, benign phobic hallucinations may occur in young children. Such hallucinations are visual and tactile, anxiety based, present at night, and self-limiting. Examples of psychiatric disorders with hallucinations are schizophrenia, major depressive or bipolar disorder with psychotic features. Furthermore, children with autism, disruptive disorders, and anxiety disorders may present with hallucinations. Seizure semiology in patients with partial epilepsy may also include hallucinations.

In the 2 cases that we described, there was no history of precipitating stressful or traumatic events or toxic ingestion. Furthermore, the girls had never experienced hallucinations during previous seizures. The absence of encephalopathy and the normal results of ancillary investigations make a diagnosis of anti-N-methyl-d-aspartate receptor encephalitis, limbic encephalitic syndromes, or steroid responsive encephalopathy associated with autoimmune
thyroiditis unlikely. Psychiatric disorders with hallucinations were considered, but neither girl fulfilled the criteria necessary to diagnose another psychiatric disorder. In the first case, benign phobic hallucinations could be an alternative explanation. However, these hallucinations are only short-lasting and occur during the night, whereas this girl continued to hallucinate for 2 days. In the second case, the behavioral problems and psychotic symptoms could be related to her autism. Because the psychotic symptoms disappeared after VPA was restarted but did not occur again after second withdrawal, a relation with her autism is unlikely.

The most obvious and remaining explanation seems thus that hallucinations in both girls occurred because of a too fast withdrawal of VPA. This is supported by the rapid disappearance of the hallucinations and anxiety after restarting VPA.

In the last decades, VPA has been broadly administered in patients with epilepsy or psychiatric symptoms (such as aggression, impulsivity, and psychosis). Several pharmacological mechanisms for the clinical effects of VPA have been proposed. The antiepileptic action of VPA has been suggested to be due to enhancement of γ-amino butiric acid (GABA). Hallucinations and delusions in an adult with schizophrenia have been reported after withdrawal of VPA.5 This was postulated to be the result of increased dopamine release in the subcortical mesolimbic system due to decreased GABA activity.6 After reinitiation of VPA, the psychotic symptoms were controlled to the level before the withdrawal of VPA. Therapeutic effect of VPA may also result from reduction of glutamatergic activity.7 Theoretically (relatively fast) withdrawal of VPA could lead to a temporary rebound increase of hyper-glutamatergic transmission in some patients. Previous studies have revealed that an increase in glutamatergic activity can generate psychotic symptoms via increased dopaminergic activity.7–9

**CONCLUSIONS**

Rapid discontinuation of VPA may have resulted in psychotic symptoms in our patients. The observed effects may be explained by enhancement of dopaminergic neurotransmission possibly elicited by a decrease of GABA activation or a rebound of glutamatergic activity after withdrawal of VPA. A more gradual discontinuation of VPA after chronic treatment probably prevents occurrence of psychotic symptoms as was demonstrated in both cases.

We report our patients to create awareness of a link between withdrawal of VPA and hallucinations and a possible role of VPA in controlling a predisposition to hallucinations.

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