

## Case Report

# Antiepileptic Drugs as a Cause of Seizures or Seizure Worsening in Children

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**ABSTRACT**

The phenomenon of seizures aggravated by antiepileptic drugs is frequently overlooked by physicians. It should be considered a side effect of antiepileptics, especially in epileptic cases treated with multiple antiepileptics (polytherapy) and in cases of intractable epilepsy. In this report, we discuss this phenomenon after demonstrating its occurrence in four cases in different clinical settings. A child presented with status epilepticus as a complication of acute intoxication with carbamazepine. Another child who after starting treatment with carbamazepine developed myoclonic seizures, as a new type of seizure which disappeared after stopping carbamazepine; these myoclonic seizures represent a paradoxical reaction to

carbamazepine. A third child who was treated for absence epilepsy with carbamazepine developed worsening of the seizures. This represents an inappropriate choice of antiepileptic drug for this type of seizure. A fourth epileptic child while on polytherapy with usual doses of sodium valproate and lamotrigine unexpectedly developed frequent prolonged absences and encephalopathy; he reverted to his base line state with dose reduction of both drugs. It is important to recognize this phenomenon, as it will help in reducing morbidity in epileptics by early and appropriate intervention.

**KEYWORDS:** antiepileptic paradoxical reaction, epilepsy

**INTRODUCTION**

Epilepsy is a common chronic neurological disorder with prevalence of 0.5-1 % of the general population world wide<sup>[1]</sup>, with overall incidence of 0.5 %, being highest in the first year of life (0.8 %) and in ages 75 years (1.4 %)<sup>[2]</sup>. After five years from onset of epilepsy, 20-30 % of epileptics would not have achieved a two-year seizure free period, i.e. they continue to be on antiepileptic medications<sup>[3]</sup>. During the course of management, particularly in intractable cases of epilepsy, physicians may be faced with spontaneous and natural fluctuations in the frequency of seizures, or with the appearance of different seizure types during the natural course of evolution of a particular "epileptic syndrome" as it is seen for e.g., in children with the Lennox-Gastaut syndrome<sup>[4]</sup>. Taking these facts into consideration, physicians may overlook the possibility that antiepileptic drugs (AED) themselves may be the cause of appearance of a new seizure type, or may be the cause of deterioration in the degree of seizure control.

In this article, we describe cases which demonstrate, in different clinical circumstances, the fact that AED can cause seizures or make them worse.

**CASE DESCRIPTIONS****Case-1: Antiepileptic Toxicity**

HM a five-year old previously healthy girl with no history of seizures or any significant past medical problems, was admitted with status epilepticus in the form of recurrent non-febrile seizures that started one hour before her arrival to the emergency room. The seizures were generalized tonic-clonic with up-rolling of the eyes. The patient did not regain her consciousness after the second seizure and had a total of ten seizures within thirteen hours. Her sister is on treatment for epilepsy with both carbamazepine and topiramate. Clinically she was unconscious, not responding to sound but responding to painful stimuli by withdrawal of her limbs. She had some spontaneous movement and moaning sound, her breathing was spontaneous and regular, eye movement was obtained by the doll eye maneuver, pupils were equal and reactive to light, and fundoscopy examination and deep tendon reflexes (DTR) were normal. Other systemic examinations were all normal. Investigations: serum electrolytes, glucose, amylase, liver and renal functions tests, CT scan brain (with and without contrast) and ECG were all normal. Toxicology screen revealed carbamazepine level of 85 µmol/ L (on admission), confirming accidental intoxication with

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carbamazepine. Seizures did not respond initially to intravenous (IV) diazepam (repeated doses), and IV phenytoin (20 mg/kg), but responded to midazolam (loading dose: 0.15 mg/kg, followed by IV infusion at a rate of 0.1 mg/kg/h). She regained consciousness 24 hours after admission and she was discharged on the fifth day without any neurological or systemic complications.

#### Case-2: Antiepileptic Paradoxical Reaction

KA, a three-year old boy was a known case of epilepsy since the age of seven months. He had unremarkable perinatal history and normal developmental milestones. His seizures were brief (1-5 min), tonic-clonic, bilateral or unilateral, either left or right side, occasionally followed by transient unilateral weakness (Todd's paralysis). Physical examination was normal apart from mild bilateral ankle clonus. Detailed metabolic investigations were normal, together with a normal MRI and MR angiography. EEG showed occasional left focus of sharp slow waves. He was treated initially with phenobarbitone which was changed later to sodium valproate. Lamotrigine was added to valproate. Patient developed thrombocytopenia related to valproate which was tapered off and replaced with carbamazepine at age 20 months (platelet count returned to normal). Within two weeks of starting carbamazepine a new seizure type appeared in the form of daily frequent myoclonic jerks. These myoclonic seizures were thought to be related to carbamazepine which was then tapered off. This led to a prompt disappearance of these myoclonic seizures. Topiramate was added to lamotrigine and this combination was continued until the age of 33 months, and after a six months seizure free period, lamotrigine was tapered off and the child was continued on topiramate only.

#### Case-3: Inappropriate Antiepileptic Choice

AS, a six-year old girl presented with a four months history of recurrent absences. They were brief, less than ten seconds, associated with mild automatism, during which she was not interactive. There was no loss of tone and she recovered promptly after each episode without any recollection. She was treated by another physician with carbamazepine. She became worse regarding the frequency of the absences; from about ten per day to more than 30/day. Physical examination (neurological as well as systemic) was normal. Clinically, hyperventilation precipitated the absences. CT scan brain was normal. EEG showed typical generalized 3 Hz spike-wave complexes enhanced by hyperventilation. She was diagnosed as a case of childhood absence epilepsy, carbamazepine was

stopped and she was treated with sodium valproate (30 mg/kg/day) on which she improved dramatically.

#### Case-4: Antiepileptic Polytherapy toxicity

SS, an 11 year-old boy with intractable epilepsy presented at the age of ten years with convulsive status epilepticus which needed ICU care. He was diagnosed and managed as possible encephalitis (lumbar puncture was refused). CT scan and MRI brain as well as metabolic work up were all normal. Since then he was having daily seizures (rate: 2-5/day) in the form of : simple sensory seizures (over the face), atypical absences (unresponsiveness up to 15 minutes) as well brief generalized convulsive seizures, treated initially with clonazepam (0.06 mg/kg/day), followed by the addition of sodium valproate (30 mg/kg/day). The EEG showed bilateral foci of sharp waves and spike-wave complexes with slow disorganized background. He had a fluctuating course. Clonazepam was tapered off to be replaced by lamotrigine (which was slowly introduced). He showed definite initial response to lamotrigine at a dose of 1 mg/kg /day, as he would be seizure free for days (up to 2 weeks). Because of the fluctuant course, lamotrigine was further increased gradually to 4 mg/kg/day. He presented four weeks later with progressive deterioration; initially as frequent convulsions mainly during sleep to be replaced later by frequent atypical absences, some prolonged (30 min or more) with encephalopathic state (hypoactive, severe clumsiness, slurred speech and poor appetite). Blood valproate level was 850 µmol/L, which is not considered toxic (therapeutic range: 345-690 µmol/L), Blood ammonia, liver functions tests and serum amylase were normal. He was suspected clinically to have epileptic encephalopathy with episodes of non-convulsive status epilepticus (EEG was not available to confirm these immediately). Reduction in the doses of both valproate (to 20 mg/kg/day) and lamotrigine (to 3 mg/kg /day) reduced the frequency of the absences and resolved the encephalopathic state though he remained with frequent seizures (i.e. back to his basic state). On follow up, lamotrigine was replaced with clobazam on which he showed improvement in both the seizures frequency and in his cognition.

#### DISCUSSION

There is a growing awareness of the fact that AED may cause seizures or seizures aggravation in epileptics under different clinical circumstances<sup>[5]</sup>. **Antiepileptic intoxication**, as a cause of seizures, is defined as symptoms (i.e., seizures) occurring with

serum AED levels well outside the therapeutic range. This phenomena is well known for phenytoin with levels above 120  $\mu\text{mol/L}$ <sup>[6,7]</sup> and this fact is important to remember, particularly during the management of status epilepticus where levels of phenytoin should be monitored and maintained below 120  $\mu\text{mol/L}$ <sup>[8,9]</sup>. Accidental carbamazepine intoxication as a cause for seizure, as was seen in Case-1, has been reported occasionally<sup>[10,11]</sup> and occurs usually after massive doses resulting in variable degrees of coma, with status epilepticus resistant to anticonvulsant therapy. There may be associated systemic complications and death<sup>[10]</sup>. The lowest reported serum carbamazepine level, in cases with acute intoxication that was associated with seizures was 82  $\mu\text{mol/L}$ <sup>[12]</sup>. Our patient had a carbamazepine level of 85  $\mu\text{mol/L}$  and she had no evidence of systemic complications other than neurological symptoms. Seizures as a complication of antiepileptics intoxication have also been reported with lamotrigine<sup>[13]</sup>, sodium valproate<sup>[14]</sup> and tiagabine<sup>[15]</sup> in case reports.

Seizure worsening is considered to be a **paradoxical reaction** when an AED appears to exacerbate a type of seizure against which it is usually effective, or when it leads to the onset of new types of seizures<sup>[13]</sup>. This usually occurs soon after the introduction of the AED in usual doses and normal serum levels<sup>[5]</sup> and is confirmed by the clinical improvement after dose reduction. In Case-2 described, the patient was started on carbamazepine which was considered appropriate choice since the patient had generalized convulsive seizures that may start on one side of the body and occasionally end with transient weakness on the side of the onset of convulsion. This was suggestive of focal onset of the seizure, and the patient had no history of myoclonic or absence seizures before. Soon after introduction of carbamazepine he developed progressively increasing myoclonic seizures as a new seizure type. These myoclonic seizures disappeared promptly after discontinuation of carbamazepine. Carbamazepine induced myoclonic seizures (in non-myoclonic epilepsies) have also been reported in cases of epilepsies with centro-temporal spikes<sup>[5,16]</sup>. As a manifestation of seizure aggravation, carbamazepine may also induce absence seizures, or worsening of the same original seizure type for which it was originally prescribed, either in epileptic patients with partial seizures<sup>[17,18]</sup>, or with generalized seizures<sup>[19,20]</sup>. Although the majority of paradoxical reactions were reported in relation to carbamazepine, particularly in children<sup>[13,21,22]</sup>, other AED that have been reported to worsen seizures include benzodiazepines<sup>[5,13,23]</sup>, barbiturates<sup>[13,24]</sup>, gabapentin<sup>[24]</sup>, topiramate<sup>[25]</sup>, lamotrigine<sup>[26]</sup>, vigabatrin<sup>[27]</sup> and tiagabine<sup>[32]</sup>.

Reports on valproic acid induced seizures are usually related to encephalopathy (secondary to overdose or underlying metabolic disorder)<sup>[13,24, 29]</sup>. Occasionally it is not, and it then represents a primary paradoxical reaction<sup>[30]</sup>.

To consider an AED **inappropriate** for treating a specific type of seizure, or, epileptic syndrome, enough data collected from reports should show consistent evidence of paradoxical reaction produced by this AED when used for that type of seizure or epileptic syndrome. This is, in particular, applicable to the use of carbamazepine in epilepsies with absence seizures<sup>[5,13,24,31]</sup> or with myoclonic seizures<sup>[5,24,31,32]</sup>. In Case-3 described, the child possibly misdiagnosed to have complex partial seizures for which carbamazepine was prescribed, though clinically, the seizures were typical absences, with typical EEG findings. Carbamazepine aggravated the seizures frequency in this patient. Carbamazepine has been shown to induce worsening in the EEG pattern with the development of spike and wave complexes which coincided with the clinical seizure aggravation, in both partial and generalized epilepsies<sup>[33,34]</sup>. This EEG worsening pattern was suggested as a warning for possible carbamazepine induced seizure worsening. Phenytoin has a pattern for seizure aggravation similar to carbamazepine<sup>[5,31,32]</sup> but with less reported data.

In epileptic patients on **antiepileptic polytherapy**, seizure worsening is not easy to appreciate since worsening may be due to the withdrawal of an AED that was beneficial rather than the introduction of a new one. Also, the spontaneous natural fluctuant course, particularly in intractable epilepsy cases, makes it difficult to appreciate the temporal relationship between worsening of seizures and the introduction of a new medication. This spontaneous fluctuation, unrelated to medications was clearly demonstrated in clinical placebo-controlled trials for new AED, where patients in the placebo groups showed significant deteriorations in their seizures control<sup>[35]</sup>. In Case-4 described, the patient did show initial improvement with the introduction of lamotrigine and withdrawal of clonazepam, but as the dose of lamotrigine was increased deterioration was noted in the degree of the seizure control (episodes of non-convulsive status epilepticus and associated encephalopathy) which reversed (*i.e.*, back to his base line seizure rate) with reduction of dosages of both medications, though both were given within the recommended dosages. The sodium valproate plasma level of 850  $\mu\text{mol/L}$  in our patient is not considered toxic, since what is defined as "therapeutic level" is only a rough guide in monitoring response and compliance during

management of epileptic patients. In cases of valproate toxicity, those with symptoms of nausea, vomiting and dizziness are usually expected to have plasma sodium valproate levels five to six times the "therapeutic range", and those with symptoms of CNS depression, coma and impaired respiration are usually expected to have plasma valproate levels 10-20 times the "therapeutic range"<sup>[36]</sup>. Our patient while on regular doses, had evidence of seizures worsening that reversed with reduction of doses of AED polytherapy. Therefore, it is important to note that during the course of AED polytherapy, seizure worsening may occur regardless of the dosages and serum levels of the antiepileptic medications<sup>[24]</sup>.

The mechanisms of paradoxical effect of AED are not clear. Several possible mechanisms have been postulated<sup>[5,21,24]</sup>. AED in high concentrations may have depressant effect on inhibitory interneurons resulting in disinhibition of excitatory neurons and facilitation of epileptic discharges. Toxic elevation of carbamazepine 10,11 epoxide metabolites were found in high levels in some cases with carbamazepine related seizure aggravation. Carbamazepine induced hyponatremia may be another factor. In cases with sodium valproate toxicity, hyperammonemia may be a factor in inducing seizures. Carbamazepine (as well as GABAergic drugs) may induce absences by facilitating synchronization of the firing neurons in the thalamocortical network (which is one of the postulated mechanisms of absence production in animal models).

In conclusion, physicians caring for epileptic patients should be aware of this phenomenon, and should consider it when seizure worsening occurs following the introduction of a new AED, particularly in young patients, patients on AED polytherapy and in epileptic syndromes with multiple seizure types. Carbamazepine should be avoided in patients with absence epilepsy and in infantile or juvenile myoclonic epilepsy, and should be used with caution in patients with mixed seizure types.

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