Ethosuximide in a patient with myoclonic astatic seizures

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Abstract
Myoclonic astatic epilepsy is currently treated with valproic acid as the first line treatment of choice. However, this is based on expert opinion due to the paucity of good evidence1. Described here is the case of a 7-year-old boy with myoclonic astatic epilepsy, whose seizures could not be controlled on valproic acid monotherapy, and who rapidly improved with ethosuximide as add-on therapy.

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Introduction
Myoclonic astatic (sometimes referred to as atonic) epilepsy (MAE), also known as Doose syndrome1, was first described by Dr Hermann Doose in 1970. MAE has an incidence of 1 in 10 000 children, constituting about 1 to 2% of childhood-onset epilepsies. It is more common in boys in a ratio of about 3:1. It generally appears between 7 months and 8 years of age although in 94% of cases the onset occurs within the first 5 years of life2.

MAE is a generalised epilepsy syndrome that is characterised by different seizure types, with myoclonic and myoclonic astatic seizures seen in all, causing children to fall1,4. Seizures in MAE occur frequently and last less than 2-3 seconds, with about two-thirds of children experiencing drop attacks. A 'drop attack' is synonymous with astatic seizure, which is a loss of erect posture that results from an atonic, myoclonic or tonic mechanism3,5. This may be seen as head nodding, with the child recovering balance before falling2. A myoclonic seizure is a sudden, brief involuntary single or multiple contraction/s of muscle/s or muscle groups that can occur truncally or axially. If they occur truncally, they may result in a myoclonic drop in which the child appears to be thrown to the floor2,5. These abrupt falls may result in severe injuries, especially to the nose and face1.

In MAE, the initial EEG may be normal, however, with disease progression brief bursts of 2 to 5 Hz (up to 6 Hz in some references) spike and wave, and polyspike and wave complexes, may be seen2. MAE may overlap significantly with other epilepsies such as benign myoclonic epilepsy, severe myoclonic epilepsy, atypical benign partial epilepsy of childhood, and Lennox-Gastaut syndrome (LGS), which makes diagnosis difficult2. EEG can often distinguish between MAE and LGS, as the latter is more abnormal with little to no background activity and slower (2-2.5 Hz) spike-wave runs for prolonged periods2.

In MAE, children typically have normal neurological development prior to onset, and may maintain normal cognition2,5. In LGS, however, there is often cognitive delay from the onset of the seizures2. It is thought that MAE and LGS may possibly be opposite ends of a single epilepsy syndrome, with MAE being the mild end of the spectrum and LGS at the more severe end2.

There appears to be a genetic component in children with MAE, with a high rate of seizures and similar EEG findings noticed among immediate family members2,3. Currently the genetic determinants of MAE are largely unknown6.

The course of MAE is variable and unpredictable, and in the majority of patients is self-limiting, with seizures stopping after a few years2. In more severe cases, the epilepsy remains intractable with behavioural and cognitive deterioration. The factors that influence the different outcomes are largely unknown, although it is thought that repeated, prolonged episodes of non-convulsive status epilepticus may be associated with a poor mental outcome3.

Case report
We present the case of a 7-year-old African boy, who had a history of gross developmental delay, behavioural problems, and mental handicap. He was seen for the first time at the paediatric department in 2010, at age 5. The primary reason for the encounter was his family's concern over the numerous drop attacks he experienced – these numbered in the hundreds per day. Clinically he presented with scars to the forehead from falling, inability to speak, and drooling. There was no previous diagnosis of epilepsy. He was diagnosed with MAE based on an EEG that showed a general seizure pattern in association with clinically observed head drop episodes.

The child was initiated on valproic acid (VPA), 5 mg/kg, which was gradually titrated up to 25 mg/kg. The severity of his seizures diminished on therapy in that he was less violently thrown to the floor. However, the frequency of seizures did not diminish, and he still
experienced hundreds of drop attacks daily. Adherence was ensured and serum VPA levels were within the therapeutic range. Ethosuximide (ESM) was then added to his treatment regimen at 10 mg/kg/day. Nineteen days after initiating ESM the child was reviewed and showed a substantial decrease in the number of drop attacks, with less than three drop attacks per week. After 5 months of combination VPA-ESM treatment, he began to show developmental improvement in that he started speaking, was learning to count, and could express his needs.

**Treatment**

MAE has historically been described as being difficult to treat, with a scarcity of data and few recommendations as to its management. No randomised controlled trials have been conducted to evaluate the efficacy of anti-epileptic drugs in MAE\(^1,4\). Treatment is thus based on expert advice, case series, and extrapolation from clinical experience in other idiopathic generalised epilepsies. VPA is often cited as being the first line drug of choice, although its efficacy is unclear\(^3,4,7-9\).

A literature review was conducted in Medline and Google Scholar, using the following MeSH terms: ‘myoclonic astatic’, ‘drop-attacks’, ‘Doose syndrome’ and ‘ethosuximide’. References of all articles were reviewed to identify any further relevant studies. Only articles in English were reviewed. The website of the International League Against Epilepsy (ILAE), an organisation that works to disseminate knowledge about epilepsy, was searched for treatment guidelines.

Ethosuximide, a succinimide, reduces low-threshold Ca\(^{2+}\) currents (T currents) in thalamic neurons. The thalamus plays an important role in generation of 3 Hz spike-wave rhythms. At clinically relevant concentrations, ESM inhibits the T current, which is thought to inhibit absence seizures\(^3,10\).

The current indication for ESM is for the control of absence seizures, although the evidence for this comes from small studies of poor design\(^11,12\). These studies are, however, more numerous than those for MAE, with treatment efficacy partially extrapolated from absence seizure trials for use in MAE.

Snead et al. described a small case series of 19 children with multiple seizure types, in whom the primary seizure was falling to the ground\(^13\). All patients had multiple, daily falls, which were intractable to phenobarbital, VPA, and clonazepam. All had abnormal EEGs showing generalised bursts of spikes and waves at 1 to 4 Hz. Of these children, 12 became free of epileptic falls on ESM, four showed a 50-75% decrease in the number of falls, and three showed no change in the frequency of falls.

A larger case series by Hwang et al., who retrospectively reviewed 128 patients with absence seizures, suggested that ESM had a faster onset of efficacy than either VPA and lamotrigine (LMT). However, at 12 months no difference was found in efficacy between the three treatments\(^14\). This differed to the findings of a double blind, randomised controlled trial by Glauser et al. who compared the efficacy, tolerability and neuropsychological effects of ESM, VPA, and LMT in children with newly diagnosed absence seizures. This study showed both ESM and VPA to be more effective than LMT for this indication\(^15\). The retrospective case series by Kilaru et al. of 19 children who fulfilled the ILAE criteria for myoclonic astatic seizures looked at multiple anti-epileptic drugs for the treatment of MAE. Of the four children who had ESM as add-on therapy to their other anti-epileptic treatment, one became seizure free\(^4\).

It has been suggested that the combination of VPA with ESM may be more effective, and this is thought to be due partly to an unknown pharmacokinetic interaction\(^11\). Some evidence points to ESM decreasing levels of VPA, whilst VPA increases levels of ESM when these agents are given concomitantly\(^16,17\). As this interaction may be clinically significant it is important to monitor for ESM toxicity while on both agents.

About 20% of patients on ESM experience dose-related side effects such as gastric distress, nausea, vomiting, anorexia, and central nervous system side effects, such as drowsiness, lethargy, euphoria, dizziness and headache\(^10,18\). A report presented by Chien showed a case of a 10-year-old boy who was treated for absence seizures with ESM. He started experiencing paranoia, suicidal ideation, and hallucinations on this treatment. After titrating the dose of ESM down, the psychiatric disturbances subsided\(^19\).

**Conclusion**

This case presented a 7-year old boy diagnosed with MAE and initiated on VPA. This treatment resulted in amelioration in the severity of the drop attacks, but had no effect on the frequency of attacks. Upon ESM initiation, the number of drop attacks dropped significantly from hundreds per day, to less than 3 per week. There have also been improvements in his development to the point where he may be able to start attending school. There is very little evidence for the treatment of MAE. To further complicate matters, there is an overlap in the presentation of MAE and other epilepsies, which may have different first-line therapy choices. Treatment is thus based largely on expert opinion and anecdotal evidence, together with a process of elimination of trials of therapy. A call for further well-designed research has been made to assess outcomes such as seizure freedom, seizure reduction, quality of life, and cognitive outcome, so as to determine what the initial and add-on anti-epileptic drugs of choice for the management of MAE should be\(^1\).

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**References available on request.**