Clinical Brief

ACTH Therapy in Refractory Generalized Epilepsy

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ABSTRACT

Adrenocorticotropic hormone (ACTH) has a long track record for the treatment of infantile spasms. However, there is paucity of data on the use of ACTH in the treatment of epilepsy beyond infantile spasms. We report the use of ACTH in two children with refractory generalized epilepsy. Both patients responded well. ACTH may be considered as a useful adjunctive therapy in patients with intractable generalized seizures. Side effects and cost however, remain important concerns.

CASE REPORTS

Case 1

A 3-yr-old boy with normal premorbid development was brought for evaluation of seizures occurring since 2 yr of age. At the onset, he had myoclonic jerks, 5-6 times per day; however over a period of 4 months, he developed multiple types of seizures: generalized tonic, drop attacks, and atypical absences. He had been treated without success with multiple AED including valproate, lamotrigine, clobazam, levetiracetam, and clonazepam. He had gradually become irritable, hyperactive and spoke only few words, compared to three-word sentences that he was able to speak earlier. There were no visual, hearing or motor problems. At the time of presentation, he was having 25-30 seizures every day and was on 3 AED: valproate 45 mg/kg/day, levetiracetam 50 mg/kg/day and clonazepam 0.1 mg/kg/day. Examination was normal.

Investigations revealed normal MRI brain, fundus, and baseline metabolic profile. EEG showed slow background (2-3 Hz) with generalized polyspikes, and multifocal spikes and sharp waves (Fig. 1). He was diagnosed to have Lennox-Gastaut syndrome and was treated with ACTH, 40 IU/day, given intramuscularly daily initially for 4 weeks and then shifted to alternate day therapy for next 4 weeks, then tapered off over the next month. Within a week, his seizure frequency reduced to 1-2/day, and the drop attacks stopped. He was seizure free 2 weeks later. Blood pressure was monitored twice weekly during therapy. He had developed hypertension 2 weeks after starting treatment (BP 110/80 mm Hg). Amlodipin was started and BP normalized. Amlodipin was stopped when ACTH was tapered off, and subsequent BP records were normal. He also gained 1 kg weight during the ACTH course, which he subsequently lost.

Fig. 1. EEG of Case 1 at presentation: Sleep record showing slow background activity (2-3 Hz, 60-80 μV) with frequent generalized polyspikes and multifocal sharp waves.

Key words : Refractory epilepsy; Adrenocorticotropic hormone (ACTH)
A repeat EEG obtained 3 months after starting therapy showed normalization of background and disappearance of epileptiform activity. His other AED were gradually tapered, and he is presently only on valproate 40 mg/kg/day. He also became more alert, started speaking sentences again, and now goes to play school. He has not experienced recurrence of seizures in 6 months following cessation of ACTH therapy.

Case 2

This 7-yr-old male presented with seizures since last 1 year. Initially he had generalized tonic convulsions (GTCS) 3-4/day which increased to 12-15/day. He also developed tonic seizures, atypical absences and drop attacks of both atonic and myoclonic type. He exhibited behavioral problems in the form of masturbatory movements and self-stimulation by rubbing on bed.

Birth and perinatal history was unremarkable. He had delayed development. He attained neck control at 9 months, started walking and spoke first word with meaning at 30 months. Presently he could ride bicycle (limited by his drop attacks), was toilet trained, and spoke in 3-word sentences. As per his parents, his cognitive level had remained static after onset of seizures. He had failed multiple AED including valproate, lorazepam, oxcarbazepine, lamotrigine, clobazam, and zonisamide in appropriate doses. At the time of presentation, his seizure frequency was GTCS 1-5/d and drop attacks 4-9/d. He was on valproate 60 mg/kg/d and clonazepam 0.1 mg/kg/d. Examination was unremarkable except for hyperactivity and excessive irrelevant speech.

His EEG revealed a diffusely slow background (1-2 Hz) with multifocal epileptiform activity. MRI brain and metabolic screen were normal.

He was started on intramuscular ACTH 40 IU/d. After starting ACTH his seizure frequency decreased sharply. ACTH was given 40 IU/d for 4 wk and then tapered off over next 8 wk. He did not develop any side effects during therapy. On follow-up after 4 months he is seizure free except for occasional drop attacks. His hyperactivity and behaviour problems have also improved.

DISCUSSION

ACTH was first reported to have beneficial effects in the treatment of intractable seizures in 1950. Since the efficacy of ACTH in infantile spasms was demonstrated, it has been one of the first line treatments for West syndrome. Efficacy in epileptic spasms without hypsarrhythmia has also been reported. However with the development of multiple new AED, epilepsy surgery and ketogenic diet, the use of ACTH in the treatment of epilepsy beyond infantile spasms has been reported only in a few studies.4,7

Snead et al described their experience in 64 children with intractable epilepsy (mostly myoclonic seizures) treated with either ACTH or prednisolone.4 Treatment was successful in 74% of those treated with ACTH and in none of those treated with prednisolone. Okumura et al reported a series of 15 children with intractable seizures treated with ACTH.4 Seizure freedom was obtained in 13 patients, however 6 of them had recurrence within 3 months after stopping ACTH. ACTH was most effective in patients with atypical absence seizures. Both our patients too had frequent atypical absence seizures. Recently the role of corticosteroids and ACTH in childhood epilepsy other than epileptic spasms was analysed in a Cochrane review.2 The authors concluded that no evidence was found for the efficacy or safety of corticosteroids in treating childhood epilepsies. A significant drawback of this review was that only 1 study was included, which was the only randomized control trial (RCT) assessing the efficacy of ACTH/corticosteroids in childhood epilepsy.7 This RCT recruited 5 patients in double blind crossover trial. As one patient was withdrawn prematurely from study, and another had spasms; the number of patients in this study was too small for any conclusion. There is definitely a need for well planned RCTs to evaluate the role of ACTH in refractory childhood epilepsy.

The mechanism of action of ACTH in epilepsy is not fully understood. ACTH has both endocrine and neuromodulatory properties. As a neuropeptide, ACTH may have anti-convulsive properties by itself. ACTH also induces synthesis of deoxycorticosterone which is an allosteric modulator of GABA-A receptors.8 Downregulation of corticotrophin releasing hormone (CRH) expression may also play a role, as CRH has a pro-convulsant effect in the immature brain.9 Lastly the immunomodulatory properties of ACTH may be beneficial in immune-mediated epilepsies like Landau-Kleffner syndrome.5

There are some advantages of ACTH therapy over the newer AED or ketogenic diet. The duration of therapy is short. The response is fast, and there is usually an all or none response. A 4-week trial is long enough to evaluate possible benefit and minimize side effects. Side effects including weight gain, obesity, hypertension and increased susceptibility to infections remain a concern, apart from the cost and logistics of daily intramuscular injections. These side effects however can be managed medically, and are short-lived. ACTH is definitely worth trying in refractory epilepsies, especially generalized epilepsies associated with atypical absences, if therapy can be supervised appropriately.