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Management issues in severe childhood epilepsies

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The severe epilepsies of childhood are described briefly and information available on the efficacy of newly developed antiepileptic drugs (AEDs) in their control is reviewed. Therapeutic advances are awaited for early infantile epileptic encephalopathy, early myoclonic encephalopathy, progressive myoclonus epilepsies and Kojewnikow syndrome. West syndrome may respond to vigabatrin, and less predictably to lamotrigine. Lamotrigine can be helpful for severe myoclonic epilepsy and myoclonic absences. Astatic seizures may be dramatically controlled by lamotrigine, whereas vigabatrin may worsen myoclonic attacks. In the Lennox–Gastaut syndrome, the efficacy of felbamate has been demonstrated by a controlled trial; vigabatrin and lamotrigine can also be helpful. Non-idiopathic partial and secondary generalized epilepsies are responsive to vigabatrin in a useful percentage of cases, and some children improve with felbamate, lamotrigine or stiripentol.

A trial which compares the efficacies of the newer AEDs against each other could provide very useful information for the clinician.

Key words: severe childhood epilepsies; new antiepileptic drugs.

INTRODUCTION

In childhood, epilepsies can be usefully divided into those in which a good, remitting outcome is anticipated; those where a response to therapy is expected but not inevitable, and where continued treatment into adulthood may be required; and the severe, resistant forms where seizures are likely to persist despite therapy. These latter are listed in Table 1.

Table 1: Severe childhood epilepsies

Early infantile epileptic encephalopathy
Early myoclonic encephalopathy
Severe myoclonic epilepsy in infants
Epilepsy with myoclonic absences
West syndrome—infantile spasms
Myoclonic-astatic epilepsy
Lennox–Gastaut syndrome
Non-idiopathic partial epilepsy, with or without secondary generalization
Progressive myoclonus epilepsies
Landau–Kleffner syndrome
Kojewnikow syndrome

The management of all the severe epilepsies includes recognition of cognitive and social disabilities, as well as, for some children, physical handicap. This paper concentrates on the information currently available on the drug treatment of severe epilepsies. Much of this comes from recently presented work, and some is frankly anecdotal, but patterns of response to some of the newer antiepileptic drugs (AEDs) are beginning to emerge. The information available is examined individually for each syndrome. Full details of the syndromes considered can be found in Roger *et al*[1]. When controlled, blinded studies are cited, these are identified; for all other information the patients were being treated in an unblinded manner.

EARLY INFANTILE EPILEPTIC ENCEPHALOPATHY

Frequent tonic spasms commence within the first few months of life, and are associated with suppression-burst on electroencephalograph (EEG). Partial seizures can occur but myoclonic attacks are rare. Seizures are intractable and cognitive development is very limited. Early death is not unusual. Occasionally, adrenocorticotrophic hormone (ACTH) may be helpful, but no other AED has been found effective.

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EARLY MYOCLONIC ENCEPHALOPATHY

Fragmentary myoclonus progressing to erratic partial seizures, massive myoclonias, or tonic spasms presents before the age of 3 months. Suppression-burst characterizes the EEG. Severe retardation is invariable and early death likely. Neither corticosteroids, ACTH or conventional AEDs are effective, but in one patient treated personally by the author, there was a useful reduction in seizures with lamotrigine.

SEVERE MYOCLONIC EPILEPSY IN INFANTS

The seizures start during the first year of life as unilateral or generalized clonic attacks with feverish illnesses. Evolution to myoclonic jerks and partial seizures occurs in the second year of life. Generalized spike or polyspike-waves, early photosensitivity and focal abnormalities are found on the EEG. Developmental arrest, cerebellar and pyramidal signs complicate the epilepsy which is resistant to virtually all AEDs. Responses to vigabatrin have been noted to wear off[2]. Of three patients personally treated with lamotrigine by the author, two have had their seizures reduced by more than 50%, but the third child failed to show any response. Further studies of newer AEDs seem to be indicated.

EPILEPSY WITH MYOCLONIC ABSENCES

Myoclonic absences, which are associated with 3 Hz spike-wave on EEG, are accompanied by severe bilateral rhythmic jerking, usually of the limbs, but the lower face may also be involved. Infrequent generalized tonic–clonic seizures also occur. Poor cognitive progress is usual once the absences commence.

Response to ethosuximide or valproate given singly is very poor, but some children remit on a combination of these two AEDs. Recent experience with lamotrigine is encouraging. Of six children who had lamotrigine added to existing anti-absence drugs, five had more than 75% reductions in seizure frequencies, and three were seizure-free for several months, though relapse later occurred in two[3]. Another study found a greater than 50% reduction in seizures in four out of nine patients given lamotrigine[4]. Further investigation of the efficacy of lamotrigine, and the role of concomitant AED is required.

WEST SYNDROME

Infantile spasms, arrest of cognitive development and hypsarrhythmia characterize West syndrome. ACTH and steroids were the mainstays of treatment for about 20 years. Doses of ACTH 20–40 IU/day are reported to be as effective as much higher levels[5,6]. Following the suggestion that valproate controlled infantile spasms[7], this drug has been used mainly at the regular dose of 20–30 mg/kg/day. Higher doses, up to 100 mg/kg/day, can be more effective, but at the expense of thrombocytopenia and muscle hypotonia[8]. Benzodiazepines are likely to produce only temporary relief. Appropriate doses are clonazepam starting at 0.01–0.03 mg/kg/day or nitrazepam initially 0.5 or 0.1 mg/kg/day[9]. High-dose pyridoxal phosphate (30–400 mg/day) has been reported to be effective in a small percentage of patients[10]. Likewise, some infants respond to i.v. immunoglobulin 100–400 mg/kg given at 2–3 weekly intervals[11,12].

There seems no doubt that vigabatrin should now be an early choice. The largest study relates to 70 children[13]. Forty-seven were aged less than 2 years, and the remainder up to 12.5 years. Thirty-seven had cryptogenic and 33, including 14 with tuberous sclerosis, symptomatic West syndrome. Vigabatrin dosages were 50–150 mg/kg/day in older children and 100–200 mg/kg/day in infants. During the evaluation phase lasting up to 150 days, of 14 patients with tuberous sclerosis, 10 became seizure-free and a further two had a greater than 50% reduction in seizures; of another 18 with symptomatic spasms, six became seizure-free and six had a greater than 50% reduction in attacks; and in the group of 36 with cryptogenic spasms, 12 went into complete remission and nine were more than 50% better. During a longer-term follow-up there was some loss of control, particularly in the cryptogenic group, and partial seizures emerged in eight patients, of whom six had tuberous sclerosis. On the whole, vigabatrin seemed less likely to be effective if the duration of the illness was more than 1 year. Other reports confirm that vigabatrin can be very useful for control of infantile spasms[2,14–17]. The relative efficacies of hydrocortisone and vigabatrin 150 mg/kg/day in the

treatment of infantile spasms in tuberous sclerosis have been explored[18]. Seizures disappeared sooner but relapsed earlier in those treated with vigabatrin.

Lamotrigine can also be effective[4]. After 3 months of lamotrigine, of 13 children treated, two were seizure-free and two had a greater than 50% reduction in seizures, but the remainder were either unchanged or worse. All three children treated with felbamate had initial reductions in seizures of at least 60%, but one relapsed[19].

MYOCLONIC-ASTATIC EPILEPSY

Myoclonic, astatic, myoclonic-astatic, absence with tonic and clonic components and tonic–clonic seizures occur. The EEG initially may be normal, but fast spike-waves or polyspike-waves are usual.

Responses to AEDs of each of the seizure types listed above, as well as of the complete syndrome are considered in this section. Of the established drugs, valproate is considered the first choice, but no controlled trials have been conducted for this or any other therapy. Further details about the propensity of vigabatrin to precipitate[14] or accentuate[4,20–22] myoclonic seizures have been reported in a single case study[23] and in five of a cohort of nine patients[20]. Two reports on lamotrigine are at variance. In one group, of 13 children with non-progressive myoclonias treated with lamotrigine for 3 months, only one had more than 50% reduction in seizures and one was more than 50% worse[4]. On the other hand, in a series of eight children with myoclonic-astatic epilepsy treated with lamotrigine by the author, two became seizure-free and a further five had a greater than 50% reduction in seizures. All those with incomplete control tended to relapse, but over periods of up to 3 years overall improvement has been maintained with dosage adjustments.

When children with astatic seizures are considered as a group, lamotrigine has been found to be very useful[24]. Of 17 children tolerant of lamotrigine, six became seizure-free and four had long-term reduction in seizure frequency. A further three had an early response, but relapsed and did not come under control with dosage adjustments. Felbamate is also reported to have controlled more than 50% of drop attacks in six of 12 children[25].

LENNOX–GASTAUT SYNDROME

The main seizure types are tonic–axial, atonic and atypical absence, but myoclonic, generalized tonic–clonic or partial attacks may also occur. Some of the more recently developed AEDs appear promising but longer established therapies probably still have a place. Valproate has been the main approach, with benzodiazepines, particularly clonazepam or nitrazepam contributing to temporary relief. A ketogenic diet can produce dramatic results[26] and intravenous immunoglobulin[27], or thyrotropin-releasing hormone[28] have their advocates.

Felbamate is the only drug to have been studied with the specific aim of control of Lennox–Gastaut syndrome[29]. Seventy patients participated in a double-blind, placebo-controlled, add-on trial. All had multiple seizure types and a minimum of 90 atonic or atypical absence seizures per month. With an age range of 4–36 years (mean 12 years), this group is on the whole older than patients usually seen in exclusively paediatric practices. Carers' diaries were supplemented by seizure counts obtained by video-EEG for 4-hour periods prior to and at standardized intervals throughout the trial. Prior to dosing, patients later randomized to felbamate had higher counts for atonic seizures. Atonic seizures occurred in 28 patients randomized to felbamate and 22 on placebo. During a maintenance period of 56 days, counts of atonic seizures fell by 44% in the felbamate group and 7% with placebo ($P = 0.002$). Total seizure counts, as recorded by carers, fell by 26% for felbamate and rose by 5% for placebo ($P < 0.001$) during maintenance dosing at 45 mg/kg/day. Four patients in the felbamate group had no seizures of any sort, and five no atonic seizures, during maintenance treatment. At the end of the double-blind study, 70 patients continued in an open-label trial[30]. Total seizures were reduced by more than 50% in 21 of 36 subjects who converted to felbamate after placebo; 12 of 22 with atonic seizures were improved by more than 50% on conversion to felbamate. The results of an investigation of the tolerability and greater efficacy of increasing felbamate dosage to 60 mg/kg/day are awaited[31].

The findings with vigabatrin are rather variable. In an open, add-on, non-controlled trial, six out of 26 patients had an excellent result, but 13 were either unhelped or worse[17]. Of a further seven treated in a single-blind,

placebo-controlled trial, two had a more than 50% reduction in seizures, but four were worse[22]. Other small studies include good responses in three of six[20], one of four[32], 12 of 20[33], one of three[34] and none of six patients[21]. Beneficial effects tend to wear off with time[2].

Lamotrigine also shows rather variable promise. Of 10 children treated on a compassionate basis or in a single-blind, add-on trial, or as part of a pharmacokinetic study, three became seizure-free, three improved by more than 50% and none were worse[4]. In 14 cases treated by the author, eight had a more than 50% improvement, but none became seizure-free and one had an increase in seizures. Moderate or marked improvement has been reported in eight of 25 patients treated on a compassionate basis[35]. Two studies which looked primarily at adults report good results in 10 of 11[36], and 12 of 27 patients[37].

NON-IDIOPATHIC PARTIAL EPILEPSIES, WITH OR WITHOUT SECONDARY GENERALIZATION

Since, in adults, partial epilepsies are those most likely to be resistant to AEDs, the majority of new drugs are first examined in this context.

Most reports related to vigabatrin, but there is no 'blind' study. Scaling-up dose–response assessments[20,23,38] suggest that at least 40 mg/kg/day is needed, although lower doses can be effective[39]. Most authors use 80–100 mg/kg/day, but as much as 175 mg/kg/day has been given[2]. Between one- and two-thirds of patients benefit from addition of vigabatrin to previous therapy[17,20,21,32,38,40,41]; but a few are made worse[17,20,41].

Of 15 children treated with add-on lamotrigine for 3 months, three improved substantially and one deteriorated[4]; and of a further nine, observed personally, two have improved and two deteriorated.

Two reports, totalling 20 children, suggested felbamate can be effective in abolishing or reducing partial seizures[25,42].

A single communication has found that three-quarters of children treated with stiripentol in a single-blind, add-on trial responded[43].

Reports on the use of gabapentin in children are awaited. Meanwhile 20–40% improvement has been recorded in adults with resistant partial seizures[44].

PROGRESSIVE MYOCLONUS EPILEPSIES

These are usually secondary to biochemically definable disorders, such as ceroid lipofuscinoses, sialidoses or mitochondrial encephalopathies; or to Baltic/Mediterranean myoclonus or Lafora disease. Valproate continues to be the most used AED, but there are anecdotal reports of improvement with lamotrigine, particularly in ceroid lipofuscinoses. Phenytoin leads to worsening in Baltic/Mediterranean myoclonus.

LANDAU–KLEFFNER SYNDROME

Acquired aphasia is associated with multifocal spike and spike-wave discharges. Seizures, generalized tonic–clonic, partial, or atypical absences are infrequent and present in 75% of cases. There is a close relationship with epilepsy with continuous spike-wave during slow sleep. After testing a wide range of AEDs, it has been concluded that valproate, ethosuximide and benzodiazepines are most likely to be effective[45]. There is also considerable support for the use of steroids, initially in high dosage and continued over a prolonged period at a lower maintenance dose[46]. Single cases have been improved by lamotrigine.

KOJEWNIKOW SYNDROME

Epilepsia partialis continua, not secondary to a definable lesion, remains an intractable problem.

UNWANTED EFFECTS OF NEWER AEDS

Vigabatrin

The main undesirable features relate to behaviour. Agitation led to discontinuation in about 5–10% of all cases described. Somnolence was sometimes a problem. The worsening of myoclonic seizures recorded by some observers has already been noted.

Lamotrigine

A sensitivity rash is most likely to occur if lamotrigine is added to valproate monotherapy. The risk can be minimized by starting lamotrigine at a very low dose (0.02 mg/kg/day) and

escalating very slowly. Drowsiness and unsteadiness may result from high dosage.

Felbamate

Anorexia, vomiting and somnolence are reported. Fatal cases of aplastic anemia and hepatic failure now preclude its use in all but the most resistant cases.

Stiripentol

Anorexia, drowsiness and vomiting may complicate the use of stiripentol.

CONCLUSIONS

For most of the severe epilepsies of childhood, the newer AEDs have some beneficial effects in some children. On the whole, vigabatrin seems better for epilepsies with partial or secondary generalized seizures and lamotrigine for those of generalized onset. The merits of stiripentol and gabapentin are in the early stages of definition. A multicentre blind comparison of newer AEDs in the treatment of severe epileptic syndromes of childhood should be conducted.

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