Acta Neurol. Belg., 2011, **111**, 175-182

Review articles

Epileptic syndromes: differential treatment in infants, children, and adolescents

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Working group of francophone reference centres for refractory epilepsy

Abstract

This paper proposes therapeutic guidelines for the management of some epileptic syndromes in infants, children, and adolescents, based on available medical literature and clinical practice in the French Community of Belgium. The guidelines address both epileptic encephalopathies (West syndrome, Lennox-Gastaut syndrome, and Dravet syndrome) and idiopathic epilepsies (typical absence seizures, epilepsy with centro-temporal spikes and juvenile myoclonic epilepsy).

Key words: Epilepsy syndromes; infants with epilepsy; children with epilepsy; adolescents with epilepsy; antiepileptic drugs.

Introduction

Several new antiepileptic drugs (AEDs) have been commercialized during the last 15 years which provide to clinicians new therapeutic options. Treatment of epilepsies in infancy and childhood is different from treatment of epilepsies in adulthood. There are several reasons for this. Firstly, the underlying causes of epilepsies differ, depending on the age group. Genetic susceptibility to seizures and structural malformations of the cerebral cortex are more prominent in children, and brain networks involved in seizure generation and propagation vary according to the aetiology and localisation. Secondly, maturation results in a changing balance between excitation and inhibition in brain networks, explaining why an anti-epileptic drug that is effective in adults may be proconvulsive in the immature brain. Thirdly, the pharmacokinetics of some drugs differs in infants compared with children and adults.

The aim of this paper is to propose guidelines for the treatment of some relevant epileptic syndromes of infancy and childhood. Some of them are classified among idiopathic epilepsies, i.e. epilepsies resulting from a known or presumed genetic defect (1), whereas others belong to the group known of epileptic encephalopathies, i.e. a very difficult to-treat-group of epileptic syndromes in which the epileptiform abnormalities may contribute to neurological dysfunction (2).

Among the idiopathic epilepsies, we selected three syndromes: childhood absence epilepsy, benign epilepsy with centro-temporal spikes and juvenile myoclonic epilepsy. Altogether, these account for 30 to 50% of all cases of epilepsy, occurring between the ages of 1 and 15 years (3, 4, 5). Epileptic encephalopathies that will be discussed in this article include West syndrome, Dravet syndrome and Lennox-Gastaut syndrome. Epilepsies with continuous spike-waves during slow-wave sleep (CSWS) were discussed in a previous issue of this journal (6).

Our guidelines are based on published studies with special consideration of the few class I studies performed in children, and to the guidelines set out by the International League Against Epilepsy (7). We also took into account the opinions of international experts (8, 9) and the paediatric epileptologists who belong to our working group.

1. West syndrome and step-by-step treatment recommendations

West syndrome consists of a characteristic triad of epileptic spasms, arrest and later regression of psychomotor development and hypsarrhythmic EEG. The cause of this epilepsy can be identified in about two-thirds of the cases, and control of the seizures and suppression of hypsarrhythmia should be obtained as quickly as possible in order to protect cognitive development and limit the risk of refractory epilepsy.

Vigabatrin (VGB) is considered as the first choice drug in Europe and particularly in Belgium (10) and should be started at a dosage of 100 mg/kg/day. If the epileptic spasms or hypsarrhythmia are not controlled, dosage should be increased to 150 mg/kg/day after one week (11). VGB allows the control of seizures in 40% to 70% of cases, with a recurrence rate of 10% to 30%. West syndrome associated with tuberous sclerosis is a subgroup that responds particularly well to VGB.

If a 2-weeks VGB trial has failed, it should be tapered off and another drug should be started. The second choice depends on the aetiology. In cryptogenic cases, restricted symptomatic lesions (focal cortical dysplasia, vascular insult, tuberous sclerosis), or some chromosomal anomalies, corticosteroids should be started. Some studies suggest that high doses of ACTH are more efficient than oral corticosteroids (12). However, as low doses of ACTH may still be effective with limited side effects, we propose an ACTH dose escalation scheme, depending on the response (13) (Table 1).

ACTH seems to be more effective than VGB, and suppresses spasms in 50% to 90% of cases, with recurrence in 20% to 40% of cases. The United Kingdom Infantile Spasms Study (UKISS) trial compared the effects of hormone treatments (prednisone or ACTH) with those of VGB (14, 15). Infants enrolled were randomly assigned to hormone treatment (n = 55) or VGB (n = 52) and were followed up until clinical assessment at 12-14 months of age. Hormone treatment was initially more effective than VGB in controlling spasms, but not at the final assessment at 12-14 months. However, better initial spasm control by hormone treatment in subjects with no identified underlying aetiology led to improved developmental outcome (15).

In cases of West syndrome associated with severe encephalopathy (lissencephaly, Aicardi syndrome, metabolic disease, severe neonatal asphyxia, ...), we recommend topiramate (TPM) as a second choice since the benefits of corticosteroid treatment are likely to be very low, considering its side-effects and the underlying aetiology. The doses of TPM that are needed to control spasms may be very high, up to 20-30 mg/kg/day. Three open studies (16, 17, 18) demonstrated spasm control in 45% of cases, with efficacy maintained in the long-term and good tolerability.

For the third step, epilepsy surgery should still be considered if a focal lesion is identified or suspected. In the remaining cases, drug combinations should be considered. Bitherapy should be encouraged with either drugs previously shown to provide partial symptom control (TPM or VGB) or other AEDs, for instances valproate (VPA) or benzodiazepines.

For the fourth step, a ketogenic diet (KD) consisting of a high-fat, low-carbohydrate, low-protein regimen can be prescribed and supervised by a nutrition support team. This treatment showed efficacy against various seizure types in children in a recent, well-designed, controlled study (19). In a retrospective study, the KD stopped spasms in nearly two-thirds of cases, and had fewer side effects and relapses than ACTH (20).

2. Lennox-Gastaut syndrome (LGS) and step-by-step treatment recommendations

This syndrome is characterised by polymorphic seizures (tonic fits, atypical absences, as well as atonic and myoclonic seizures), neuropsychological decline, and slow spike-waves with fast nocturnal rhythms on EEG.

Unlike the conventional management of epilepsy, which aims for complete freedom from seizures, the aim of LGS treatment is to suppress or reduce the frequency of the more disabling seizure types (21, 22). Physicians should always be vigilant for adverse drug effects and should not increase doses or number of drugs when significant adverse effects are already present.

As a first step, monotherapy should be implemented. Although there is no randomized study to date, valproate (VPA) is considered the first-choice drug (8, 9). VPA, a broad-spectrum AED, has been reported to be effective in all types of seizures seen in LGS.

For the second step, a second drug should be introduced. TPM and lamotrigine (LTG) are valid candidates, as two class I studies have confirmed their effectiveness. LTG (23) and TPM (24) were shown to significantly decrease the frequency of drop attacks and tonic-clonic seizures.

For the third step, another bitherapy including VPA and the alternative option from step 2 should be implemented.

For the fourth step, felbamate (FBM) should be added. FBM was found to be effective in patients with LGS in a randomized double-blind, placebo-controlled adjunctive therapy trial (25). The percentage of patients experiencing at least 50% reduction in total seizure frequency was 50% for the FBM group compared with 11% in the placebo group. However, FBM has been rarely associated with aplastic anaemia and hepatic failure, with some fatalities. The suggested management strategy is to perform routine laboratory blood tests every 2 weeks, and to discontinue the drug if no substantial

Table 1

Dosage regimens of antiepileptic drugs for the different syndromes

AED	SYNDROME	DOSE mg/kg/d	TITRATION
VGB	West	100-150	First week: 100 mg/kg/day Second week depending on the response: 150 mg/kg/day
ACTH	West		Start at a low dose: 3 IU/kg/day im, every morning After 2 weeks of treatment: – in the case of response: taper gradually – in the case of no response: 6 IU/kg/day for 2 weeks After 4 weeks of treatment: – in the case of response: taper gradually – in the case of no response: 12 IU/kg/day for 2 weeks After 6 weeks of treatment, taper gradually
TPM	West Lennox-Gastaut JME	20-30 3-10	Start at 1 mg/kg/day. Increments of 1-3 mg/kg/day at 3-day intervals Titrate more slowly for the other conditions: Children < 25 kg: start at 1 mg/kg/day. Increments of 1 mg/kg/day at 2 week intervals Children > 25 kg: start at 25 mg/day. Increments of 25 mg at 2 week intervals
VPA	Lennox-Gastaut Dravet CAE BECTS JME	20-30	Children < 30 kg: start at 10 mg/kg/day in three doses if drops or sirup Increments of 10 mg/kg/day at 3-day intervals Children > 30 kg: start at 300 mg/day in one or two doses
LTG With VPA	Lennox-Gastaut CAE JME	1-5	Start at 0,15 mg/kg/day once daily weeks 1 and 2 0,3 mg/kg/day weeks 3 and 4. Thereafter increments of 0,3 mg/kg at 2-week intervals
LTG with enzyme inducing AED	Lennox-Gastaut	5-15	Start 0.6 mg/kg/day weeks 1 and 2 1.2 mg/kg/day weeks 3 and 4 Thereafter increments of 1.2 mg/kg at 2-week intervals
LTG monotherapy (over 12 years)	CAE	2-8	Start at 25 mg/day weeks 1 and 2 50 mg Weeks 3 and 4 Thereafter increments of 50 mg at 2-week intervals
ESM	CAE	20-30	Start at 5-10 mg/kg/day Thereafter increments of 10 mg at 1-week intervals
CBZ	BECTS	10-20	Start at 5 mg/kg/day Thereafter increments at 1-week intervals
OXC	BECTS	30-40	Start at 10 mg/kg/day Thereafter increments of 10 mg at 1-week intervals

AED: antiepileptic drug; BECTS: benign epilepsy with centrotemporal spikes; CAE: childhood absence epilepsy; CBZ: carbamazepine; ESM: ethosuccimide; JME: juvenile myoclonic epilepsy; LTG: lamotrigine; OXC: oxcarbazepine; TPM: topiramate; VGB: vigabatrin; VPA: valproate.

clinical benefit is observed after 3 to 6 months of therapy. Rufinamide is a new AED that was shown to be efficacious and well-tolerated in LGS (26), but this drug is not yet available in Belgium for its use in children.

Finally, a non-pharmacological management can also be taken into consideration.

KD is an interesting therapeutic option in refractory LGS, as evidenced by a recent controlled study (27).

Several open-label, prospective trials have been performed to assess the response of patients with LGS to vagus nerve stimulation (VNS) (28, 29, 30). The effects of VNS varied, depending on the seizure type. Best effects were observed in atonic seizures and tonic seizures. Side-effects were minor and transient. Quality of life was improved in responders. Based on these results, VNS is likely to be an effective and safe adjunct therapy in the treatment of LGS.

In addition, complete or partial callosotomy is a palliative surgical treatment for children with LGS who have drop attacks. This surgical procedure may also be considered for intractable tonic seizures,

particularly in cryptogenic cases (31). The morbidity may be significant in children having a good level of language and cognitive functioning (32), and there is a tendency for seizures to return after 2 years. Therefore, VNS is now recommended prior to callosotomy (22).

In very specific cases, focal resection may be discussed, especially if a focal lesion or regional epileptogenic zone is identified.

3. Dravet syndrome (severe myoclonic epilepsy in infancy) and step-by-step treatment recommendations

Described in 1978 by Charlotte Dravet (33), this clinical entity appears to be responsible for 7% of severe epilepsy cases starting before the age of 3. Three stages of development are described. The first stage of development is onset with first seizure, which always occurs within the first year of life, around the fifth month. Generally provoked by fever, it may be generalized or focal and its duration may be long, febrile status epilepticus being very frequent. The second stage begins in the second year of life. Myoclonus can occur with a frequency ranging from rare and mild to very severe and frequent. In some borderline cases, myoclonia are even completely absent. Because of the possible absence of myoclonia, the term "severe myoclonic epilepsy in infancy" has been replaced by "Dravet syndrome" (2). Upon reaching the age of two, all patients have a developmental retardation, and cognitive abilities and language skills cease to develop. Following a period of prolonged generalized seizures, these children may present transient ataxia, which may eventually become permanent. The third stage is associated with improvement of seizures, but with serious residual mental and neurological impairment. Although metabolic exams and brain imaging are usually normal, 50% to 80% of cases demonstrated *de novo* mutations in the neuronal sodium channel alpha subunit SCNIA (34).

As a preventive measure, hyperthermia should be avoided, and fever should always be adequately controlled (35). When seizures occur, they should be promptly treated using fast acting benzodiazepines (intra-oral midazolam or intra-rectal diazepam).

As Dravet syndrome is a severe epileptic encephalopathy, it often necessitates polytherapy, but one should not use more than three AEDs simultaneously.

For the first step, VPA should be administered.

In the second step, TPM should be added to VPA (36).

For the third step, small doses of benzodiazepines such as clonazepam, clobazam, and lorazepam may prove effective for short periods.

For the fourth step, an association of stiripentol, VPA, and clobazam may be effective (37). Ethosuccimide (ESM) and levetiracetam (LEV) may be valid alternatives in case of myoclonic seizures and complex absences.

The following AEDs should be avoided because of the risk of seizure exacerbation: phenytoin (PHT), LTG (38), carbamazepine (39) (CBZ), and VGB (40).

4. Childhood absence epilepsy (CAE) and step-by-step treatment recommendations

CAE is not synonymous with any type of absence seizures starting in childhood. The ILAE broadly defines it as a syndrome with frequent (several to many per day) and typical absences, school age at onset (peak at 6-7 years), and common remission. The EEG is typical, with generalized spike-slow wave discharges of 3Hz.

As a first step VPA, LTG and ESM may be recommended.

In a double-blind, randomized, controlled clinical trial, Glauser (41) compared the efficacy, tolerability, and neuropsychological effects of ESM, VPA, and LTG in 453 children with newly diagnosed CAE. ESM and VPA were significantly more effective than LTG in controlling seizures without causing intolerable side effects. However, ESM had a significantly smaller negative effect on attention measures as compared to VPA. Therefore, we recommend ESM as first choice, and VPA as second step.

LEV may be a valuable AED in the treatment of patients with CAE (42, 43), but further studies are needed.

For the third step, if monotherapy is not successful, a VPA/LTG bitherapy is recommended, with VPA given at moderate doses and LTG administered at low doses, taking into account the beneficial pharmacokinetic interaction between LTG and VPA. The combination of VPA and ESM is also considered a valid option.

The following AEDs should be avoided because they may aggravate seizures: CBZ, oxcarbazepine (OXC), PHT, phenobarbital (PB), tiagabine and VGB (44).

5. Benign epilepsy with centrotemporal spikes (BECTS) and step-by-step treatment recommendations

This syndrome is characterized by onset after the age of 3 years, normal development, infrequent and

brief partial seizures, paradoxically abundant interictal EEG abnormalities, and spontaneous remission before the end of adolescence. Anamnesis, physical examination, and awake and sleep EEG will lead to the diagnosis. In the last 10 years, there have been several studies indicating that patients with BECTS have a variety of cognitive disturbances including language impairment, memory dysfunction, and auditory processing difficulties. The data suggest that perhaps one-half or more reported patients manifest one or more of these disorders (4, 45, 46). If the child presents psycho-motor impairment or learning disability, a neuropsychological and speech evaluation should be performed. In a few cases, cognitive or severe language disorders associated with continuous spike waves during sleep (CSWS) may develop (6). Massa (47) has established some EEG prediction criteria for this condition.

For the first step, since the prognosis is excellent, AEDs should be avoided or they should be started only if the seizures are frequent (47).

For the second step, VPA and CBZ/OXC were proposed by ILAE (7). However, we should keep in mind that CBZ may in a small proportion of cases provoke a cognitive, behavioural, or language regression associated with CSWS (48).

In the third step, LEV has been shown in two open studies to be effective and well-tolerated in children with BECTS (50, 51).

The following AEDs should be avoided: PB and LTG (5) which may aggravate BECTS.

6. Juvenile myoclonic epilepsy and step-by-step treatment recommendations

Juvenile myoclonic epilepsy (JME), which develops around puberty, is characterized by bilateral, arrhythmic, irregular myoclonic jerks predominantly in the arms, soon after awakening and without disturbance of consciousness. JME continues to be under-or misdiagnosed because the myoclonic jerks may occur briefly or infrequently and are rarely reported spontaneously by patients. JME is frequently associated with generalized tonic-clonic seizures (> 90%). Infrequent absences may also be observed.

JME is an idiopathic generalized epilepsy with complex inheritance. Depending on racial/ethnic and geographic origin, the JME trait is transmitted as a mendelian dominant or recessive trait or as complex oligogenic traits (52).

Counselling on lifestyle is essential, and precipitating factors such as lack of sleep, early or sudden awaking, and excessive intake of alcohol should be avoided (53).

Patients with JME usually require lifelong AED treatment even if seizure freedom is achieved, as relapse rates are high following AED withdrawal (54). However, this notion has been recently challenged in a long-term study on the development of classic JME in 23 patients, which concluded that one-third of JME patients had complete remission of seizures and did not require , AEDs anymore (55). To identify prospectively those JME patients who will be able to discontinue AED treatment is the scope of further studies.

There are no class 1 studies to guide the initial therapy of JME.

In the first step, VPA is the AED of choice, with good seizure control obtained in about 80% of cases (56). VPA is effective in all three seizure types of JME. Moderate doses (800 to 1000 mg) frequently control seizures.

For the second step, LEV has recently been approved by the US Food and Drug Administration as adjunctive therapy for controlling myoclonic seizures in patients with JME (57). Two randomised, double-blind, placebo-controlled studies (58) support the use of adjunctive LEV for JME, juvenile absence epilepsy, and generalized tonic-clonic seizures on awaking.

For the third step, a randomized open-label study showed that TPM at moderate doses may be an effective, well-tolerated alternative to VPA (59).

In the fourth step, LTG may be an option, though it may aggravate myoclonus (58).

PHT and CBZ should be avoided. They are the AEDs with the most prominent aggravating effect on JME, exacerbating both absence and myoclonic seizures and even inducing new seizure types or leading to atypical myoclonic status epilepticus (44, 60).

Conclusion

The growing number of available therapies has increased the need to identify optimum treatments for epilepsy syndromes. The ILAE treatment guidelines (3) conclude that: “There is an especially alarming lack of well-designed, properly conducted randomized controlled trials for patients with generalized seizures/epilepsies and for children in general”. Only a few class I studies exist for West syndrome, Lennox-Gastaut syndrome, CAE and JME. Thus, expert opinion based on available medical literature and experience is useful to identify adequate treatment options (8, 9). New AEDs appear to offer better tolerability and may thus contribute to preserve cognitive functions and behavioural abilities. Non-pharmacologic interventions such as

epilepsy surgery, VNS and KD must be considered as therapeutic options in case of failure of medical management. Today, there is hope for an improved quality of life for children and adolescents with epilepsy. However, the large number of therapeutic options remains a challenge for the physician attempting to select the best treatment for his patient.

Acknowledgments

All authors of this article participated in a consensus meeting, with the discussion forming the basis of this review. The first draft of the paper was prepared by Martine Foulon, with Sophie Ghariani, Benjamin Legros, Michel Ossemann, Kenou Van Rijckevorsel, Pascal Vrielynck and especially Patrick Van Bogaert participating in drafting the manuscript.

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