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The need for broad spectrum and safe anti-epileptic drugs in childhood epilepsy

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Abstract

In this short review, the challenges in the treatment of children with epilepsy are highlighted. It is argued that in many cases, broad spectrum anti-epileptic drugs are the best and logical choice at the start of the treatment. At this moment, valproate, lamotrigine, topiramate, levetiracetam and possibly zonisamide can be considered as safe broad spectrum anti-epileptic drugs.

Key words: Childhood epilepsy; treatment; AED; lamotrigine; valproate; levetiracetam; topiramate; side-effects; broad spectrum.

Introduction

Childhood epilepsy poses unique challenges to the treating physician. First of all, and more than in adults, epilepsy should be considered as a symptom of an underlying brain dysfunction and a thorough diagnostic work-up has to be done in many children presenting with epileptic seizures. This includes detailed neuro-imaging, genetic and tailored metabolic work-up. Not uncommonly, this diagnostic work-up, together with the uncertainty about seizure type delays the exact epileptic syndrome diagnosis. Second, adequate treatment has to be considered. Only in a few circumstances, the choice can be not to start treatment. For instance, in benign rolandic epilepsy with only nightly, partial seizures without secondary generalization, one can discuss with the parents not to start anti-epileptic medication (Peters *et al.*, 2001). However, for more than 90% of the children with proven epilepsy, preventive treatment has to be initiated and in the large majority, first line treatment equals anti-epileptic drugs. In some cases, such as hemi-megalencephaly or Sturge-Weber syndrome with status epilepticus and acquired hemiparesis, early referral for epilepsy surgery is needed (Cross *et al.*, 2006), but still in these cases anti-epileptic drugs are necessary during the pre-surgical work-up.

How to make an adequate treatment choice?

A first issue is what to expect from a treatment with anti-epileptic drugs. The most important and obvious outcome parameter is a total prevention of future seizures or a 100% seizure reduction. A frustration in epilepsy is that we cannot predict full seizure control in most children. In this respect, the golden-standard randomized controlled registration trials or even the international guidelines, as valuable as they might be (French *et al.*, 2004; Beghi, 2004, Dunkley *et al.*, 2006; Glauser *et al.*, 2006) are of little value in a particular child with seizures. They are useful tools in a rather statistical discussion with the parents. We can only estimate that in a particular epileptic syndrome, treatment with drug x gives a chance of y % that the child will become seizure free (see Geelhoed *et al.*, Epilepsia 2005). But the problem is that the delineation of the syndrome is not always possible at the onset of the seizures. Who can predict that a 4 year-old normal child presenting with 2 tonic-clonic seizures will go on to develop the devastating Lennox Gastaut syndrome? Who can predict that a 9 month-old normal developing infant presenting with a first period of long lasting febrile seizures will eventually be diagnosed with severe myoclonic epilepsy of infancy? In the latter case, EEG studies typically remain normal for another year before slowing and interictal epileptic activity is seen.

Another problem to face is that we have a large variety of anti-epileptic drugs that can indeed prevent seizures, but they do not stop or fundamentally influence the ongoing epileptogenic process in the brain (for a review see Lagae *et al.*, 2003). In clinical practice on the other hand, we have the impression

that an earlier start of effective anti-epileptic drugs does have a positive influence on seizure frequency and also on the other crucial outcome parameter in childhood epilepsy: the preservation of a normal cognitive development. It was shown that early control of idiopathic seizures in infants with an onset before the age on 1 year is an important protector of cognitive development (Vanderlinden and Lagae, 2004). In other words, although we realize that we cannot stop the epileptogenic process, full control of the seizures is an important and in many cases the only way to prevent cognitive problems in many children with epilepsy.

The very important distinction between partial and generalized seizures is not always straightforward in children. Especially in very young child seizure characterization is difficult and sometimes ictal (video) EEGs are necessary the confirm the exact nature. The introduction of the notion of 'dialeptic seizures' illustrates the fact that the clinical differentiation between typical absence and hypomotor complex partial seizures is difficult in young children (Luders *et al.*, 1998). Nowadays, more and more drug studies in infants with epilepsy require prolonged video EEG to verify that the seizures are partial or generalized. Second, seizure type can change during the course of the epileptic disease. Typical absence seizures in a 6 year old child can disappear after a few years and later myoclonic jerks can arise in the same child. Long-lasting and apparently generalized febrile seizures can be followed after a couple of years by typical complex mesiotemporal seizures. Third, in a child different seizure types can occur at a certain time in the disease process. For instance, in a young adolescent with Lennox Gastaut syndrome both partial and different generalized seizures can be seen.

The question now is how to make an adequate choice in the more than 15 available anti-epileptic drugs? The academic answer is that this decision should be based on the epileptic syndrome: the nature of the epileptic syndrome determines the treatment and prognosis. But here starts the problem. At this moment, there is no short list of the optimal drug per epileptic syndrome. This is not surprising because in many epileptic syndromes the underlying cause is not fully known yet. For instance, in infantile spasms, and especially when these are associated with tuberous sclerosis, vigabatrine often gives a dramatic and immediate cessation of the seizures (Elterman *et al.*, 2001). But we do not understand why exactly this increase of inhibition caused by the increased GABA concentrations is particularly favorable in this very specific epileptic situation. Or take the spectrum of benign partial epilepsy, with epilepsy types ranging from infrequent benign rolandic seizures at night to frequent seizures and continuous spike wave discharges during the night and consequently cognitive deterioration. It seems difficult to prescribe the optimal anti-epileptic drug that would cover this full spectrum of phenotypic variations of a presumably unique genotype.

Even in the epileptic syndromes with a known (genetic) background, there is no obvious link with treatment. In autosomal nocturnal frontal lobe epilepsy, different mutations in the acetylcholine receptor have been described, but at this moment this has no everyday implications in the choice of an optimal AED (DiCorcia *et al.*, 2005). The expanding world of sodium channel mutations in generalized epilepsies has not changed our prescribing habits fundamentally, although clinical experience learns us that AEDs with a major influence on the sodium channel (such as carbamazepine and lamotrigine) might aggravate the epilepsy in some children (Ceulemans *et al.*, 2004).

The notion 'broadspectrum anti-epileptic drugs'

Therefore, at this moment, it seems most straightforward to use those anti-epileptic drugs that are effective against the most common seizure types in childhood epilepsy. The other condition is that these drugs are safe: they should have minimal side effects and should especially be safe for cognition and behavior. But perhaps as important is the fact that they should not exacerbate seizures when incorrectly used. Taking all these conditions together it is clear that the optimal broad spectrum anti-epileptic drug does not exist yet.

What is known about the broad-spectrum profile of the available major anti-epileptic drugs? In the older category, valproic acid seems to be the anti-epileptic drug with the broadest spectrum. This is mainly based on long lasting clinical experience and not on rigorous (registration) studies (for a review see Aldenkamp *et al.*, 2006). Actually, valproic acid is a logical first line drug in many childhood epilepsy syndromes. Strict contra-indications are well known: possible metabolic diseases with liver involvement and very young age are indeed risk factors. Weight gain and behavioral problems are common and are possible reasons for changing to another medication. Valproic acid also exist in intravenous form, which makes it suitable in children in whom oral medication has to be stopped for diagnostic and surgical interventions. It also becomes a drug that can be used for status epilepticus although rigorous studies in young children are not available yet (Misra *et al.*, Neurology 2006).

Carbamazepine and the newer but related oxcarbazepine are very effective medications for partial epilepsies but have a much more restricted spectrum. For many physicians, it remains the first choice in the common benign rolandic epilepsy. This should not be taken as standard: in German speaking countries sulthiame definitively is the first choice for rolandic epilepsy (Rating, 2000). It is known that carbamazepine and oxcarbazepine can aggravate generalized seizures or even induce generalized seizures (Liu *et al.*, 2006). Carbamazepine or oxcarbazepine should therefore not be the first choice for typical absence epilepsy and other primary generalized epilepsies. In cases where seizure classification is a problem, these 2 drugs are not the best to start with.

In the category of the so-called newer anti-epileptic drugs, 3 drugs fulfill the criteria of broad-spectrum to some extent: lamotrigine, topiramate and levetiracetam. Lamotrigine is already available for a long time and is indeed effective in many epileptic seizure types and syndromes. In the guidelines of the American Academy of Neurology, published in 2004, lamotrigine was the only new anti-epileptic drug that got an A/B recommendation for use in absence epilepsy, based on the available literature at that time (French *et al.*, 2004). The only disadvantage of lamotrigine is that it can induce or worsen myoclonic seizures, although this possible side effect should not be overestimated (Guerrini *et al.*, 1998). It user-friendliness is also somewhat limited because of its important interactions with valproic acid. Careful and slow titration is necessary; it is not unusual to reach optimal dosages only after 8 weeks.

Topiramate is a very potent anti-epileptic drug that has been extensively studied, also in childhood epilepsy. In the registration trials, it was shown to be effective in all seizures types. For instance, in the Lennox Gastaut trial, topiramate not only significantly reduced the total seizure frequency, but also the frequency of the different seizure types that occur in that syndrome: generalized tonic-clonic, atypical absences, myoclonic and atonic seizures (Sachdeo *et al.*, 1999; Glauser *et al.*, 2000). It is also one of the few drugs that can be used in refractory infantile spasms , as was shown in the studies of Glauser *et al.* (Glauser *et al.*, 1998; Glauser *et al.*, 2000). A possible drawback is the cognitive side effect profile of this drug. In contrast to all other anti-epileptic drugs that can have a negative influence on attention and working memory (Lagae, 2006), topiramate also can influence a more specific cognitive process, namely language and more specifically word finding. The nature of this specific side-effect has not been elucidated yet, but it should be stressed that with the more recent guidelines, using lower maintenance dosages of topiramate in monotherapy, this side effect is not as frequent (Silberstein *et al.*, 2005). In this respect, topiramate becomes a true first line broad spectrum anti-epileptic drug.

Levetiracetam was introduced about 10 years ago in most countries and is increasingly being used in childhood epilepsy (Lagae *et al.*, 2005). It is known as a very well tolerated drug with few side effects, and also as an anti-epileptic drug that could be introduced relatively rapid without drug interactions. Clinical experience however has learned that also this drug can cause side effects. Especially, behavioral side effects are seen in children with epilepsy. This seems to be linked to pre-existing behavioral or mental problems (Dinckelacker *et al.*, 2003; Opp *et al.*, 2005). Other side effects are indeed rare and transient. At the efficacy level, levetiracetam is effective both in partial and generalized epilepsies. However it is not an optimal drug for pure absences seizures. Levetiracetam, as well as topiramate, were shown to be effective in one of the most frequent generalized epilepsy syndromes in adolescence and adulthood, namely juvenile myoclonic epilepsy (Specchio *et al.*, 2006; Biton V., 2005).

Conclusion

In summary, only a few drugs can be called 'broadspectrum' anti-epileptic drugs and can be used as first line drugs in a child presenting with epilepsy: valproic acid, lamotrigine, topiramate and levetiracetam. Evidence is accumulating that zonisamide might become another broad-spectrum AED. The side effect profile, and especially the effect on cognition and behavior become discriminating factors in the choice of the optimal drug. This broad-spectrum view on anti-epileptic drugs should definitively not be understood as the easy way to treatment in childhood epilepsy. Diagnosing the correct epilepsy syndrome remains crucial for diagnostic guidance and prognostic purposes. The point is that we now can start with a safe treatment in the majority of the children with epilepsy during our diagnostic work-up, after which we can tailor our treatment according the diagnostic, clinical background, and the correct epilepsy syndrome.

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