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A Risk-Benefit Assessment of Treatments for Infantile Spasms

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Contents

Abstract

Infantile spasms are a devastating epileptic encephalopathy of the young child. The continuing spasms and hypsarrhythmia have a deleterious effect on brain maturation and further cognitive development.

Corticotropin (adrenocorticotropic hormone) or corticosteroids have been the gold standard treatment for the last 40 years, but there is little agreement on the best agent to use, or the dosage and duration of the treatment. Despite this empirical approach, corticotropin or corticosteroids are effective in controlling spasms and normalising electroencephalograms in about 60% of cases. The major concern with this treatment is the occurrence of frequent and severe adverse effects.

The introduction of vigabatrin in the 1990s improved the outcome of infantile spasms. Vigabatrin shows an efficacy at least equal to that of corticosteroids, and even higher in specific groups such as those with tuberous sclerosis. The major advantages of vigabatrin are the ability to initiate treatment at the full dosage, rapid efficacy, suitability for outpatient treatment and particularly good tolerability with only minor adverse effects. Recently, however, the safety of vigabatrin

has caused concern since a specific visual field loss has been reported in treated adults.

The current problem is determining the risk-benefit ratio of vigabatrin and corticosteroids/corticotropin in children with infantile spasms, and to specify the groups where their use could be optimal. Visual field loss is usually asymptomatic and can be detected only by perimetric visual field studies. In children, especially in the young or disabled, it is difficult if not impossible to detect the visual field loss and it is not yet known if children are at higher or lower risk for this adverse effect. Until a clear answer about the occurrence of this adverse effect in children has been established through randomised study, vigabatrin may still be considered first-line therapy in infantile spasms. Children who do not achieve a good response to vigabatrin should be switched to corticotropin/corticosteroid therapy.

Despite the efficacy of corticosteroids and vigabatrin, the use of the conventional antiepileptic drugs, the newly developed antiepileptic drugs and some promising results with ketogenic diet, 25 to 30% of patients with infantile spasms continue to have spasms and experience psychomotor regression. These drug-resistant patients could be candidates for surgery.

Infantile spasms are the most frequent epileptic syndromes of the first year of life. According to the classification of the International League Against Epilepsy (ILAE), infantile spasms are characterised by the association of epileptic spasms, psychomotor regression and a specific electroencephalogram (EEG) pattern with paroxysmal interictal activity called hypsarrhythmia.[1] Epidemiological studies suggested that 1500 to 2000 new cases occur every year in the US.[2]

This syndrome is age specific – 85 to 90% of cases begin before 1 year of age. Spasms with a later onset are also reported but they will not be discussed in this review.

Infantile spasms can be categorised into 2 major groups. In the symptomatic group, almost 80% of cases, a specific aetiology can usually be determined. Various underlying brain pathologies can be observed. They are either diffuse (as in metabolic diseases, Aicardi syndrome, lissencephaly and holoprosencephaly) or more localised (as in hemimegalencephaly, cortical dysplasia and tuberous sclerosis). In the cryptogenic group (10 to 15%), a cerebral lesion is highly suspected but cannot be demonstrated by currently available neuroradiological means. Reports of focal hypometabolism on positron emission tomography (PET) in several patients of the cryptogenic group would suggest that these groups have to be redefined.[3] In a small proportion of cases, infantile spasms appears to be idiopathic. The outcome is favourable and children recover completely.[4,5] The term infantile spasms has been used to refer to either a seizure type or an epilepsy syndrome, causing confusion in the medical literature. Recent recommendations tend to distinguish the seizure type (infantile spasms) and the epilepsy syndrome (infantile spasm syndrome or West syndrome).

The pathophysiological basis of this syndrome has not been yet clarified. A trigger cortical zone may activate a cortico-subcortical circuit involved in generating spasms. Whether the cortex is diffusely or focally abnormal, the whole brain activity is disturbed. This is obvious from the clinically generalised aspect of seizures and on the hypsarrhythmia shown on EEGs. This EEG pattern is attributable to the characteristics of the immature brain at the age of occurrence of spasms. They include hyperexcitability, a high tendency to diffusing paroxysmal activity and the inability to synchronise spike activity of both hemispheres.

Children with infantile spasms rapidly develop a regression in psychomotor skills. In patients with diffuse brain malformation, it is difficult to determine the contribution of hypsarrhythmia because of pre-existing psychomotor delay. On the contrary,

the deleterious effect of hypsarrhythmia is obvious in cryptogenic cases. In this group, there is a clear break in the previously normal psychomotor development. Therefore, the goal of treatment is to achieve a rapid control not only of the spasms but also of hypsarrhythmia.

This devastating epileptic encephalopathy was controlled for the first time by corticosteroids. Since their effect was identified in 1958, corticotropin (adrenocorticotropic hormone) or corticosteroids have become the treatment of reference in infantile spasms.[6] Other conventional antiepileptic drugs do not produce such a good response, with the exception of valproic acid (sodium valproate) and benzodiazepines in a few patients. However, the tolerability of corticosteroids is known to be quite poor. In addition, there is no consensus about the type of corticosteroid to be administered, or the dosage and duration of treatment.

The treatment of infantile spasms improved dramatically with the introduction of vigabatrin in the early 1990s.[7,8] The efficacy of vigabatrin proved to be at least comparable to that of corticosteroids, with better tolerability. It is progressively becoming the first line treatment for infantile spasms around the world, except for some countries where it has not yet been registered, i.e. in Japan and the US. However, recently, visual field loss has been reported in patients treated with vigabatrin, and this has raised concerns about the safety of this agent.

Despite the reported efficacy of these 2 drugs, and promising results with other new agents, almost 30% of patients with infantile spasms remain drug-resistant and rapidly develop an irreversible mental and motor deterioration. Some patients in whom a focal cortical anomaly could be detected might benefit from surgery.

This paper presents a critical review of the treatments used for infantile spasms in an attempt to highlight their risk-benefit ratio. Corticotropin/corticosteroids and vigabatrin are extensively reviewed as they are the 2 treatments with proven efficacy. Recent advances in the surgery of specific cases of refractory infantile spasms are also addressed.

1. General Considerations for Drug Treatment of Infantile Spasms

The evaluation of potential treatments in infantile spasms is difficult to carry out. It is confounded by the characteristics of this syndrome, in particular by the diversity of aetiologies. They include patients with no underlying pathology and others with major lesions. As a result, outcome may vary depending on the pre-existing pathology independently of the treatment. The aim of drug treatment must be disappearance of both spasms and so-called interictal paroxysmal EEG activities.

The efficacy of the drug is difficult to assess clinically. Only video-EEG (sleep and awake recording) can confirm the disappearance of clinical and subclinical spasms. Therefore, trial designs necessitate, in addition to rigorous clinical monitoring, several video EEGs. The EEG tracings are also of high interest because they highlight the disappearance of hypsarrhythmia, an essential criterion of positive response.

In addition, a rigorous methodology is difficult to achieve. Blinded comparative studies using the reference drug (corticosteroids) are difficult to accomplish because of the easily identifiable adverse effects in the corticosteroid group. Studies versus placebo are complicated by ethical issues because of the rapid psychomotor regression and the availability of a known active drug. Finally, it is almost impossible to compare the results of clinical series because of their nonhomogeneity and the different definition of response rates used. These shortcomings apply to most, if not all, the studies done with conventional and new compounds in patients with infantile spasms.

2. Conventional Treatments

2.1 Corticotropin and Corticosteroids

Corticosteroid therapy is still considered the treatment of reference for infantile spasms. Corticotropin was the first and remains the most extensively used agent.

Response rates vary between 50 and 85% in different studies, with a better response in cryptogenic

infantile spasms.[9-12] However, most studies have been uncontrolled and retrospective. To date, only 2 prospective studies have been carried out in cryptogenic infantile spasms.[9,10] Symptomatic cases were not included, considering that their outcome depends mainly on the underlying pathology.

Another drawback to the use of corticotropin is the empirical determination of the dosage. A wide range of daily dosages has been reported. At 20 IU/day, only 25% of patients achieved full control of spasms.[13] Thus, some authors support a high dosage regimen of up to 150 IU/m^2/day.[11] At these dosages, they obtained a complete control of spasms in all treated patients, but with relapses over the long term. This impression of better response at very high dosages was not confirmed in a prospective study: no difference was observed regarding efficacy between corticotropin 150 IU/m^2/day and 20 IU/day.[14] Similarly, in a review of 7 studies, the overall long term response rate ranged from 53 to 91%, with no difference observed between dosages over a range from 40 to 150 IU/day.[15]

The treatment duration is another problem to resolve with corticotropin. A short (2 weeks) schedule produced a poor outcome,[13] and the response rate ranged from 32% for patients treated for less than 1 month to 87% if treatment continued for 5 months in patients treated with 40 IU/day.[16] In addition, a high relapse rate occurs even after an initially favourable response[11] and seems to be correlated with the duration of treatment. All treatment regimens agree that corticosteroids should be withdrawn gradually if the duration of treatment with the full dosage exceeds 1 or 2 weeks.

The effect on seizures and developmental outcome seems to be better when corticosteroids are started earlier, with a significant difference ($p < 0.01$) between infants who began on corticotropin within 1 month of onset of spasms and those who began later.[9]

Few studies have focused on oral corticosteroids. Their use is highly desirable since they do not need parenteral injection. Prednisone and hydrocortisone have been the most studied. Prednisone 2 mg/kg/day was less effective than corticotropin 150 IU/m^2/day in a prospective randomised trial,[12] but equally effective as corticotropin at lower dosages, 30 IU/day, in a double-blind randomised prospective study,[17] and in another open study.[18] For hydrocortisone, no controlled data are available except for a single nonblind prospective study in which hydrocortisone was administered at 15 mg/kg/day for 2 weeks together with valproic acid at 40 mg/kg/day. 74% of patients stopped having spasms and adverse effects were less than with corticotropin.[19] The best results were, as expected, in the cryptogenic group, with 90% showing a good response, but over 60% of the symptomatic group also showed control of spasms. These investigators suggested a better response in symptomatic infantile spasms attributable to perinatal insult of the brain compared with infantile spasms resulting from congenital anomalies.

The long term prognosis for seizures and intellectual outcome with corticotropin/corticosteroid therapy has not been extensively studied. When follow-up was continued for at least 24 months, loss of efficacy has been reported, with relapse rates ranging from 33[20] to 56%.[21] Relapse usually occurs during the first 2 months following remission. Relapse may respond to another course of corticosteroids; when it occurs earlier, during drug tapering, it responds to an increase of dosage (unpublished observations).

All studies have reported improved mental outcome or neurological condition, or both. In the long term, intellectual functions benefit from corticosteroid treatment in both the symptomatic and cryptogenic forms of the disease. A better outcome, measured using IQ and DQ, has been reported in the cryptogenic group (31 to 38%) compared with the symptomatic group (5 to 14%).[9,10]

The main problem with corticosteroids in general, but corticotropin in particular, is the frequently reported adverse effects,[9,14,22] although hydrocortisone seems to be better tolerated.[19] They appear in up to 35% of patients, although Cushingoid features occur in virtually all children. These adverse effects may be serious enough to require the withdrawal of the treatment. In large

series including more than 100 patients, mortality rates of 2.3 to 4.9% were reported,[9,22] with severe infections and cardiomyopathy being the major causes of death.

Adverse effects consist of infections, arterial hypertension, hyperexcitability, agitation, hypertrophic cardiomyopathy, gastritis and adrenal insufficiency. Blood pressure, electrolytes, calcium, phosphorus and glycosuria should be monitored before and during the first days of treatment. Therefore, a 2- to 3-day hospital admission is recommended to initiate treatment. Monitoring should continue, since blood pressure and glycosuria should be checked at least twice weekly until the end of the treatment. A higher susceptibility to infection is reported because of impairment of immunity. Another major problem with corticosteroids is cerebral atrophy.[23] In most patients, the changes are reversible but in others, subdural effusions occur or recovery from 'cerebral atrophy' is delayed.[24]

Because of these adverse effects, some authors have advised not to administer corticosteroid treatment to patients with symptomatic infantile spasms. They point out that it is not worth exposing these patients to major adverse effects because there is no hope of full recovery, even if seizures can be controlled.[25] However, there is growing evidence that the quality of life is improved if seizures are controlled (unpublished observations).

In order to minimise these adverse effects, corticotropin or corticosteroids should be given at the minimum effective dosage and for the minimum effective time. Tapering must be performed slowly to avoid unresponsiveness of the pituitary-adrenal axis.

The mechanism of action of corticosteroids remains unclear. They may act on receptors in the CNS, since *in vitro* they reduce the excitability of the hippocampal pyramidal cell.[26] Recent studies have reviewed the effect of corticotropin treatment on several amino acids in the brain, and reported increases in γ-aminobutyric acid (GABA) and serotonin (5-hydroxytryptamine) and decreases in *N*-acetylaspartate levels in the cerebrospinal fluid.[27,28] Another possible mechanism is the increasing levels of nerve growth factor in cerebral spinal fluid and an acceleration of brain maturation.[29] No evidence, however, proves that corticotropin offers better results than hydrocortisone, and corticotropin fragments devoid of stimulating effects on the adrenal glands were unsuccessful in treating infantile spasms.[30]

2.2 Valproic Acid (Sodium Valproate)

Valproic acid is a wide spectrum antiepileptic drug. The available evidence implicates inhibitory actions of valproic acid on a variety of central nervous system pathways. At high concentrations, valproic acid enhances the GABA-ergic inhibitory system at the cortical and subcortical levels and blocks neuronal firing by blocking voltage-gated sodium channels.

In retrospective studies, valproic acid has been reported to be effective in 20 to 45% of children with infantile spasms.[31-33] The only prospective study was reported by Siemes et al.,[34] who treated 22 newly diagnosed patients (18 symptomatic and 4 cryptogenic) with increasing doses of valproic acid. A complete cessation of spasms occurred in 27% of patients who were treated with 20 to 60 mg/kg/day. Increasing the dosage up to 100 mg/kg/day (mean 74 mg/kg/day) increased the percentage of controlled patients to 50% within 4 weeks of treatment. The tolerability at these high dosages was good, since no major adverse effects, such as hepatitis, were encountered.

In addition to a modest rate of response, the problem with valproic acid is a high rate of recurrence. The addition of low dosage corticotropin is therefore often necessary, as reported in protocols using valproic acid as first treatment as monotherapy or in association with pyridoxine (vitamin B6).[35-36]

The major limiting factor in using valproic acid is hepatic insufficiency. Liver toxicity is reported to occur in 1 in 10 000 to 50 000 treated patients.[37] The most common presenting signs are decreased alertness, jaundice, vomiting, increased seizures, anorexia and haemorrhage. Bryant and Dreifuss,[38] in a recent retrospective study, emphasised the

main risk factors as being polytherapy, young age, developmental delay and coincident metabolic disorders. Patients less than 2 years old receiving valproic acid as polytherapy were at the greatest risk (1 : 600) of developing this complication. This risk is lesser in our experience,[39] and one must be aware that some cases of valproic acid–related hepatic fatalities have occurred in patients with Alpers disease.[40,41] A pre-existing enzymatic defect of the urea cycle has also been reported in patients treated with valproic acid and who developed severe hyperammonaemic encephalopathy.[42]

The more common but less worrisome adverse effects are gastrointestinal upsets, bodyweight gain, drowsiness, ataxia, elevation of hepatic enzymes, hyperammonaemia and thrombocytopenia. These adverse effects are mainly dosage-related. In most situations, they can be reversed with dosage reduction; drug discontinuation is rarely required.[43,44,45]

2.3 Benzodiazepines

Nitrazepam and clonazepam are the 2 major benzodiazepines used in infantile spasms. As with the other benzodiazepines, they modify the sensitivity of GABA receptors.

Nitrazepam is the benzodiazepine most used for infantile spasms, although the drug is only available by investigational protocol in the US. In the largest series with nitrazepam, complete control of seizures was achieved in 50% of patients at 0.6 to 1 mg/kg/day but only in 33% at 0.1 mg/kg/day.[46]

A single prospective randomised multicentre study comparing corticotropin with nitrazepam did not show significant differences in efficacy,[47] but no further studies have been reported so this efficacy has not been confirmed.

High dosages of benzodiazepine are often required to obtain an optimal response in infantile spasms. At these dosages, patients develop serious adverse effects such as excess sedation, hypersalivation, difficulty in swallowing and excessive bronchial secretions.[48,49,50] The thickening of bronchial secretions is more pronounced with nitrazepam (unpublished observations), giving rise to mucous plugs and atelectasis. Bradypnoea and apnoea may result from a direct action on the respiratory centre.[51] A nasogastric feeding tube, bronchial mucus suction and monitoring of respiratory and heart rates are necessary in patients treated with high dosages. Therefore, tolerability is no better than with corticosteroids.

The initial dosage of clonazepam is 0.01 to 0.03 mg/kg/day in 2 or 3 doses. The maintenance dosage is from 5 to 10 times the initial dosage and is reached gradually if necessary. The daily dosage of nitrazepam is 0.5 to 0.7 mg/kg/day and is highly dependent on the individual child. A mortality rate of 20% has been reported with nitrazepam at dosages higher than 1 mg/kg/day.[52]

2.4 Pyridoxine (Vitamin B6)

Pyridoxine is a coenzyme of glutamic acid decarboxylase and enhances GABA synthesis.[53] Pyridoxine is the only drug that prevents seizures in pyridoxine-dependent convulsions of neonates or older children. Two reasons make this drug a rational treatment: GABA is found to be lower in the cerebrospinal fluid of infants with infantile spasms[54] and infantile spasms might be the first manifestation of pyridoxine dependency.

In infantile spasms, a complete control of seizures was claimed at high dosages of pyridoxine (>1 g/day) in 35 to 40% of cryptogenic infantile spasms but in only 10% of symptomatic cases.[55] Some reports suggest association of pyridoxine with low dosages of corticotropin. In a nonblind randomised study[35] including 28 patients with infantile spasms (22 symptomatic and 6 cryptogenic), high dosages of pyridoxine (40 to 50 mg/kg/day) and low dosages of corticotropin (0.01 mg/kg/day) were administered. 54% of patients were seizure-free within 4 days. During follow-up for 35 months, 29% of patients had recurrences and 48% had normal development. Only 1 patient developed a serious adverse effect (arterial hypertension).

Extensive use of pyridoxine has not demonstrated high efficacy for this agent in infantile spasms. This treatment has not been investigated much recently, since the development of new treatments.

3. New Treatments

3.1 Vigabatrin

Vigabatrin is an irreversible inhibitor of GABA transaminase, the main enzyme of GABA catabolism. It acts by increasing levels of GABA, an inhibitory neurotransmitter, in the brain. The first add-on trials with vigabatrin revealed significant efficacy in refractory partial epilepsy in adults[56] and children.[57]

In 1990, Chiron et al.[8] reported the efficacy of vigabatrin in a nonblind add-on trial. 43% of patients previously refractory to conventional antiepileptic drugs and hydrocortisone became seizure-free. This response was obtained within the first week of treatment at dosages from 100 to 200 mg/kg/day. Moreover, efficacy was maintained in 55% of patients during 8 to 33 months of follow-up with continued therapy. The optimal response to vigabatrin was achieved in symptomatic infantile spasms (70% with complete control) and particularly in infantile spasms attributable to tuberous sclerosis (85% with complete control). This efficacy was not maintained in the cryptogenic group, since only 25% showed complete control of spasms and the recurrence rate was higher than in the symptomatic group. Response was better in patients who began taking vigabatrin less than 12 months after onset of spasms. No withdrawal of vigabatrin for adverse effects was necessary and only 13% of children experienced mild adverse effects, mainly sedation or excitation. The withdrawal of comedication with other antiepileptic drugs was possible in the majority of responders. Other reports have confirmed the efficacy and the good tolerability of vigabatrin in infantile spasms.[58-60]

The results obtained in these early studies were supported by a multicentre European study using vigabatrin monotherapy as a first-line treatment.[61] The only significant difference was a better response in the cryptogenic group (69% of cases).

Vigabatrin was then compared with corticotropin or corticosteroids. A randomised prospective study compared vigabatrin 100 to 150 mg/kg/day with corticotropin 10 IU/day in 42 patients with newly diagnosed infantile spasms.[62] In the symptomatic group, vigabatrin was more effective for patients with tuberous sclerosis and brain malformations, whereas corticotropin was more effective in patients with hypoxic/ischaemic injuries. No significant difference was found in the cryptogenic group. The improvement in EEG tracings was comparable in both groups. The relapse rate was lower in patients who responded to vigabatrin compared with those who responded to corticotropin. Adverse effects occurred more often with corticotropin compared with vigabatrin (37 *vs* 13%). The investigators recommended vigabatrin as first choice treatment because of better efficacy and tolerability, and less relapses.

In a series of 22 patients with infantile spasms attributable to tuberous sclerosis, first-line treatment with vigabatrin 100 to 150 mg/kg/day was compared with hydrocortisone 15 mg/kg/day in a randomised trial. Vigabatrin was more effective and better tolerated.[63] Thus, vigabatrin was recommended as the first drug for infantile spasms. In a recent retrospective study, vigabatrin showed the same efficacy but fewer adverse effects than corticotropin.[64]

The role of vigabatrin was recently supported by the first placebo-controlled randomised study, reported by Appleton and colleagues.[65] 40 children with infantile spasms received either vigabatrin 50 to 150 mg/kg/day or placebo for 5 days. Then, all patients received vigabatrin in a nonblind fashion for 6 months. Compared with placebo, the number of spasms was significantly reduced in the group treated with vigabatrin (78 *vs* 26%). In the nonblind phase, 42% of patients were spasm-free with vigabatrin monotherapy. No responders had experienced relapse at the end of the study. Although a correlation between the aetiology and the response cannot be established because of small numbers in the study, vigabatrin seemed to be more effective in cryptogenic than in symptomatic cases. This finding was expected because the series lacked patients with tuberous sclerosis, who exhibit the best response to vigabatrin.

All these results support the use of vigabatrin as first-line monotherapy in all types of infantile

spasms because of its rapid efficacy and good tolerability. However, concerns about the safety of vigabatrin were raised after many recent reports of a visual field defect in adults.[66-76] This visual field defect is usually asymptomatic and can be elicited only by visual field examination.[76] Visual acuity, colour vision and fundal appearance are usually normal. The visual field defect is highly specific and consists of a bilateral constrictive nasal loss.[75,76] Other facts suggested a causal link between vigabatrin treatment and this visual field defect. In a recent comparative study,[75] perimetry examination was performed in 3 groups of adults, the first receiving vigabatrin monotherapy, the second receiving carbamazepine monotherapy and the third as control. Only the first group treated with vigabatrin showed the typical visual field defect. In another recent study,[76] the prevalence of visual field defect in adult patients treated with vigabatrin was 29% independently of comedication with other antiepileptic drugs. One study showed a cumulative dose effect, with a maximum incidence in patients who had received ≥3g.[69] This was not confirmed by further studies in which daily dose of vigabatrin, cumulative dose of vigabatrin, age, bodyweight, duration of epilepsy and concomitant antiepileptic drugs were not found to predict the occurrence of visual field defect in vigabatrin monotherapy and polytherapy.[75,76]

This visual toxicity of vigabatrin does not seem to be related to the white matter microvacuolation reported in rodents and dogs, but not in monkeys.[77,78] Previous longitudinal magnetic resonance imaging (MRI) and visual evoked potential studies in treated patients did not show relevant changes.[79,80] Moreover, no myelin vacuolation as reported in neuropathological studies following surgery or at autopsy.[81] In patients presenting a visual field defect, MRI of the ocular tract and visual evoked potentials were also normal.[75,76,79] Only the electroretinogram was altered, and a possible hypothesis is a direct toxicity of the increased levels of GABA on the retina.[75,76]

The problem is unresolved yet in children. The electrophysiological studies are not specific and the visual field test cannot be performed in the first decade, especially in disabled children. In older children, visual field defects have been reported.[82,83] In these studies, patients had never complained of ophthalmological disturbances. Moreover, visual field defects were reported in a child treated with lamotrigine and valproic acid.[84] Visual field defects were found to be reversible in 2 children treated with vigabatrin when the drug was withdrawn.[81,85] In a consensus guideline in 1998, Appleton[86] concluded that vigabatrin remained the drug of choice for infantile spasms. After the reports of visual field defects in adults, the author revised these guidelines[87] and vigabatrin remains, in their opinion, the drug of choice for infantile spasms, particularly when it is caused by tuberous sclerosis,[87,88] although this has been challenged by others.[89,90] The important role of vigabatrin in the treatment of infantile spasms has been recently emphasised by other authors.[91,92]

3.2 Lamotrigine

This new antiepileptic drug shows a wide spectrum of efficacy both in generalised and partial epilepsies. In the paediatric population, lamotrigine is particularly indicated in Lennox-Gastaut syndrome in association with valproic acid. Lamotrigine is a well tolerated molecule in children. A common adverse effect is the cutaneous rash that occurs in 1 to 3% of cases. This rash disappears with treatment withdrawal and is usually benign. Rare cases of Stevens-Johnson have been reported in the paediatric population.[93]

The usual dosage is variable depending on the comedication with valproic acid. The recommended dosage of 15 mg/kg/day is decreased to 5 mg/kg/day when the drug is given in combination with valproic acid. The treatment should be introduced slowly and the final dosage is obtained within an average of 2 months.

In a single-blind, placebo-controlled, add-on study,[94] 30 patients with infantile spasms refractory to conventional antiepileptic drugs and to vigabatrin and corticotropin were studied. At 3 months of treatment, 9 patients showed a >50% decrease

in seizure frequency, with complete control of spasms in 5 of them. Only 1 patient exhibited cutaneous rash and lamotrigine was stopped. Combination with valproic acid and postnatal brain damage as aetiology were significant factors in good response. The complete control was maintained in all patients after 2 years of follow-up on lamotrigine and valproic acid. However, patients in this series were mostly aged over 2 years and they exhibited, in addition to spasms, tonic seizures and atypical absence seizures.

Efficacy was also reported in a review on lamotrigine in 120 children with epilepsy.[95] Four children among 19 with infantile spasms were controlled by lamotrigine as add-on therapy.

These data need to be confirmed by further studies in order to establish the efficacy of lamotrigine in infantile spasms.

3.3 Topiramate

This new antiepileptic drug acts by potentiation of GABA neurotransmission, antagonism of glutamate and blockade of sodium channels. Topiramate is reported to be effective in partial seizures in adults, as add-on therapy as well as in monotherapy.[96,97] Encouraging results were obtained in a double-blind placebo-controlled trial as add-on therapy in patients with refractory Lennox-Gastaut syndrome.[98] Drop attacks showed a significant reduction. As Lennox-Gastaut syndrome may follow infantile spasms, a nonblind add-on pilot study was conducted in 11 children with refractory infantile spasms.[99] Complete control of seizures was obtained in 45% of children, and over 50% reduction in 82%. Recently, Glauser et al.[100] reported the long term follow-up (mean 18 months) of their add-on study.[99] Eight children were continuing topiramate with 4 children spasm-free. Topiramate was well tolerated in this series. However, the sample size is too small to pursue further analysis and these patients did not receive vigabatrin at any time of the study. In a preliminary study at our centre, as yet unpublished, the response of infantile spasms to topiramate was not as good as reported by Glauser et al.[99] and the children did not tolerate such high dosages well.

Major adverse effects with topiramate in children are speech disturbances, psychomotor slowing and bodyweight loss. They are dosage-related, and in our experience they are frequent after a dosage of 20 to 25 mg/kg/day. Topiramate is better tolerated when introduced slowly at 0.5 to 1 mg/kg/day and increased by 0.5 mg/kg/day every 15 days until a final average dosage of 20 mg/kg/day.

3.4 Zonisamide

The experience with this drug in children is almost exclusively from Japan where this molecule was developed. Zonisamide showed some promising results as add-on therapy after failure of pyridoxine and valproic acid to control seizures in infantile spasms.

In the first add-on nonblind study, zonisamide was introduced at a dosage of 4 to 20 mg/kg/day in 27 children with infantile spasms (25 were symptomatic and 3 cryptogenic).[101] 33% showed cessation of seizures, including all 3 with cryptogenic infantile spasms. The response was obtained within the first week of treatment and disappearance of hypsarrhythmia was documented. A recurrence rate of 50% was reported but adverse effects were absent.

In the second study, 16 patients (13 symptomatic) were treated with zonisamide 4 to 8 mg/kg/day after failure of a combination of valproic acid and pyridoxine.[102] Four were responders (25%), with 2 showing cessation of seizures. No adverse effects and no recurrence were observed after 26 months.

Other recent nonblind studies[103,104] involving a smaller number of patients have confirmed this promising efficacy, but these results remain preliminary and further studies comparing zonisamide to reference drugs are necessary.

The recommended dosage in children is 2 to 4 mg/kg/day increased if necessary to 4 to 8 mg/kg/day. The most reported adverse effects are drowsiness, loss of appetite, gastrointestinal disturbances and urinary lithiasis.

3.5 Felbamate

After the report of bone marrow aplasia in patients treated with felbamate,[105] no large series has been reported in children. Felbamate use requires strict monitoring of blood cell count and must be restricted to highly intractable epilepsy syndromes with a well-established response to this drug.

No randomised studies have been reported, but 2 nonblind add-on trials have included 4 and 6 patients, respectively.[106,107] In the first study, felbamate resulted in a complete control of seizures in 3 of 4 patients, all refractory to conventional antiepileptic drugs (vigabatrin was not administered). In the second, 4 of 6 patients refractory to both corticosteroids and new antiepileptic drugs (vigabatrin and lamotrigine) showed a 75% decrease in seizure frequency. Neither adverse effects nor long term efficacy were reported.

3.6 Ganaxolone

Ganaxolone belongs to a novel class of neuroactive steroids called epalons. It is chemically related to progesterone but is devoid of any hormonal activity. Its antiepileptic response is mediated by its action on GABA receptors. The safety and tolerability of this molecule has been established since the majority of reported adverse effects were mild in healthy volunteers.[108] They were limited to headache, dizziness, somnolence and gastrointestinal disturbances. This treatment is not yet marketed.

Encouraging results were recently obtained in pentylenetetrazol-kindled mice, where ganaxolone suppressed tonic seizures and lethality. Its effect was similar to that of valproic acid and diazepam.[109]

In a recent nonblind add-on study by Kerrigan et al.,[110] only 33% of their patients experienced >50% reduction of spasms and none of them became spasm-free. In an unpublished add-on nonblind study at our hospital, ganaxolone was administered to 20 children with infantile spasms refractory to corticosteroids, vigabatrin and lamotrigine. Only 1 child stopped experiencing seizures but a decrease of over 50% was reported in 50% of the cases. The developmental response was more encouraging, since 60% of the series showed improvement in cognitive skills. The major adverse effect reported in children was hyperkinesia, but ganaxolone was well tolerated overall. Further investigations with randomised and controlled studies are warranted.

4. Miscellaneous Treatments

4.1 Ketogenic Diet

The ketogenic diet is an energy-restricted, high fat, low protein, low carbohydrate diet developed in the 1920s for the treatment of children with intractable seizures. It was established as a way to duplicate the beneficial effect of fasting on seizure control. This diet has experienced a new resurgence recently. The mechanism of action of this diet is unknown but it seems to rely on a fundamental change in brain metabolism from glucose to ketone body substrates. The efficacy rate in intractable childhood epilepsy ranges between 20 and 60%.[111-116] The most recently reported series include all intractable seizures in children, with a few patients with individualised infantile spasms. In a current study at our hospital, 70 children with intractable epilepsy are being treated with ketogenic diet. 23 patients have infantile spasms, but only 1 of them has responded.

Adverse reactions to the ketogenic diet are uncommon, and include the development of renal stones (5 to 8%), gall bladder stones (less frequently), hypoproteinaemia and hypoglycaemia. Combination with topiramate should be avoided given the increased risk of renal stones with both treatments. In a study looking at the complications of this diet, a possible interaction of the diet with valproic acid treatment was evoked.[116] The adverse effects were higher in the group treated with valproic acid (80 *vs* 53%). Severe haemolytic anaemia and Fanconi's renal tubular acidosis developed in this later group. Routine biochemical screening did not predict the adverse effects.

The ketogenic diet, although it seems 'natural therapy', should be initiated in the hospital and needs close ongoing medical and dietary supervision. A further series of patients with infantile

spasms would be necessary to evaluate its efficacy in this syndrome.

4.2 Immunoglobulins

In 1977, an enthusiastic report described a favourable effect of intravenous immunoglobulins (IVIg) in symptomatic generalised epilepsy.[117] The antiepileptic effect might be based on the Fc fragment. Some years later, this efficacy was supported by another series.[118] In a series of 7 children with infantile spasms (6 cryptogenic and 1 attributable to perinatal insult), all were controlled following administration of 100 to 200 mg/kg/day of IVIg at intervals of 2 to 3 weeks (1 to 8 administrations).[119]

Other reports were less encouraging. Only 5 of 23 patients experienced cessation of seizures with 1 g/kg of IVIg for 2 days, repeated every 3 weeks for 6 months.[120] Tolerability was excellent, except for anaphylactic shock and fever in 1 patient.

5. Surgical Treatment

Epilepsy surgery is nowadays a well established approach in drug-resistant partial seizures. In infantile spasms, until recently, few studies were reported concerning surgical treatment. The young age of the patients, the diffuse cortical anomalies in the majority of patients with symptomatic infantile spasms and the absence of a visualisable cortical anomaly in cryptogenic infantile spasms made the neurosurgeons reluctant to treat these patients.

The development of MRI and particularly of functional imaging techniques of the brain has allowed a better identification of the underlying lesions. Chugani and colleagues[3] reported 5 patients in whom a focal lesion was identified by PET. All of them had favourable outcome after surgery. The same authors reported a series of 23 children operated for drug-resistant infantile spasms.[121] 13 of them showed a normal MRI, whereas the others had various malformations (hemimegancephaly, pachygyria, tuberous sclerosis and Aicardi syndrome). All infants showed either an anatomical (computed tomography/MRI) or a metabolic ([^{18}F]fluorodeoxyglucose/ PET) lesion. Convergence between EEG and neuroimaging localisation was a prerequisite to surgery. The type of procedure varied according to the pathology, ranging from hemispherectomy when the anomaly affected the whole hemisphere to focal resection when it was more localised. The surgically resected tissue proved to be dysplastic. On follow-up (4 to 67 months), 15 children were seizure-free. The developmental outcome showed an improvement in cognitive skills at 2 years after surgery. Results were better for the children who underwent surgery when younger.[122]

After these encouraging results, it appears important to determine the candidates for surgery. Two studies have evaluated the incidence of cerebral lesions and candidacy for surgery.[123,124] In the first study, 66% of patients with infantile spasms had focal manifestations such as asymmetric spasms, hemihypsarrhythmia and partial seizures associated with spasms.[123] In the second study, including 140 children, additional cortical anomalies were detected up to 90% of the symptomatic cases after PET scan exams.[124] However, these studies do not provide epidemiological data because both populations were biased toward intractable spasms (arising from epilepsy reference centres).

Recently, Pinard et al.[125] reported 17 patients with refractory infantile spasms and no single focal lesion. Complete callosotomy was successful in 80% of patients, with major improvement of seizures and behaviour.

Nevertheless, the most appropriate time to consider surgical treatment to treat drug-resistant infantile spasms has not been clearly defined. The balance between early and possibly unnecessary surgery and late surgery with the risk of losing developmental potential is not easy to reach, and each patient must be evaluated individually by a team including an experienced neurologist, neurophysiologist, neuropsychologist and neurosurgeon.

6. Conclusions and Practical Implications

Because of the proven efficacy of vigabatrin in infantile spasms, vigabatrin has become first-line treatment in all countries where it is available. This

newly developed antiepileptic drug seemed to be the ideal treatment for this syndrome. It shows high efficacy in all types of infantile spasms, although having the highest efficacy in tuberous sclerosis. It is easily initiated orally with no need for hospitalisation. The full dosage is achieved immediately, and the response is evident within the first week of treatment. This rapid response is of particular interest with regard to the deleterious effect of long lasting hypsarrhythmia. All of these advantages were coupled with good tolerability and minor adverse effects.

Although all infantile spasms do not respond to vigabatrin, this antiepileptic drug used as monotherapy allows the control of almost 50% of infantile spasms, and 85% of those attributable to tuberous sclerosis. Patients nonresponding or resistant to vigabatrin should receive corticotropin/corticosteroids after a trial of vigabatrin. In practice, vigabatrin seems to be synergistic with corticosteroids. Patients seem to be better controlled on the combination, and recurrence of spasms may occur on vigabatrin withdrawal after initiation of corticosteroids.

Recent reports of a specific visual field loss linked to vigabatrin treatment have raised concern about the safety of this drug in adults and children. This adverse effect is usually asymptomatic and can be detected only by perimetric visual field studies. In children, especially in the young or disabled, it is difficult if not impossible to detect the visual field loss and it is not yet known if children are at higher or lower risk for this adverse effect. Until a clear answer about the occurrence of this adverse effect in children has been established through randomised study, vigabatrin may still be considered first-line therapy in infantile spasms. This is supported by the possible reversibility of the visual field defects in this age group.[83,85] The use of vigabatrin for a period of up to 2 weeks (which is necessary to assess the response) is probably acceptable because it is unlikely that the visual field loss will develop in this short time. If there is no response to vigabatrin treatment after 2 weeks, it would then be safer to withdraw the drug. However, it is important to emphasise that in the case of infantile spasms caused by tuberous sclerosis, vigabatrin shows synergy with corticosteroids and we advise dual therapy. Where there is a good response, vigabatrin should be continued; the benefit of stopping spasms and hypsarrhythmia is higher than the risk of this possible adverse effect. To date, our opinion is shared by many paediatric epileptologists although it has been challenged by Riikonen in her recent review.[90] This, however, emphasises the need to determine the subgroups of infantile spasms where the response to vigabatrin is higher than to corticosteroids, such as in tuberous sclerosis. Additionally, a more rigorous evaluation of the response is essential in the face of this worrisome adverse effect. A positive response is defined by the cessation of spasms and normalisation of the EEG. If any of these criteria is not achieved, the patient must be considered as resistant and switched to other therapies. Short term vigabatrin treatment in spasm-free children could be an interesting alternative. Vigabatrin has been successfully withdrawn in a subgroup of infants with infantile spasms controlled for 6 months. They are still spasm-free after a follow-up of 2 to 4 years (unpublished observations). This exposure time might be too short for the visual field defect to develop.

Children who do not achieve a good response to vigabatrin should be switched to corticotropin/corticosteroid therapy. Unfortunately, corticosteroids do not control all infantile spasms. Moreover, the frequent and sometimes severe adverse effects of these compounds, particularly corticotropin and less so for prednisone and hydrocortisone, have led to trials of new antiepileptic drugs for this indication. Even though topiramate and zonisamide seem to be promising treatments in infantile spasms, more studies are necessary to determine their efficacy and tolerability. Furthermore, their requirement for slow and progressive titration during introduction (especially for topiramate) limits their use in infantile spasms, where a rapid response is highly desirable.

Despite the efficacy of corticosteroids and vigabatrin, the use of the conventional antiepileptic drugs (valproic acid and benzodiazepines), the newly de-

veloped antiepileptic drugs and some promising results with ketogenic diet, 25 to 30% of patients with infantile spasms continue to have spasms and experience psychomotor regression. These drug-resistant patients could be candidates for surgery. The optimal timing of surgery is not well defined and depends on each particular case.

Finally, the optimal drug schedule must take into account the availability of the various drugs, particularly vigabatrin, hydrocortisone and natural corticotropin, in various countries. Vigabatrin is not available in the US and Japan, and natural corticotropin is not available in Japan and most European countries.

In conclusion, a better understanding of the aetiology of infantile spasms and an improvement of our knowledge of cerebral maturation are necessary to provide optimal treatment for patients presenting with infantile spasms. The ultimate goal should be the prevention of infantile spasms, given the irreversible and profound neurodevelopmental sequelae of this condition.

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