Seizure 19 (2010) 159–164

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Treatment and long term outcome in West syndrome: The clinical reality. A multicentre follow up study

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ARTICLE INFO

Article history:
Received 16 July 2009
Received in revised form 12 December 2009
Accepted 15 January 2010

Keywords:
Infantile spasms
West syndrome
Childhood epilepsy
Anti-epileptic drugs

ABSTRACT

We systematically reviewed the files of 51 infants presenting with infantile spasms and hypsarrhythmia in order to study the initial treatment strategies and the long term outcome. 80% of the infants were classified as symptomatic. In the nine participating centres, different treatment protocols were used, but the large majority of the children received vigabatrin as first line treatment. Second line options included hormonal treatment, topiramate and valproate. The time to reach cessation of infantile spasms was significantly shorter in the cryptogenic group than in the symptomatic group (50% at 13 days versus 66 days respectively) and was irrespective of the treatment used. The late follow up data (>2 years) showed that 60% of the children had epilepsy and that 75% of the children had a delay in their psychomotor development. Again, outcome in the cryptogenic group was better than in the symptomatic group, but also in the cryptogenic group, 50% of the children had a clear developmental delay, even if spasms were controlled early in the course of the disease. Our retrospective study illustrates that not only the underlying brain dysfunction is the major determinant for later outcome in infantile spasms (symptomatic group) but also even a short period of infantile spasms can be responsible for later developmental delay (cryptogenic group).

1. Introduction

Infantile spasms (or epileptic spasms, see new ILAE definition[1]) remain one of the most catastrophic seizure types in childhood and are usually indicative of a true epileptic encephalopathy, especially when these seizures are associated with hypsarrhythmia on the EEG. Children presenting with infantile spasms and hypsarrhythmia have a high risk of developing cognitive deterioration (the so called West syndrome).[2,3] In contrast with other epilepsy syndromes, early and aggressive anti-epileptic treatment is warranted, since an early control of the infantile spasms is associated with a higher chance of a normal cognitive outcome.[3–5] In this respect, both seizure control and long term cognitive outcome have to be considered as major outcome parameters in any study on infantile spasms.[6,7]

Different treatment modalities have been studied in infantile spasms, and several lines of evidence point to hormonal treatment (ACTH, oral steroids) or vigabatrin as first line options in the treatment of infantile spasms.[2,8,9] In the recently published prospective United Kingdom Infantile Spasms Study, hormonal treatment was shown to be superior in the early outcome measurements at 13–14 days, but the difference did disappear at 14 months.[10,11] At the cognitive level, developmental outcome was better after initial control with hormonal therapy in those without an identified underlying etiology. It should be noted that children with tuberous sclerosis were excluded in this study, because in many European centres vigabatrin has already become the first line approach. In an earlier study by Vigevano and Cilio[12] also comparing ACTH versus vigabatrin, similar effect estimates were obtained.

In other smaller studies, older and newer anti-epileptic drugs have been advocated as potential treatments in infantile spasms; valproate,[13] levetiracetam,[14] nitrazepam,[13] sulthiame,[15] zonisamide,[16] pyridoxine[15] and topiramate.[17–20]

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doi:10.1016/j.seizure.2010.01.008

In a practice parameter published by the American Academy of Neurology and the Child Neurology Society, nine prospective studies were analyzed, but an optimal treatment option could not be recommended.[21] It was concluded that ACTH is probably effective and that vigabatrin is possibly effective in the short term treatment of infantile spasms. This absence of strong evidence was further underscored in a recent Cochrane review. The available studies do however show that the resolution of spasms is faster with ACTH than with vigabatrin.[9] Concerning long term developmental outcome, evidence is even weaker and multiple factors to explain normal or abnormal developmental outcome have to be taken into account. The underlying brain etiology certainly is a strong determining factor. In the symptomatic group, with an identifiable cause for the infantile spasms, outcome seems always worse than in the cryptogenic group,[7–10] in which despite a thorough diagnostic work-up, no cause for the spasms is found.

With the availability of different hormonal products and different anti-epileptic drugs (vigabatrin, valproate, topiramate, zonisamide, benzodiazepines, sulthiame), and the lack of convincing guidelines with clear treatment preferences, the treating physician is left with different treatment possibilities.[22,23] In the best case, each centre develops a strict treatment protocol based on personal experience, existing guidelines, practice parameters and availability of anti-epileptic drugs.

We studied the efficacy of the different treatment protocols that are currently being used in nine large neuropediatric units (including six university centres) in Belgium. Apart from zonisamide, all major anti-epileptic drugs are available in Belgium, although not all of them are registered for use in this young age group. We were especially interested in the number of children becoming seizure free in the early course of the disease, in the developmental outcome, and in the relationship between underlying cause (symptomatic versus cryptogenic groups) and efficacy (=epilepsy and cognitive outcome).

2. Methodology

This is a standardized retrospective file review of all new cases with infantile spasms presenting between 1 January 2002 and 31 December 2005 in one of the nine participating centres in Belgium. In all participating centres, qualified pediatric neurologists were responsible for the initial treatment and follow up of the children. Since it was our belief that the large majority of the children presenting with infantile spasms were referred to one of these centres, our study sample should reflect the clinical reality in Belgium concerning treatment and follow up of children with infantile spasms.

Formal inclusion criteria for the study were:

- presentation with infantile spasms between 1 January 2002 and 31 December 2005, and for which treatment was started between 1 January 2002 and 31 December 2005;
- hypsarrhythmia or modified hypsarrhythmia on the EEG before the start of the treatment;
- age at onset of the infantile spasms between 1 month and 2 years of age;
- follow up period of at least 18 months.

From each patient file, the following data were retrieved:

- Reported age at onset of the infantile spasms.
- Pediatric and neurological diagnosis.
- Apparent delay between presentation of the spasms and start treatment.
- Presence and type of seizures before the diagnosis of infantile spasms.
- Age at start treatment of the infantile spasms.
- Initial treatment for infantile spasms.
- Ages at subsequent follow up visits.
- Changes of treatment throughout the follow up period.
- Efficacy of the different treatments: seizure frequency at each follow up visit. Only presence or absence of infantile spasms was determined. More specifically, three categories were used: positive response, relapse, or persistent. A positive response indicates that the child was spasm free for more than 1 week at the time of the visit. Seizure frequency was assessed by seizure diaries.
- Developmental outcome at the long term follow up visit (see below).

For each individual child, we selected four visits in the 'early follow up period'. Visit 1 was defined as the visit when the treatment for infantile spasms was started. Visit 2 (median: 15 days, range: 9–42 days) was a visit occurring within 4–5 weeks after the start of the treatment. Visit 3 (median: 41 days, range: 25–70 days) and visit 4 (median: 110 days, range: 66–212 days) were regular follow up visits scheduled within the first 3–4 months after start of the treatment. The majority of the children had indeed more than four visits in the first 4 months, but only those visits with sufficient clinical data on file were used for analysis. Although the variability (between centres and within centres) of the follow up visits, this methodology allowed us to construct Kaplan–Meier plots to see the effect of treatment during this early follow up period.

Visit 5 was defined as the 'long term follow up visit', at least 18 months after the start of the treatment for infantile spasms. Visit 5 took place between 2.07 years and 2.55 years (median: 2.38 years).

At this last visit, an assessment of the development was made. To be valid, a written comment on the development and the instruments used to assess the development had to be found in the patient files. As different centres used different semi quantitative scales to assess cognitive and developmental outcome, we dichotomized this outcome parameter as normal or abnormal. 'Abnormal' refers to a significant delay in one or more of the different developmental fields.

For further analysis, each patient was classified into one of the following groups, following the proposed ILAE and West Delphi classification Schemes[1–6]:

- Cryptogenic group: no identifiable cause found, normal development at the onset of the spasms, 1.5T MRI normal, pediatric and neurological examination normal, genetic and metabolic screening when applicable: no abnormalities found ('no proven etiology').
- Symptomatic group: a clear cause for the spasms was shown or suspected.

It should be noted that this classification for each child was only made at the end of the study, sometimes after a long lasting diagnostic work-up.

This protocol was discussed with the different principal investigators of the different participating centres and was approved by the ethical committee of the leading centre (Leuven UZ).

3. Results

Overall, 51 children could be included in this study. In view of the yearly number of live births in Belgium (about 100,000) and the estimated incidence of 2–4 new cases per 10,000 living births,[24] our study sample roughly covers 50% of the expected cases in these 4 recruiting years.

Table 1
Number of patients per diagnostic group.

• Cryptogenic	10
• Symptomatic	30
– Perinatal problems, HIE	15
– Tuberous sclerosis	3
– Chromosomal	5
– Congenital malformations	4
– Infection	1
– Trauma	1
– Tumor	1
– Only abnormal development before spasms start	11
Total	51

Table 1 shows that the large majority of the children ($n = 41/51$, 80%) presenting with infantile spasms were classified in the symptomatic group. Of those, 11 presented with a developmental delay at the onset of the spasms, but no definite underlying diagnosis could be made, even at the end of the early follow up period of 3–4 months. In the other 30 children a variety of causes for the infantile spasms were found. The largest group consisted of children with perinatal hypoxic-ischemic problems. Three children suffered from tuberous sclerosis.

Despite extensive work-up no diagnosis could be found in 10 children with a normal development at the onset of the spasms: these were considered as cryptogenic.

The onset of the infantile spasms was not significantly different in both groups. The median age at onset in the symptomatic group was 6.2 months (IQR 4.4–9.3 months) and in the cryptogenic group 6.5 months (IQR 6.2–8.6 months). Interestingly, 41% (17/41) of the children in the symptomatic group were already known with other seizures before the onset of the infantile spasms. In 12 of these 17 children, these pre-existing seizures were classified as generalized seizures. Only in one child in the cryptogenic group, a single short lasting generalized febrile seizure had occurred before the start of the infantile spasms.

We also assessed the delay between the onset of the infantile spasms and the start of the treatment (visit 1). This period reflects the time needed to recognize the infantile spasms but also included the time to organise and perform a diagnostic EEG as well as the time to refer the child to one of the specialized clinics. Overall, this delay period was very short with a mean delay of 6 days, illustrating a very fast recognition of the spasms. The longest delay was 155 days. This particular child was known with myoclonic seizures. After 5 months the character of the seizures changed and appeared in clusters, and the EEG now showed (modified) hypsarrhythmia. The 'delay' between onset of infantile spasms and start of treatment at visit 1 was longer in the symptomatic group (mean: 7 days, range: 0–155 days) than in the cryptogenic group (mean: 2 days, range: 0–19 days).

3.1. Initial treatment (Table 2)

Looking at the medications that were prescribed at visit 1 and during the early follow up period, it is obvious that there is no uniform treatment protocol (Table 2). Nevertheless, 34/51 children got vigabatrin as initial therapy. Only one child got hormonal therapy (ACTH) as first line treatment. As can be calculated, the sum of all the treatment options at visit 1 exceeds 51, which indicates that some of the children were already on anti-epileptic medication before the start of this study. This was the case for four children: three were already on valproate and one was on pyridoxine before the actual start of the specific treatment for infantile spasms. This means that in nine children valproate was prescribed as first drug for infantile spasms. Topiramate was considered first line drug in four children. There were only minor differences between the two patient groups, with first line use of vigabatrin in the cryptogenic group (7/10, 70%) and in the symptomatic group (27/41, 66%) being very similar. For the other children in the symptomatic group valproate ($n = 11$) and topiramate ($n = 4$) were prescribed as first line treatment. In contrast, only one child in the cryptogenic group received valproate as first line treatment (Tables 2A and 2B).

Table 2
Total group: prescribed treatments per visit.

Visit	1	2	3	4
Steroids/ACTH	1	5	8	8
VGB	34	41	38	27
TOP	4	14	21	23
VPA	12	17	19	15
PB	1	1	1	1
BZP	0	1	5	5
PYR	3	1	1	1
Other AEDs	0	2	3	4

During the following visits, the variability becomes even more striking. At visit 2, the large majority (41/51, 80%) children were on vigabatrin. Throughout the follow up, more children were put on steroids/ACTH, on valproate and on topiramate. Also, the use of benzodiazepines (clobazam, clonazepam and nitrazepam) became more prevalent. The other two anti-epileptic drugs that were prescribed in a minority of the children, in this early follow up period were levetiracetam and lamotrigine.

3.2. Efficacy

Because of the large variability of the scheduled follow up visits in the early course of the disease, efficacy of the given treatment for infantile spasms was first formerly assessed at visit 4 (median: 110 days, range: 66–212 days). Overall, 69% were free of infantile spasms at visit 4. In the cryptogenic group, 9/10 children were free of infantile spasms (versus 27/41; 66% in the symptomatic group). Two of the children (both in the symptomatic group) who presented at visit 4 with infantile spasms, were spasm free at visit 2 or 3, but had a relapse (Fig. 1).

Fig. 2 shows the cumulative probability of becoming spasm free (Kaplan–Meier analysis). Overall, 50% of the children reached seizure freedom by 45 days. Here, major differences were found between the cryptogenic and symptomatic groups. In the cryptogenic group the 50% level was reached at 13 days, and at 66 days for the symptomatic group. Actually, 4/10 children in the

Table 2A
Symptomatic group: prescribed treatments per visit.

Visit	1	2	3	4
Steroids/ACTH	0	3	5	7
VGB	27	32	33	26
TOP	4	12	17	21
VPA	11	14	16	13

Table 2B
Cryptogenic group: prescribed treatments per visit.

Visit	1	2	3	4
Steroids/ACTH	1	2	3	1
VGB	7	9	5	1
TOP	0	2	4	2
VPA	1	3	3	2

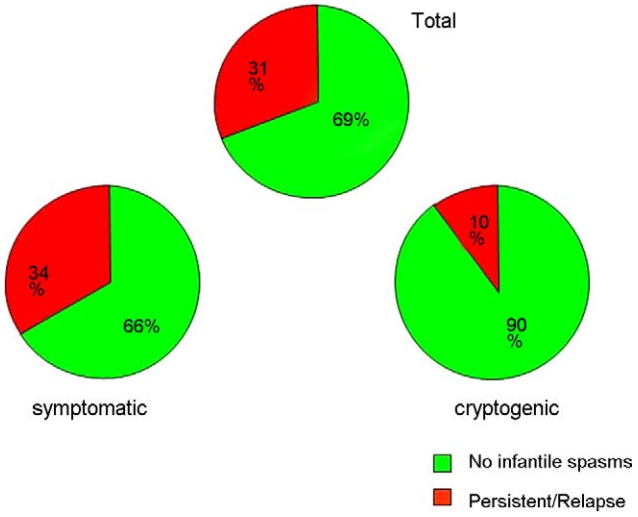

Fig. 1. Outcome (infantile spasms) at visit 4.

cryptogenic group had a 100% response within the first week after start of the treatment. This significant finding is also illustrated by looking at the 'positive response at 1 month', which is only 14% in the symptomatic group and 90% in the cryptogenic group. The figure further shows that after 120 days, chances of becoming seizure free became very low.

We also analyzed what medication the children were taking at the time of the control of the infantile spasms, whenever this happened during the follow up. In the symptomatic group, 60% was on vigabatrin, in monotherapy (19%) or in combination therapy with valproate or topiramate. In the cryptogenic group, eight of the nine children were on vigabatrin and 2/9 on ACTH (one together with vigabatrin).

3.3. Long term efficacy and effect on development

Long term outcome was assessed at visit 5, which was done after a minimal follow up of 2 years (median: 2.38 years, range: 2.07–2.55). One child was lost to follow up and two children died during the study period (one because of septic shock during ACTH treatment and one due to an underlying mitochondrial encephalopathy; both in the symptomatic group).

In contrast with the outcome measures in the early follow up phase, we focused on the presence or absence of epilepsy (and thus not only on the presence or absence of infantile spasms) and on the development. 40/48 children were still on anti-epileptic treatment. Different anti-epileptic drug schedules were used. The majority of the children were on VPA ($n = 23$) in monotherapy ($n = 10$) or in combination with other AEDs. Most commonly used were topiramate ($n = 15$), levetiracetam ($n = 5$), or vigabatrin. 10 children were still on vigabatrin at visit 5. Other AEDs used at visit were phenobarbital, lamotrigine and sulthiame. Benzodiazepines were being used in six children at visit 5. Overall, 60% of the study group was seizure free (Fig. 3). As expected, the epilepsy outcome in the cryptogenic group was excellent with 9/10 children completely seizure free. On the other hand, in the symptomatic group, only 54% of the children were seizure free. In those children without epilepsy control, 44% had generalized seizures.

The presence of infantile spasms at visit 4 (last visit early follow up) was highly predictive for epilepsy outcome at the long term follow up visit. 84% of the children with infantile spasms at visit 4, had epileptic seizures (epileptic spasms and/or other seizure types) at long term follow up. In contrast, 77% of the children without infantile spasms at visit 4 were completely seizure free at long term follow up.

The results on development were less straightforward (Fig. 4). As mentioned in Section 2, we considered a developmental delay only when a description of the deficit was detailed in the patient file. On the other hand a child was considered normal, when this was explicitly stated in the patient file. Overall, 75% of the children at long term follow up did show a developmental delay. In the symptomatic group, this percentage was as high as 80%. However in the cryptogenic group, with 90% of the children being spasm free at visit 4 and epilepsy free at the long term visit, 5/10 (50%) showed a developmental delay. One child in this group was never infantile

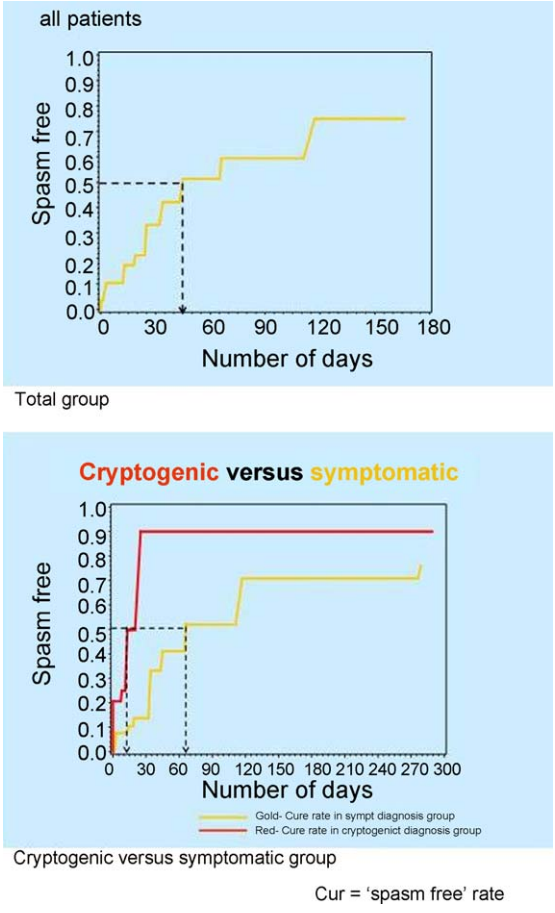

Fig. 2. Efficacy cumulative probability of becoming infantile spasm free.

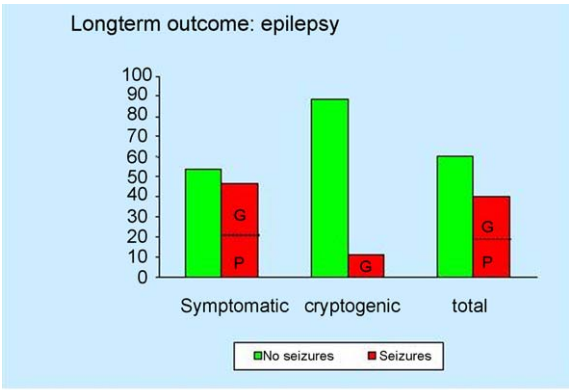

Fig. 3. Long term outcome: epilepsy.

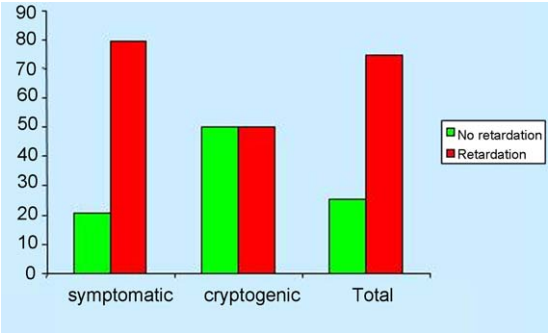

Fig. 4. Long term outcome: development.

spasm or seizure free and developed a language delay during the follow up. The four other children in the cryptogenic group with developmental delay had an early control of the infantile spasms and did not develop other seizure types, but had extra speech therapy ($n = 2$) for language delay or/and physiotherapy for motor delay at Kindergarten-age ($n = 3$). In two of these five children, an autistic spectrum disorder was suspected.

4. Discussion

Our retrospective analysis of the treatment practices for infantile spasms in Belgium between 2002 and 2005, largely confirms the data that are available in the literature, and certainly illustrates the clinical reality beyond the world of randomized controlled trials. Because of its retrospective nature, we should be very cautious not to over-interpret our findings. However, as recognized by many authors, there is definitively a need for more data that show how and what treatment options are offered to children presenting with infantile spasms in clinical reality.

We were surprised by the relatively small number of children included in the study. The major Belgian neuropediatric centres participated in the study, but only about 50% of the possible subjects were included. This was partly due to the study requirements, but it also indicates that some infants are being followed at smaller non-university centres. Probably, this indicates an inclusion bias with the more severe cases referred to the larger participating centres.

We were confident that the necessary diagnostic studies were performed in all subjects, and our distinction between the symptomatic and cryptogenic group was made only at the end of the study. This explains why we could classify as much as 80% in the symptomatic group, which is larger than for instance in the UKISS study, where the classification was made earlier in the study.[10,11] There is an ongoing discussion in the literature about the classification in idiopathic, cryptogenic and symptomatic groups.[6] We pragmatically followed the ILAE guidelines with two groups: a symptomatic and cryptogenic group.[1]

A first major difference with the current knowledge was the very short delay between onset of infantile spasms and the start of the treatment. This treatment delay was very short (2 days) in the cryptogenic group and also shorter in the symptomatic group than what is known in the literature. It points to an adequate recognition of the disease by pediatricians and (pediatric) neurologists in Belgium, and to the fast referral system. Some papers have shown that the delay between the onset of the spasms and the start of the treatment partly explains the long term developmental outcome.[4,25] As this period is shorter in our study, this factor will play a lesser role to explain the (high frequency of the) possible developmental delay. Also, the presenting phenotype and hence the classification into cryptogenic or symptomatic will not be obscured by a long lasting pre-treatment period with infantile spasms.

It is obvious that there is a need for a more uniform treatment protocol in Belgium. Even within the single centres, we could not always find a strict protocol. However, our study shows that vigabatrin certainly is the first line treatment choice. Overall 42 out 51 children were offered vigabatrin as first or second treatment option. To our surprise, only a minority of the children were put on steroids or ACTH in this cohort. We checked the dosages that were used. In the small group, daily dosages were all <50 IU/day (given for an average of 8 days). In the symptomatic group but also in the cryptogenic group, valproate and topiramate were also frequently used. In a recent comparable survey in Japan, valproate, ACTH, zonisamide and pyridoxine were the drugs of choice with pyridoxine as a major first line.[26] Only in four children in our study, pyridoxine was tried.

Of course, cessation of spasms is the most important outcome measure in the early phases of the disease, as it is generally believed that the earlier the control of the spasms, the better the developmental outcome can be. Our data allow us to study the cumulative probability of becoming infantile spasm free. We also determined outcome at the end of the early follow up period (visit 4). In contrast with the controlled studies, but perhaps in concordance with the clinical reality, we did find that it took longer than expected to get the children spasm free. Especially in the symptomatic group, it was not infrequent to need more than 40 days before spasms could be controlled. This probably also explains the many changes in the treatment schedules during the follow up, aiming to stop the spasms as fast as possible.

On the other hand, looking at the number of children being spasm free at visit 4, we find a somewhat higher proportion of children being seizure free than in the UKISS or the Vigevano study.[11,12] Here, perhaps the largest difference between the cryptogenic and symptomatic group was found. In the cryptogenic group, control occurred very early in 90% of the children, while it took significantly longer in the symptomatic group to get a smaller percentage spasm free. As vigabatrin was used equally frequent in both groups, this temporal difference in control is probably not due to the treatment started (as shown in the Cochrane review[9]), but rather to the underlying presence or absence of a brain dysfunction.

The incidence of epilepsy at the long term follow up showed that 60% of the children had no seizures at this last visit, but all were still under medication. Again the percentage of seizures was significantly higher in the symptomatic group than in the cryptogenic group. The number of children with partial seizures was comparable to what was found in other long term follow up studies[3] and reflects the focal brain lesions in the symptomatic group. Although we did not study the medications taken at that long term visit systematically, we did not observe a major shift to for instance AEDs with a narrower spectrum profile (especially carbamazepine, oxcarbazepine).

Our developmental outcome data do underscore the importance of finding the possible brain dysfunction: in the symptomatic group, 80% of the children remained developmentally delayed. Although counter-intuitive for the parents, not finding a cause for the infantile spasms should be considered as a positive prospective factor concerning epilepsy and developmental outcome. However, we also found a high incidence of developmental problems in the cryptogenic group. These were children without a pre-existing developmental abnormality or neurological abnormalities, and with a 90% chance of becoming infantile spasms free early in the follow up, but still 50% had a developmental problem at the long term follow up period. Of course, it is possible that an underlying diagnosis was missed in these children. The diagnostic examina-

tions in these five children were not different or less detailed in these children however.

This difference in outcome could also be explained by the treatment choice. In our population, the large majority was treated with vigabatrin. In recent studies, it was clearly shown that initial ACTH treatment might give a better developmental outcome compared to vigabatrin.[7,10]

Overall, our retrospective survey actually indicates that comparable outcome measures were obtained with the use of vigabatrin early in the course of the disease, and with patient-driven changes in the drug treatment. ACTH or steroids were used as second lines, together with topiramate and vigabatrin. Although early response appears later than expected, the ultimate outcome regarding development and epilepsy is very comparable to the ones reached with more prospective and controlled studies. A major conclusion is that the finding of a cause for the infantile spasm is related with a worse outcome.

Disclosure

This study was partly supported by Janssen-Cilag Medical Affairs Belgium.

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