Reviewer's report

Title: Clinical course and seizure outcome of idiopathic childhood epilepsy: determinants of early and long-term prognosis.

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Reviewer: Willem FM Arts

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It is certainly an interesting idea to study the prognosis of certain types of childhood epilepsy in the same way the large cohort studies on the prognosis of childhood epilepsy in general (Sillanpää et al., Camfield et al., Berg et al., the Dutch Study) have done this. I especially like the way in which the authors have concentrated not only on final outcome, but also on the course of the epilepsy, demonstrating again that epilepsy has a dynamic course, and that the “final” outcome depends at least partly on the moment the outcome is determined (Geerts et al). The use of four different patterns to define the course of the individual patients helps to obtain a better picture of this matter.

Major compulsory points

1. In their report, the authors concentrate on the so-called idiopathic epilepsies, i.e. those epilepsies in which a genetic or constitutional factor seems to be most important for the pathogenesis, and not structural abnormalities. This is still a relatively large group of epilepsy types (partial, generalized) and syndromes. Of some of these syndromes, the specific prognosis has already been elucidated in prospective studies or meta-analyses (Callenbach et al, Bouma et al). In the latter studies, some syndromes show a relatively homogeneous picture (e.g. benign rolandic epilepsy), others, however, have a more heterogeneous outcome (e.g. absence epilepsy). Also, variables appearing to influence the outcome vary between the different syndromes. So, drawing conclusions from a study that focuses on the common denominator of these syndromes, i.e. their idiopathic aetiology, may be problematic. The authors should, therefore, extend the rationale for their study, and come back to this issue in the discussion.

2. A drawback of this paper is the seemingly over-optimistic picture that the authors find for the idiopathic childhood epilepsies (see especially the section on “Proportion of seizure remission during follow-up”). These figures are too good to be true, and I suspect that methodological issues may explain at least part of it. This was a largely retrospective study with only a small proportion of the participating children being followed only prospectively. In the prospectively followed group (47 out of 303), there were apparently no false-positive diagnoses of epilepsy. Such a diagnostic accuracy (100%) seems unlikely to me. In daily clinical practice, one regularly encounters patients initially diagnosed with epilepsy, who after follow-up appear to have reflex-anoxic spells, vasovagal spells, breath-holding spells etc. with their inherently good prognosis. Such false-positive diagnoses may have occurred especially in the prospective, but
also in the retrospective group. Moreover, in the retrospectively followed group, yet another mechanism may have been at work. How were the patients selected for the follow-up study? Simply taking all children labelled with a diagnosis of any type of idiopathic epilepsy in their file will probably result in underdiagnosis because children with atypical or initially unclear pictures will not be included. Did the authors analyse their entire cohort of epilepsy patients for the diagnosis of idiopathic epilepsy at the moment of the intake for the study? If not, they may have missed false-negative cases. Including false-positive cases and neglecting false-negative cases may both influence the outcome in a too favourable direction. The paper should certainly address these issues, and preferably present data about them. The data presented in the first paragraph of the Results do not suffice in this respect.

3. My next point concerns diagnosis and classification of the epileptic syndromes (table 2). I will focus on a few items. First of all, the authors mention 31 children with idiopathic partial epilepsy, not being rolandic or Panayiotopoulos or Gastaut type of IPE. What or which syndrome(s) do these patients have? Or do they have cryptogenic partial epilepsy? It is noteworthy that especially in this group, a relatively large number of children with a poor or relapsing course is found. Then, the authors present 8 cases with myoclonic-astatic seizures. Inasmuch as this is synonymous with Doose syndrome, I would not consider this to be a type of idiopathic generalized epilepsy but rather of secondarily generalized epilepsy.

Minor but essential points

1. An issue that this study could try to answer, is whether idiopathic generalized epilepsy with rare generalized tonic-clonic seizures and a relatively short and benign course is indeed a separate syndrome, so far unrecognized, or should still be grouped in the category of IGE not otherwise specified. In the Dutch Study, we had the impression that this could very well be a specific syndrome, but we were unable to provide definite proof for it. It would be very interesting to see whether the authors can find such patients in their material.

2. In the second paragraph of the section “Definitions”, the authors define early remission and initial non-response. I cannot completely understand these definitions, since they seem to overlap. A patient with seizures until, say, the 10th month of follow-up and seizure-free thereafter, is he considered to be in early remission (seizure-free from within the initial 12 months of treatment) or as initially not responding (seizures occurred within the same period of time)? In other words, should early remission not be defined as being in remission from the start of follow-up? It is also confusing that Terminal Remission is not defined as the length of the period of remission at the last follow-up moment, but as a fixed duration of remission (> 2 years) at that moment.

3. In the section “Statistical analyses”, I cannot find the authors’ definition of what they consider to be significant. Usually, P-values of <0.05 are chosen. However, in Table 3, status epilepticus is considered to be significant with a P-value of 0.051, poor-average academic performance with a P-value 0.056, and multiple seizure types with a P-value of 0.069.

4. Also in Table 3, four variables have an inverse relation with the outcome under
study. That would mean that age at seizure onset 6-9 ears old would be associated with a decreased chance of remission, that poor-average academic performance would be associated with an increased chance of remission, that age at seizure onset less than 4 years old would be associated with a decreased chance of a relapsing course, whereas immediate response to treatment would be associated with a decreased chance of an excellent or improving course. To me, these do not seem to be logical findings. The authors mention in the section “Predictive variables” that immediate response to treatment was strongly correlated with remission and an excellent course, and this recurs in the Discussion. Therefore, I wonder whether the authors can explain this, or else correct their data.

5. The section “Epileptic syndrome” deserves further details, since it now concentrates on BCECTS and CAE (with results that are not new in my opinion), but does not mention other syndromes. In the Discussion, the authors comment on the benign nature of both syndromes as far as seizure control is concerned. However, it has been known since a long time (Gastaut) that the prognosis of CAE is less good in terms of cognitive outcome. I think the authors should present their data about this and comment on it.

6. The Discussion should be revised in the light of the preceding comments.

7. Minor issues not for publication, language etc.
   a. P. 3, 2nd paragraph: However, it has been proven …
   b. P. 4, Patients: All were prescribed AED treatment … (omit “with”)
   c. P. 5, Study protocol: … during the initial 12 months was recorded for …
   d. P. 13, Discussion, 2nd paragraph: … childhood epilepsy has been addressed in various … (omit “to”)
   e. P. 15, 1st paragraph: These differences confirm … (omit “that arise”)
   f. P. 17, 2nd paragraph, last line: often, not oftentimes

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I do not have any competing interests.