Author's response to reviews

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

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Version: 3 Date: 5 November 2013
Author's response to reviews: see over
The Biomed Central Editorial Team

**Object:** MS: 8988115501006048 - Clinical course and seizure outcome of idiopathic childhood epilepsy: determinants of early and long-term prognosis.

Thank you for consideration of our manuscript for publication in your journal. On behalf of the co-authors, I am submitting the revised manuscript Version 3. The authors have read carefully the reviewers' and editorial comments and provide you with the ‘point-by-point’ analysis of all the changes made as requested. Moreover, the manuscript was reviewed and corrected where needed (syntax and grammar), by an English native-speaking colleague. The name of the ethical committee was added in the Methods section of the main manuscript.

**Reviewer #1:**

**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 [...] 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.

**Answer (A):** Thank you for this detailed remark expressing your reasonable reservations. In an attempt to respond to them, we the authors argue that we decided to perform a prognostic study following a homogeneous group of children with epilepsy, which also allowed for a significant number of subjects to be enrolled, adding to the statistical value of the study. Idiopathic epilepsies, considered as being “epilepsy-only” or “genetic” according to their most recent ILAE definition provided a good example of the desired target group. Moreover, idiopathic epilepsies are by far the most commonly encountered epilepsies in childhood, with a large number of children attended and followed-up even by general pediatricians in everyday clinical practice, adding to our rationale. Knowing that different epileptic syndromes of idiopathic aetiology carry a different course and outcome, in the current study we focused on careful syndromic classification and allocation of the results not only on idiopathic epilepsies as a group but on each different epileptic syndrome as well.

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. [...] 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 labeled 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 analyze 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 favorable 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.

A: Thank you for pointing this out. In the original Methods section of the manuscript the authors acknowledge a lack in detail explaining the criteria used to select the subjects of our study. We attempted to correct this by adding statements of further clarification in the revised manuscript. Our study was not designed to be an epidemiological register of all idiopathic epilepsies diagnosed in daily clinical practice over a period of time, but rather a focus on the course and long-term outcome of children diagnosed with certain idiopathic epileptic syndromes and given AED treatment.

For the retrospective group the diagnosis was based on sufficient and detailed clinical and EEG documentation, review of their entire records by a team of two child neurologists (Prof. Zafeiriou, Prof. Kontopoulos) and reevaluation by phone at the end of the data collection period (December 2012). Following the above mentioned method, syndromic classification was able for the majority of the retrospective cases with as few false-negative cases as possible.

As far as the prospective arm of the study is concerned, subjects were enrolled after Jan 2008 when an idiopathic epileptic syndrome was diagnosed to them and AED treatment was started and were then followed-up until the end of data collection in December 2012. In those cases in which matters of non-compliance were noted during the child’s therapy, episodes initially considered to be epileptic seizures proved to be of non-epileptic nature or even the initial diagnosis of idiopathic aetiology was contradicted by newer findings, subjects were excluded from the study in order to end up with a cohort that reflected our initial goal, with as few false-positive cases as possible. We think that indeed this homogeneity of the study group (idiopathic epilepsies only) is portrayed in our optimistic findings regarding course and outcome, as -to our experience- non epileptic paroxysmal events most often run a course of their own not responding to AED treatment when given.

3. My next point concerns diagnosis and classification of the epileptic syndromes (table 2). I will focus on a few items.

a. 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 are found.

**A:** The majority of these cases are among the retrospective group of patients. Based on their EEG recordings and clinical characteristics the team of child neurologists could not reach a safe syndromic classification, however being that all patients had both a normal MRI of the brain and a normal neurological examination they were grouped as idiopathic partial epilepsies. Among these cases the diagnosis of familial frontal or temporal epilepsy could be presumed but not safely made based on existing data. Also, the possibility of cryptogenic partial epilepsy on the grounds of undiscovered cortex dysplasia could not be overlooked, especially in those drug-resistant cases, because imaging with a 3,5 tesla MRI was not available in any of these children.

b. Then, the authors present 8 cases with myoclonic-astatic seizures. In as much 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.

**A:** The category under which Doose syndrome is classified has been a matter of great debate, and many authors, including Doose himself, thought that it may be considered as a primary generalized idiopathic disorder with a genetic predisposition. However, there have been some reports of children with Doose syndrome who have identified underlying abnormalities, and thus symptomatic–structural aetiologies to explain the phenotype. Following the new ILAE classification scheme by Engel J. of the ILAE Task Force on Classification and Terminology (Epilepsia, 42(6):796–803, 2001), the authors considered Doose syndrome synonymous to “Epilepsy with myoclonic astatic seizures” and classified this epileptic syndrome among idiopathic generalized epilepsies as proposed by the ILAE Task Force.

**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.

**A:** Among our study population 30 patients were diagnosed with idiopathic generalized epilepsy with GTCS, 16 of whom fall under the syndromic classification of “Epilepsy with GTCS only.” Among those, 11 patients started treatment with 1 AED after 1-2 episodes of GTCS and followed a benign course (82% early remission, 100% long-term remission, only 1/11 relapsing course) and 5 patients were treated after having 2-5 episodes of GTCS with 1-2 AEDs. While having a favorable initial response to treatment (80% early remission), one or more relapses were reported in 3/5 patients of the latter group, thus having a less favorable course. Analyzing the descriptive and clinical characteristics of the two groups, we could not find enough reasonable evidence to support a separate syndromic classification, such as specific age at seizure onset, EEG findings or neurological background, however the difference in clinical course that was noted in our study too justifies further focus on this subject.
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.

A: We agree that certain confusion arises with the definition of the term “early remission” and further clarification is indeed useful regarding this point. Defining the response to treatment during the initial 12 months, we considered the occurrence of any seizures during the above period as “initial non-response,” thus making the absence of any seizures be considered as “immediate remission.” However, we were faced with certain cases of, say, absence seizures that were controlled within the initial 2-3 months of treatment and were seizure-free thereafter, which we decided to classify as cases of “early remission” as opposed to “non-responders”. This way, children who exhibited seizure freedom from the start or within the first 3 months of treatment were classified as “early responders”. Taking into account the example of a child who experiences seizures until the 10th month of treatment and then becomes seizure-free, he or she is classified as having “initial non-response” according to the above definitions.

In order to clarify this point we have replaced the definition of “early remission” in the revised manuscript as follows: In this study, “early remission” was defined as seizure-freedom achieved immediately or within the initial 3 months of treatment, whereas “initial non-response” was defined as the occurrence of seizures beyond the first 3 months of follow-up during the initial year of treatment.

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.

A: Thank you indeed for pointing this out. We address this issue accordingly in the section “Statistical analysis” of the revised manuscript. As clarified in this paragraph, Table 3 displays the variables which remain in the final multivariate models. In the univariate analysis preceding the multivariate, potential prognostic factors were assessed using P-value <0.05 as a cut-off criterion. In the multivariate analysis though, we used backward elimination stepwise procedure where variables having p-value greater than 0.10 were removed from the models [1].


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.

A: Thank you again for pointing this out. Following your carefully aimed comments, Table 3, presenting the results of the multivariate analysis, was reevaluated for its statistical accuracy by the team’s data analyst. All of the results displayed on this table were confirmed and so were the conclusions made at the section of the Discussion on the basis of these data. However, significant discrepancies were acknowledged in the presentation of these figures leading to misinterpretation of the actual results of the study. In the revised manuscript we have corrected Table 3 accordingly.

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.

A: Thank you indeed for pointing this out. We absolutely agree that the section regarding “epileptic syndromes” of the Results deserves further details as far as epileptic syndromes other than CAE and BCECTS are concerned and also any available data regarding the cognitive outcome of children with idiopathic epilepsy. In the revised manuscript a new paragraph is added to the Results section “Epileptic syndromes” presenting the course and outcome of other epileptic syndromes. In addition, we present the academic performance of children with CAE and BCECTS, the only two syndromes where the number of patients would allow conclusions to be drawn by statistical analysis. The above mentioned results are commented on in the Discussion of the revised manuscript.

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

A: The Discussion of the manuscript has been revised by the authors in order to address all of the preceding issues and hopefully provide adequate answers and clarifications.

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

A: Thank you for the detailed grammar and language assessment of the original manuscript. All of the above mentioned corrections were made to the revised manuscript.
Reviewer #2:

1. In your paper you have allocated your results on two syndromes, CAE and BCECTS. Only during the discussion some general comments are made to few idiopathic syndromes.

**Answer (A):** Thank you for pointing this out. The section of the Results regarding “epileptic syndromes” was rewritten following both your remarks and the remarks of Reviewer #1. In the revised manuscript, results on the course and prognosis of other major idiopathic epileptic syndromes were added and commented upon in the Discussion. Table 2 summarizes the clinical course and outcome of each epileptic syndrome.

2. Some specific corrections and comments

   a. Page 3: background 4th line should read ...without any identifiable or suspected cause, other than a genetic predisposition.

      **A:** Thank you, this sentence of further clarification and accuracy was added to the revised manuscript.

   b. Page 4, last line add if seizures continued using an appropriate daily dose.

      **A:** Thank you again, this sentence was added to the revised manuscript.

   c. Page 5, definition, first paragraph, 7th line add ...anatomic brain lesion or other neurological signs or symptoms.

      **A:** This sentence was added too.

   d. Page 5, 2nd paragraph: Patients were defined as having a "relapse" when seizures were controlled for more than 12 consecutive months and relapsed. Q: compliance?

      **A:** All the subjects of the original cohort who were considered as being non-compliant to the treatment suggested and the follow-up required were excluded from the study and therefore no results were recorded and analyzed of such patients. A “relapse” was defined as the recurrence of seizures after a complete seizure free year and this definition applied to fully compliant patients following the appropriate treatment. We added a clarifying sentence in the revised manuscript at the Definitions section.

3. Results. In general your results do not follow syndrome classification based on clinical and EEG characteristics but instead the syndromes are lumped together as an entity. The only syndromes you have separated are CAE and BCECTS.

   **A:** The authors agree and thank you for this remark. We have addressed this issue in response to your first comment.

4. Author for what reason 216 (71%) children and adolescents had neuroimaging studies for idiopathic syndromes?

   **A:** Naturally, performing a neuroimaging study of the brain is not encouraged as a rule for children diagnosed with a generalized idiopathic epileptic syndrome or BCECTS. The same
principle applied to our patients, with MRI brain imaging reserved for cases of focal EEG activity not consistent with a definite syndromic diagnosis or cases of drug resistant seizures. A significant number of our patients had neuroimaging studies prescribed by a former physician, either as a standard policy during hospitalization for their initial seizure episode or for the evaluation of a symptom other than seizures, i.e. a chronic headache.

5. Discussion, first paragraph. Author you state: .... in order to report the clinical course and prognosis of each epileptic syndrome and identify variables prognostic of a less favorable outcome after short and long-term follow-up. Author that is exactly what you have not done with your results.

A: The aim of our study was to investigate a homogenous group of children with idiopathic epilepsy, treated with AED, and -if possible-, identify determinants of their prognosis, both early and after long-term follow-up. After multivariate statistical analysis of our results was performed, we concluded that variables prognostic of a less than favorable outcome after short term follow-up were the presence of multiple seizure types, the occurrence of status epilepticus and the young age at seizure onset, while after long-term follow-up, the additional diagnosis of migraine and the initial non response to treatment.

6. Author your paper is very well written but in order to avoid the stated limitations, in my view, you should allocate the title and the results on CAE and BCECTS or state in your limitation that the recognition of various syndromes was not possible because the majority of subjects was followed retrospectively and alter accordingly some statements made in the text.

A: Thank you indeed for this remark and suggestion. Acknowledging the lack of sufficient presentation of idiopathic epileptic syndromes other than CAE and BCECTS in the original manuscript, we rewrote the section of Results and Discussion regarding epileptic syndromes, presenting additional data and comments on their course and outcome. Although the majority of subjects in our study was followed retrospectively based on hospital records, the EEG and clinical documentation available was meticulous and detailed enough to ensure a correct syndromic classification in most cases. Moreover, all patients diagnosed with epilepsy before Jan 1st 2008 were reevaluated at the end of the long-term follow-up and their clinical course and seizure outcome was accurately recorded. The paragraph stating the study’s limitations has been revised to clarify the above mentioned issues.