Reviewer’s report

Title: Mortality in children with classic congenital adrenal hyperplasia and 21-hydroxylase deficiency (CAH) in Germany.

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Reviewer: Paul Hofman

Reviewer's report:

This is a case series of CAH mortality in Germany using the results of two surveys. This suggests a relatively high mortality rate in the past with an apparent reduction/absence of early mortality in more recent years. Moreover the mortality appears directly related to acute illness and likely Addisonian crisis due to insufficient stress doses of glucocorticoids. While the data is not novel it adds to a similar literature from other countries…predominantly from Europe. I do have some issues that require addressing

1) There are major weaknesses in the approach the authors have taken which they do discuss. In particular new born screening was present for only part of the study duration. Thus, there is going to be underreporting of CAH during this period. Did the survey cover the whole of Germany? I suspect not as East Germany prior to 1990 would not have been included at the very least. Thus as neither the denominator or the numerator are known trying to establish a mortality rate is impossible and description only is probably the best approach. That said the same criticisms can be made of mortality rates from other national publications (that are also described in this manuscript). Thus, if the authors want to try and calculate a mortality rate they should clearly state when CAH screening started in Germany and ideally the number of CAH individuals identified before and after this date. If data are known from East Germany this should be included. Similarly, the German database of CAH is not well described. How complete is this and does it completely overlap with the mortality survey or are there differences?

2) The higher number of girls dying likely reflects the lack of CAH screening in the early years in Germany - this should be correlated against the sex ratio in this older group which I am confident is mainly female. I would like to see this sex difference discussed as I doubt if its still present when correction for sex ration in all CAH is done.

3) If rates are going to be used they should be in the result nad not the discussion. However, I consider they are so flawed as to be unusable.

4) Page 5, line 49 Pseudonymously - I think this should be anonymously
5) Apallic syndrome is not used in most medical literature now and the readers will not be aware of this- suggest the term 'persistent vegetative state' which is now more commonly used.

6) To me the main conclusion of this study is that glucocorticoid stress dosing during illness has improved and mortality has fallen. However there are little data about what was recommended in the past in Germany and what is recommended now. For instance, our country has a national approach of increasing hydrocortisone dose by 4-5 x including more frequent dosing (at least 4x daily) as well as having IM glucocorticoid available for all families, an action plan with emphasis of seeking medical care for IV hydrocortisone with persistent vomiting/ GI illnesses. There is nothing in the manuscript documenting the past or current recommendations in Germany and I would have thought that was relevant given that the deaths were probably all relating to insufficient stress glucocorticoid dosing and Addisonian crises.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

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