Author’s response to reviews

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

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To The Editors:

First of all we would like to thank both reviewers for their helpful and structural comments. We accepted all the addressed points. We marked the changes which we made in yellow. Enclosed you can find the revised manuscript.

Altogether, reports on mortality of children with CAH are very rare in the literature. This is the first report from Germany addressing this topic.

To Reviewer 1:

1. Our survey covered the whole of Germany (information added to Methods). The German Reunification occurred in 1990. Our survey was conducted two times (2001-2002, and in 2015), and 88 centres including all Paediatric University Hospitals in Germany responded.

Newborn screening for CAH was introduced in Germany in 1999. We identified 14 cases of death during the period from 1973 to 2004. In the Table, we excluded the year of death of the children in order to protect privacy; 7 cases of death occurred before screening, and 7 cases thereafter (information added).

There is no accredited registry in Germany for children with CAH (information added to Methods). In 1997, the German AQUAPE CAH initiative (AQUAPE: Arbeits-gemeinschaft für Qualitätssicherung in der pädiatrischen Endokrinologie) was installed for prospective documentation of clinical follow-up data in patients with CAH.
The database does not mirror the real situation in Germany since the participation is voluntarily and not all centres provide data (information added to Methods). Cases of deceased children were not reported in this database. We agree with you that it is impossible to calculate mortality rates in Germany with the available information. We discarded this section completely from the paper.

2. The number of girls with CAH who died before newborn screening was slightly higher (n=5) than the number of girls (n=4) who died after screening. The sex ratio (female to male) was higher before screening than after screening (2.5 vs. 1.3). Seven out of 14 children died after the introduction of newborn screening. Only 2 infants died before the age of 12 months, and no child died during the newborn period (information added).

3. We cancelled the complete section on mortality rates in Germany.

4. We corrected pseudo to anonymously (Page 5, line 49).

5. We changed “Apallic syndrome” to the term 'persistent vegetative state'.

6. We added the information on the glucocorticoid stress dosages which were recommended in the past in Germany. We have the same recommendations used in your country e.g. increasing hydrocortisone dose by 4-5 times, action plan with emphasis of seeking medical care in a specialized centre for IV hydrocortisone and fluid substitution (0.9% NaCl) with persistent vomiting/ GI illnesses. Additionally the patient should have an emergency health card.

The question is, what can you do as a “specialist” if all your instructions were not followed by the involved parties e.g. general practitioner, paediatrician, parents and/or other caregiver? For example, my own patient (no 5) fell ill with high fever and vomiting in the evening. The mother called the general practitioner who decided that the girl can stay at home. The mother addressed my recommendations (increasing the hydrocortisone dosage and i.v. fluid substitution etc.). The practitioner said to the mother:”I am here and not the specialist. The specialist is always overcautious. Most of them can “hear the grass grow”. It is not necessary to increase the dosage”. The patient deceased early in the morning at home.

Therefore, we agree with you that the deaths were all related to insufficient stress glucocorticoid dosing and Addisonian crises (see page 10, line 5).
To Reviewer 2:

1. We corrected the number of children with molecular genetic classification in relation to the severity of CAH.

2. We explained the "Null genotype" and "A genotype".

3. We deleted the term "uncomplicated" form

4. The symptom "diarrhea" was reported in Williams Textbook of Endocrinology (year 2016; see Table 15-18.

We changed “diarrhea” (page 6 and in the Table) to “gastroenteritis with diarrhea”

5. We added 2 references (review papers).

6. We cancelled the complete section on mortality rates in Germany.

7. The statement "All deaths could be related to an inadequate administration of stress doses.. " is an assumption which is based on the clinical reports given by the participating centres. We changed the statement in the Abstract.

We accepted all minor comments and marked the changes.