Author’s response to reviews

Title: A novel mutation of the StAR gene with congenital adrenal hyperplasia and its association with heterochromia iridis: a case report

Authors:

Vera Splittstösser (vera.splittstoesser@ukbonn.de)
Felix Schreiner (felix.schreiner@ukbonn.de)
Bettina Gohlke (bettina.gohlke@ukbonn.de)
Maik Welzel (maik.welzel@gmx.de)
Paul-Martin Holterhus (PaulMartin.Holterhus@uksh.de)
Joachim Woelfle (joachim.woelfle@ukb.uni-bonn.de)

Version: 1 Date: 03 Oct 2019

Author’s response to reviews:

Dear Dr. Keil,

Thank you for your recent information regarding the status of our manuscript “A novel mutation of the StAR gene with congenital adrenal hyperplasia and its association with heterochromia iridis: a case report”. According to the reviewers’ reports we have modified our manuscript as follows:

Reviewer 1: Even if hyperactive ocular melanocytes have been described in association with high ACTH levels, it does not seem plausible a primary causal association with heterochromia iridis, which is usually considered as a genetic condition. The discussion and the conclusions regarding this point should be modified.

We have modified the discussion section regarding this point. Specifically, we have added a short section discussing the physiology and pathophysiology of human eye color determination in healthy subjects as well as in heterochromia iridis and Waardenburg syndrome patients. We also modified our conclusion: “To conclude, this case report is the first to describe a co-occurrence of severe adrenal insufficiency due to a StAR defect with sectorial heterochromia iridis. We speculate that very high levels of ACTH and alpha-MSH during early developmental
stages may have disturbed early differentiation and spatial distribution of uveal melanocytes. Although we cannot clearly determine whether the association of severe adrenal insufficiency with sectorial iridial heterochromia is caused by this hypothetical mechanism or reflects only a coincidence of two very rare phenotypes”.

Reviewer 2: This article describes a rare congenital adrenal hyperplasia caused by StAR gene deficiency, and a combination of heterochromia iridis. This is an interesting case, two rare diseases coexisted. But there are some major revisions needed to be modified.

1. In the description of the manifestation of the case, please add the level of renin together with aldosterone.

As suggested, we added the measured aldosterone concentration together with renin levels in the abstract and in the case report section. Instead of giving a renin-aldosterone-quotient, which is primarily used in older individuals to further discriminate pathological aldosterone concentrations (e.g. Conn syndrome), we simply added descriptive adjectives “elevated” and “low”/ ”decreased”.

2. There are infrequent descriptions of endocrine-related symptoms in the article, which were important to differentiation diagnosis. For example, the gender of the external genitalia at birth, and the test results of gonadotropin, estradiol and testosterone should be supplied in the initial examination.

Our patient was born with normal female external genitals (information added in the case report section). Levels of gonadotropins, estradiol and testosterone were not measured in the initial examination.

3. It is a great pity that the father and sister of the patient did not have a genetic test. Could the author try to complete the genetic test of families?

We found a novel homozygote Mutation in STAR p.Ala218Thr in our patient. While her mother is heterozygote for the same mutation and the parents are consanguine we didn’t test the father.

4. The special feature of this patient is that there was a new mutation in the StAR gene and the patient had normal puberty and regular periods. It is suggested that the content of the discussion
section will be well organized, focusing on the functional changes caused by new mutations in the StAR gene, and secondly in the rare manifestations of heterochromia iridis combined with StAR gene defects.

As the Reviewer stated, it is interesting that the patient entered puberty spontaneously. However, spontaneous pubertal development in a subset of patients with StAR deficiency is already reported by several scientific reports. We therefore decided to highlight the novel (and so far not described) association with sectorial heterochromia iridis by mentioning/discussing first.

5. There is a sentence, "If confirmed in additional cases, discolorization of the iris might be a useful phenotypical feature aiding in the diagnosis of severe forms of adrenal failure." The sentence needs to be carefully revised, and it is difficult to draw conclusions based on speculation alone.

We modified this last sentence as follows:” If confirmed in additional cases, discolorization of the iris might be considered as an additional phenotypical feature in the differential diagnosis of congenital adrenal insufficiency.”

6. Since the patient has a consanguineous parents, the details of the family history need to be given in detail. If there is similar manifestation or other patients in the family.

As described in the case report, our patient’s parents are cousins of Moroccan origin. The parents and the older sister are healthy. A second cousin in the maternal family, now 3 years old, has a classic congenital adrenogenital hyperplasia with salt loss due to a homozygote CYP21A2 mutation c.1006C>T (p.Arg356Trp). This girl was diagnosed by a strongly elevated 17-OHP level (thus not indicative of a disturbance of cholesterol transport in steroid biosynthesis) in newborn screening and was not tested for a StAR gene mutation.

We hope our manuscript is now suitable for publication in the BMC journal of Endocrine Disorders. In case of any question please do not hesitate to contact us.

Yours sincerely,

Vera Splittstoesser

Joachim Wölfle