Author’s response to reviews

Title: Unilateral adrenal hyperplasia is a usual cause of primary hyperaldosteronism. Results from a Swedish population screening study

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Author’s response to reviews: see over
Correspondance to the reviewers

We are most greatful for the reviewers work in order to improve our manuscript. We have considered the comments and listed the detailed response below.

Referee #1

1) Although this revised manuscript has been improved, the authors have not fully addressed all the comments. In particular, more discussion about AVS and histological findings should be necessary.

Our response:

We discuss AVS in this paper

- in view of increasing the biochemical cure rate of PA and in minimizing the risk of adrenalectomy of a non-producing adrenal incidentaloma (Introduction, 2nd paragraph).
- as although the use of AVS and lateralization index is mandatory in defining a unilateral dominant disease it does not preclude the possibility of the contra lateral gland being entirely free from hyperplasia (Discussion, 2nd paragraph, page 13).
- as adrenalectomy with the use of a laparoscopic technique has become much easier and to be cost-beneficial over long-term medical therapy, it is of increasing interest to find patients with unilateral PA eligible for surgical therapy as surgical removal of APA or unilateral AH has been found to normalise hypokalaemia and improve hypertension (Discussion, 2nd paragraph, page 13).
- as imaging results were found to be confounding in up to half of the cases and the use of scintigraphy was not helpful in the etiological work-up of patients with PA, the importance of using AVS in detection of unilateral vs. bilateral PA was emphasized (In the Discussion, 2nd paragraph, page 14).

We did not discuss the importance of AVS to be executed by an experienced radiologist and have now added the following sentence to the Discussion, end of 2nd paragraph, page 14: „AVS needs to be executed by an experienced radiologist, due to the anatomy of the right adrenal vein, that often causes a failing procedure. This indicates that AVS should only be performed in specialised centers.“

Concerning histopathological results:

The reviewer is quite right. We have added the following sentence to the Discussion, 2nd paragraph, page 13:

„In a recent review on the subject unilateral PA is presented as 2% of PA, bilateral hyperplasia as 60% and unilateral adenoma as 35%. Our results are in huge discrepancy with this.“

We have also added the reference (WF Young Clin Endo 2007) formerly pointed out by the reviewer.

2) Table 3 should be excluded since the authors think it to be extra and not included in the aim of the study.

Our response:

The referee is quite right, the aim of the study did not include follow up of the patients with blood pressure measurements and serum potassium evaluations, even though that would have been favourable. Neverthe less, the patients were followed for longer or shorter time, and we find these results add information to the discussion.

Referee #2 strongly opposes to omit Table 3. We agree with that and recommend keeping the table.

Referee #2
Major Compulsory Revisions
1) Bland and Altman in their 1988 Lancet paper have made it lucidly clear that correlation is not the way to compare two methods of measurement. I don’t understand the reluctance of the authors to stick to correlation of the two PRA methods.
   Our response:
   We agree with the referee, that correctly refers to the Bland Altman paper. However, in our study seventy-four samples were run in parallel using both methods, and there was a highly significant correlation between the two measurements (r = 0.97, p<0.0001). The Bland-Altman analysis did not reveal any significant trend in the difference between high and low concentrations.

2) One operated patient (#2010), like Popper’s black swan, disproves the second part of the title. Why not describe the cohort as it is, without claims of mandatoriness of certain interventions?
   Our response:
   The referee is perfectly right. We therefore change the title of our paper to: Unilateral adrenal hyperplasia is a usual cause of primary hyperaldosteronism. Results from a Swedish screening study.

3) I strongly oppose to omit Table 3. Follow-up is the only way to judge with a certain level of confidence if management of patients has been correct.
   Our response:
   We agree with the reviewer and recommend keeping table 3 in the paper.

Minor Essential Revisions
4) Table 3 still contains ‘EA’ which I now understand stands for ‘endoscopic adrenalectomy’
   Our response:
   In order to minimize all misunderstanding we have excluded EA, the shortening of Endoscopic Adrenalectomy, in Table 3 and changed it to Laparoscopic Adrenalectomy without shortening.