Author's response to reviews

Title: Dose-dependent improvement of myoclonic hyperkinesia due to Valproic acid in eight Huntington's Disease patients: a case series

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Author's response to reviews: see over
Dear Sirs,

Thank You for Your writing from November 15th regarding our manuscript “Valproic acid in Huntington’s disease”, manuscript number 5348702997501659.

We would like to address the points raised by the referees as follows:

First review (Raphael M Bonelli):

We thank for the helpful suggestions and made the following changes in the manuscript:

1. We agree, tetrabenazine is not a neuroleptic. We changed the sentence and amended the suggested drugs:
   “Chorea in Huntington’s Disease (HD) is usually treated with antidopaminergic neuroleptics like haloperidol, olanzapine and tiaprid or dopamine-depleting drugs like tetrabenazine. Some patients with hyperkinesia, however, react to treatment with antidopaminergic drugs by developing extrapyramidal side effects.”
2. We deleted the sentences: “Especially in patients with signs of parkinsonism antidopaminergic medication often leads to a worsening of symptoms” and “It does not sufficiently respond on antidopaminergic medication.”
3. We added the missing publication of Kereshi 1980, like suggested:
   “Kereshi et al. described a reduction of symptoms in a 26 year old woman suffering from HD with myoclonic hyperkinesias after a combined treatment with haloperidol and valproic acid.”
4. We changed the background section as described above (see point 1.-3.)
5. Thanks.
6. We deleted the sentence “Valproic acid seems to be more efficient than antidopaminergics in those patients. Besides, valproic acid has no side effects on the extrapyramidal system.” We made some analogous changes in the main conclusion part in the paper.

Second review (Steven J Frucht):

We thank for the helpful suggestions and made the following changes in the manuscript:

1. Written consent for publication from all of the patients or their legal guardians was obtained and was faxed to the BioMed Central Editorial board. The BioMed Central Editorial board suggested to change the title in order to reflect the fact that the manuscript is a description of a case series to: “Dose-dependent improvement of myoclonic hyperkinesia due to Valproic acid in eight Huntington’s Disease patients: a case series.
2. Patients were rated by the authors themselves.
3. The relevant co-medication has been listed in table 2. We described changes in medication if undertaken. In three of the patients antidopaminergic medication could be reduced markedly (case 3, 6 and 7 (see video 3 and 4)), in the remaining patients (also case 1 (see video 1 and 2)) antidopaminergic treatment was basically unchanged (see results). In case 2 (see handwriting) no additional drug apart from riluzole was administered. Riluzole recently demonstrated not to have any effect on the symptoms and the course of HD (European EHDI-trail).

4. We tried to describe the character of myoclonus more closely in the methods section and discussed its origin as far as possible. We added: “All patients presented a multifocal positive myoclonus. In one patient (case 3) a stimulus sensitive myoclonus was observed, but movement also occurred while active. No additional electrophysiological studies were performed” and “The postulated mechanisms for myoclonus in HD have differed in literature [26]. Neurophysiological investigations in most earlier studies, documented generalised and multifocal action myoclonus of cortical origin. In some cases, myoclonus was strikingly stimulus sensitive [13]. Myoclonus, as recorded by surface electromyography consisted of 40-60 ms-synchronous semirhythmic bursts. The cortical component of somatosensory evoked potential was enlarged in some cases, representing a cortical myoclonus [1, 26]. Since additional electrophysiological studies in our cases were not performed, we can only speculate about a presumed cortical origin of myoclonus following literature and our clinical impression.”

All tables and figures were labelled, language corrections were performed by a native speaker.

We hope that this satisfactorily answers the comments of the referees and look forward to your reply with interest.

Apart from these changes we improved the technical quality of the videos 1 and 2 and kindly request Your acceptance with that.

Following Your suggestion, we went through the manuscript formatting checklist and hope that the manuscript now conforms to all of the points.

Yours sincerely

Carsten Saft