Author's response to reviews

Title: Tics as an initial manifestation of juvenile Huntington's disease: Case Report and Literature Review

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Author's response to reviews:

Dear Dr. Kuo-Hsuan Chang,

Thanks a lot for your edits and the comments from your referees. We have revised our manuscript (NURL-D-16-00647) entitled "Tics as an initial manifestation of juvenile Huntington's disease: Case Report and Literature Review" according to your suggestions and those comments. I would be grateful if you could consider for the publication of our manuscript on BMC Neurology.

The followings are our detail responses to the comments of your referees.

Sincerely,

Dr. Gang Wang
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Reviewer #1:

Reviewer 1: In this manuscript, the authors report a case of (later genetically confirmed) juvenile Huntington's Disease who initially presented with tics. The authors conclude that there is
necessity of testing for the HD mutation in young patients with tics. The manuscript has severe scientific shortcomings, in detail

1. The case report as presented is of very limited value for clinical differential diagnostics in similar patients since a conceptual approach to the clinical challenge is missing. The Figure is unnecessary.

Answer: Thanks a lot for your suggestions and we have added the clinical differential diagnosis in the Discussion as following: "However, both the symptom of cervical dystonia and the abnormal EEG are rarely mentioned in TS. Thus we screened for the secondary tics, including head trauma, stroke, certain drugs, toxins, post-infection, neuroacanthocytosis, iron deposition, Wilson disease (WD), and HD. WD, iron deposition could be excluded by the absence of KF ring, normal iron and copper metabolism, normal structural MRI imaging. Head trauma, post infection and toxins are also been excluded since the patient denied the history of streptococcus infection, trauma, drug abuse. Normal structural MRI excludes stroke meanwhile. Neuroacanthocytosis can be excluded with the absence of hemolyosis and normal blood smear. " By the way, the figure has been deleted according to your comments.

2. The result of the genetic testing needs further explanations.

Answer: Thanks and we have added the further explanations in the Discussion as following

"Although longer CAG repeats predict earlier onset, CAG repeat length only accounts for about 60% of the variability. The remaining are ascribed to additional genetic, environmental factors and other factors including somatic expansions in brain or increasing in size."

3. The literature review which is addressed in the manuscript title is not sufficiently informative both with respect to methods (search strategy is not appropriately described) and with respect to results.

Answer: Thanks and we have added the search strategy in details in the content as following:"A review of the literature yielded initial symptoms and DNA analysis in 33 JHD patients when we used “juvenile Huntington’s disease”, "juvenile Huntington’s chorea"," Huntington’s disease "," Huntington’s chorea" and “Case report”, "Clinical study" for searching in Pubmed, Embase, Cochrane Library, Web of Knowledge, CINAHL and ProQuest databases (Table 1)." According to the search results, we found that the most prevalent symptoms are ataxia, and two cases reported tics as initial and prominent manifestation in JHD. Among them, 88% patients carried CAG repeats beyond 60 and most of them have family history. The results in details are in Table 1.

Reviewer 2

I have reviewed the manuscript entitled "Tics as an initial manifestation of juvenile Huntington's disease: case report and literature review". This case describes a boy developing motor and phonic tics around age 9, then cervical dystonia around age 12. When presenting to clinic at age 17, he had symptoms of ADHD and obsessive-compulsive disorder. Overall, except for the
cervical dystonia, this would be a textbook presentation of a Tourette's syndrome. However, and for unclear reasons, the authors decided to perform EEG, EMG and genetic testing for Huntington's disease (HD) without any suspicion reported on history. The HD test came back positive for 49 CAG repeats. The authors conclude on the "necessity of testing for the HD mutation in young patients with tics even without family history [of HD]". I feel this conclusion is very excessive and certainly not cost effective. Considering the frequency of Tourette's syndrome and the relative paucity of Huntington's disease, I am more inclined to label the diagnosis of HD in this patient as incidental. In hindsight, the epileptiform discharge detected on EEG and the cervical dystonia might be abnormalities related to HD. However, it is hard to link the Tourettism in this patient to HD. Previous cases of tics in HD patients were of adult onset tics, which would then be an exclusionary diagnosis for Tourette's (which onset has to be before age 21), and usually involved cognitive decline, chorea or other symptoms suggestive of Huntington's disease. In addition, with such a low CAG repeat, one would expect a much later onset of HD symptoms, although exceptions to the rule are always possible.

Answer: Thank you for your comments. Firstly, previous cases of tics in HD patients were of adult onset tics, and however there are also some cases of tic in HD patients with young-onset before age 21 years old, including Liu et al, Clin Genet. 2014 Feb;85(2):189-93. and Xing et al, Neurol Sci. 2008 Sep;29(4):275-7. Secondly, although longer CAG repeats predict earlier onset, CAG repeat length only accounts for about 60% of the variability. The remaining are ascribed to additional genetic, environmental factors and other factors including somatic expansions in brain or increasing in size. HD should be considered in patients with juvenile-onset tic, especially with symptoms can’t be totally explained by TS, even in case of a negative family history although TS may be more prevalent.”

Finally, the argument that both HD and tics are somewhat associated to a dopaminergic system dysfunction is not enough to make the case for an association between the two syndromes. Indeed, many movement disorders are associated with dopamine dysfunction and yet are not seen with tics.

Answer: We agree with you and the molecular mechanism need further investigated in future. We have added the sentence "Both HD and tics are somewhat associated to a dopaminergic system dysfunction, however the molecular mechanism for the relationship between HD and TS need further investigated in future." in the Content.

Most importantly, the authors do not mention investigating the family for subtle tics, ADHD or OCD trait. In practice, many parents deny any Tourettism in the family, but, once probed more specifically, admit to some ADHD, OCD, or mild "sniffing and blinking" in one or more relatives. Presence of such symptoms in family history, combined with the absence of any CAG repeat expansion in the parents, would clearly points towards a coincidental coexistence of Tourette's syndrome and HD, rather than Tourettism caused by HD.

Answer: Thanks a lot for suggestion and we ask the family history about it in details. His parents had no family history of neurologic disorders including tics, HD, obsessive-compulsive disorder(OCD), attention deficit hyperactivity disorder(ADHD). Additionally, the progressive
In this case, different from the wax and wane course typically in TS give less priority to the hypothesis of comorbidity.

In addition, I think the subtitle "conclusion" is in the wrong place and the manuscript, and I would strongly suggest English editing services.

Answer: Subtitle was replaced by “Discussion and Conclusion”, and we have invited a native English writer to revise it.

Reviewer 3

This manuscript by Cui and colleagues reported a boy with tics who carried expanded CAG trinucleotide repeats in HTT. This is a very interesting report particularly in the broad clinical spectrum of juvenile Huntington's disease (JHD). However, some issues need to be addressed or corrected.

1. JHD frequently displays long CAG repeats, whereas the repeat number in this adolescent is only 49. It is very likely that tics, as a common disease, is a comorbidity rather than the initial presentation of HD in this patient.

Answer: Thank you for your comments. Although longer CAG repeats predict earlier onset, CAG repeat length only accounts for about 60% of the variability. The remaining are ascribed to additional genetic, environmental factors and other factors including somatic expansions in brain or increasing in size. Additionally, the progressive course in this case, different from the wax and wane course typically in TS give less priority to the hypothesis of comorbidity.”

2. MRI did not show pathognomonic caudate atrophy for HD

Answer: His structural MRI imaging is normal without pathognomonic caudate atrophy. We guess that both early stage of HD and relatively low CAG repeats may contribute to the normal MRI.

3. Seizures are occasionally seen in JHD. This point should be discussed.

Answer: Thanks a lot for your suggestions. We have added the sentences "Green JB have reported that 2 patients of JHD showed spikes in EEG without any type of seizure. Positive spikes at 6-7 and 14 cycles/sec. were observed in 20% of H.C. records in Reinhold E et al’s study. The underlying mechanism remains unknown. Besides, since the abnormal spikes appear during sleep, the symptoms may also appear during sleep undetectably.” in the Discussion.

4. EMG feature is also interesting. The details of tested muscles and the relation between spontaneous muscle activities and JHD should be discussed. Meanwhile, common acquired neuropathies, such as diabetes mellitus and carpal tunnel syndrome, may lead to this active denervation.
Answer: He denied any disease including diabetes mellitus and carpal tunnel syndrome, and both the laboratory test and electrophysiological assessment do not support these disease.

5. Numerous spelling or word-choosing errors are noted in the manuscript, EX

1. "Huntington disease" should be "Huntington's disease".

2. "Parental" in page 6, line 15 and table 1 should be "paternal".

3. Page 4, line 33: "he" should be "He".

4. Page 4, line 37: "choric" should be "choreic".

Answer: Thank you and we have corrected the errors and check the grammar in the text.