Author's response to reviews

Title: Pregnancy in Multiple System Atrophy - A Case Report

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Title: Pregnancy in Multiple System Atrophy: A Case Report

Dear Editorial Team,

We thank the reviewers for their critical comments and suggestions. We have edited the manuscript and made the requested revisions. We respond to the reviewers’ comments in point from below:

Reviewer 1:

The authors report a rare case of a woman with multisystem atrophy, who delivered an (almost) healthy child but who experienced neurological decline and died 8 years after disease onset. The case report is very well written, concise and the neuropathological autopsy findings are well documented. The case presentation is relevant, as it may inform and support colleagues who are confronted with a similar rare case in their practice. The discussion of the disease course is informative and covers most important issues. Maybe the authors could add a comment on whether neurological follow-up of the child is indicated in their opinion.

The child has no noticed neurological abnormalities so far. Given that MSA is usually considered to be a rare sporadic disease, neurological follow-up of the child is not indicated at this moment. So far, there is only one case report (Wullner et al, Probable multiple system atrophy in a German family. J. Neurol. Neurosurg. Psychiat. 75: 924-925, 2004) that a German mother and daughter developed probable MSA. The child should be referred to a neurologist if she develops any neurological or autonomic symptoms in the future. We added a comment at the end of the 4th paragraph of the Case Presentation.

Reviewer 2:

This is a paper of entitled “Pregnancy in Multiple System Atrophy – A Case Report” by Lirong Zhu et al, which described the clinicopathological features of MSA patient with younger onset, who successfully delivered a full-term child. It is a very interesting and important paper to elucidate that MSA can affect young women of childbearing age and pregnancy may be associated with marked disease progression. The clinical course was well described, however there are some questions.

1) Case presentation
I wonder the final clinical diagnosis of the patient was PD or not. It is well known that early stage of MSA can be difficult to distinguish from Parkinson disease. However, MRI signal
abnormalities in patients with MSA showing cross bans sign and putaminal atrophy with abnormal signals can be confirmed at least 3 or more years after onset. Did you find any abnormal findings of MRI or CT before STN-DBS?

The final clinical diagnosis was “atypical parkinsonism”, possibly due to a genetic form of Parkinsonism. The unprecedented young age of onset of this patient made MSA seem less likely at the time. In retrospect, her clinical syndrome was consistent with MSA. There was no atrophy or abnormal signals in the putamen or hot cross bun sign noticed in the MRI and CT before STN-DBS. We added this information in the 6th paragraph of the Case Presentation.

2) Case presentation, last paragraph
In abstract, authors describe “Neuropathologic examination revealed striatonigral degeneration and alpha-synuclein-positive glial cytoplasmic inclusions in brain stem nuclei, basal ganglia and white matter tracts, consistent with a neuropathological diagnosis of MSA.” However, in pathological findings, the macroscopic and microscopic pictures of putamen are minimum. Please add the adequate descriptions.

The following pathological findings in putamen were added in the last paragraph of the Case Presentation: “Although there was no macroscopic atrophy noticed in the putamen, minimal neuronal loss, mild gliosis and numerous alpha-synuclein-immunoreactive glial cytoplasmic inclusions were observed.”

3) Case presentation, last paragraph “We describe the case of a woman with pathologically confirmed MSA-P.” The MSA-P and MSA-C were designated to the clinical features. In pathological description, olivo-ponto-cerebellar degeneration and striatonigral degeneration may be adequate. In this case, which system is more severely involved?

MSA is a clinicopathological entity and neuropathology confirmed MSA as the etiological factor. According to the criteria of Gilman et al. the predominant Parkinsonism leads this case to be called MSA-P in comparison with those cases where ataxia is a prominent feature (MSA-C). In this case there was no apparent selective atrophy, or more severe burden of pathology, in either the olivopontocerebellar system or the striatonigral system; both systems in this case had comparable densities of Papp-Lantos bodies. As no formal quantitative assessment of neuronal, synaptic, or axonal loss was undertaken in this singular case, the functional burden of pathology in these two systems remains to be determined.

4) Did you find Lewy bodies in the peripheral sympathetic ganglia?

There was no peripheral tissue available for examination in this case.

Reviewer 3:

General comments:
The authors describe a patient diagnosed with dopa-responsive, idiopathic Parkinson’s disease (IPD or PD) at age 31. She started pharmacological treatment one year later and delivered a full-term, apparently healthy child at age 35. Pregnancy was complicated by severe orthostatic
hypotension and motor fluctuation. Clinical symptoms appeared to improve during the first postpartum month but they got worse subsequently. At age 37, the patient underwent sub-thalamic nuclei deep brain stimulation (STN-DBS), with limited benefit. She died at age 39. Multiple system atrophy with predominant parkinsonism (MSA-P) was diagnosed post-mortem. The report is generally well written but may benefit from some clarifications and/or precisions, as outlined below.

Minor essential revisions:

1. The case presentation is not unusual or completely unheard of. There are several reports on the effect of pregnancy on PD symptoms during pregnancy and afterwards. The course of the disease described in this report is similar in many ways to that described by authors (not all) who reported a worsening of PD in apparent connection with pregnancy. This could be indicated in the present report, especially because the initial diagnosis was one of PD.

   We added a reference (Hagell, P., Odin, P. and Vinge, E. 1998 Pregnancy in Parkinson's disease: a review of the literature and a case report. Mov Disord, 13, 34-8) to “Her pregnancy was complicated by objective evidence of substantial neurologic decline which may have been due to natural disease progression. However, her clinical symptoms transiently improved shortly after the delivery, suggesting a specific effect of pregnancy on her symptoms. Similar observation has been reported in pregnant women with PD [8, 10]” in the first paragraph of our discussion.

2. What makes this report noteworthy is that MSA-P was eventually diagnosed, which did not seem to be the case in previous reports. But this “dual diagnosis” (PD and then MSA-P) gives rise to some ambiguity in the presentation of the case, which could be avoided. For instance, since MSA-P was diagnosed only after death, the last sentence of the Introduction (second paragraph) may have to be re-written: the woman was not diagnosed with MSA-P when she became pregnant (this diagnosis was made 4 years after the pregnancy). It is clear in the Abstract and Case Presentation sections that the case started as one of PD.

   We revised the last sentence of the Introduction according to the above comment: “We describe the case of a woman with pathologically confirmed MSA-P who was diagnosed PD when she became pregnant and underwent a successful pregnancy and delivered a full-term healthy baby.”

3. If MSA-P was suspected (but not confirmed) prior to the patient’s death, perhaps this should be indicated.

   We added the sentence “All these symptoms raise the possibility of MSA-P” in the sixth paragraph of the Case presentation.

4. Case Presentation: From the clinical practice point of view, this section may benefit from adding the following precisions:
a. Country of residence of the patient, geographical location of the report. This would help because we do not know if the patient lived in Ireland or if she was of Irish descent, living in the USA (near St. Louis?)

We revised the first sentence of Case Presentation to “A 31-year-old Irish woman who resided in the midwestern United States developed progressive loss of left hand dexterity and rest tremor.” We tried to avoid details that could potentially be used to identify the patient.

b. Parity: Did the woman have other children (before or after diagnosis of PD)? Multiparity after PD diagnosis is rare but it has been reported.

She had no other children. We added “she became pregnant with her first child.” in the last sentence of the second paragraph of the Case Presentation.

c. Breastfeeding: Yes or no? Duration?

The following was added to the 4th paragraph of the Case Presentation “She did not breastfeed her child.”

d. More precisions bout the patient’s general health and nutritional status: e.g., body mass index (BMI), weight gain during pregnancy (was it normal?). Were there signs of malnutrition and/or weight loss related to PD symptoms (e.g., dysphagia) and to disease’s progression? How was nutritional status assessed (any blood analyses)? Any evidence of protein sensitivity (this may result in motor fluctuations and prolonged “off” episodes)? This shouldn’t be overlooked in PD.

Her BMI was 23 when she was diagnosed PD. We have no access to her pregnancy record to know how much weight she gained during pregnancy. Her BMI during her last office visit (2 months prior to her death) was 20.5. There were signs of weight loss after she developed dysphagia in the later course of the disease. We did not perform blood analyses to assess her nutritional status. We added this information in the 6th paragraph of the Case Presentation.

e. More precisions about the drug therapy: Because of the options available, more details should be given about the treatments used (dopamine agonist and levodopa with carbidopa): e.g., type of drug, dosage, type of release (immediate vs. controlled).

We added drug names and dosages in the first and second paragraph of the Case Presentation.

f. More details about the duration of treatment with dopamine agonist (Case Presentation, first paragraph): “She was started on a dopamine agonist with good benefit for (add number of years)”.

She had good response to pramipexole but when she decided to have a child 6 months later she was switched to levodopa/carbidopa monotherapy based upon published reports of successful pregnancies in PD. Please see the revised last sentence of the first paragraph and the first sentence of the second paragraph of the Case Presentation.
g. Case Presentation, sixth paragraph, last sentence: Was the cause of death determined? What was the nutritional status of the patient prior to her death? Did she receive nutritional support or counsel? If so, please specify.

Our patient developed inhalatory/exhalatory stridor in her later stage of the disease. A high frequency of nocturnal sudden death has been observed in MSA patients with laryngeal stridor. Although the exact cause of death was not determined, we believe that stridor likely contributed to her death. Her BMI during her last office visit (2 months prior to her death) was 20.5 and she was still taking food by mouth. We added this information in the sixth paragraph of the Case Presentation.

h. Discussion, first paragraph: “… with pathologically proven MSA”: If this case is one of MSA-P, shouldn’t MSA-P be used instead of MSA?

MSA-P is one of the subclinical types of MSA. MSA is a pathologic diagnosis and is appropriate given the reference to the autopsy results.

i. Discussion (third paragraph) and Conclusion: same question.

Please see the response to question h.

5. Case Presentation, second paragraph: “Based upon published reports of successful pregnancies in PD…”: Given the risks associated to pregnancy in PD (e.g. Calne & Kumar 2008, Robottom et al. 2008), what advice/counseling was available to the patient when she decided to become pregnant? If there are guidelines available, have they been used in this case? This may be worth indicating in the report.

We advised her and her husband that carbidopa/levodopa had been reported to be used safely in pregnant women with PD, but not dopamine agonist. So pramipexole was switched to levodopa/carbidopa. We added this information in the second paragraph of the Case Presentation.

Other revisions suggested:

6. Abstract, second paragraph: Case presentation would benefit from dating more precisely the milestones of disease progression and corresponding treatments, e.g., “… who successfully delivered a full-term child at age 35”; “Two years after post-partum, she underwent bilateral…”; “Post-mortem neurological examination…”

We have modified the abstract accordingly.

7. Abstract, second paragraph: If the diagnosis made was MSA-P (last paragraph of Case Presentation in the manuscript), shouldn’t this precision also be given in the Abstract, end of the paragraph Case Presentation: “… consistent with a neuropathological diagnosis of MSA-P”? Same question in the conclusion of the Abstract.
MSA-P is a clinicopathological diagnosis and one of the clinical subtypes of MSA. So it is more appropriate to say “Neuropathologic examination revealed ..., consistent with a neuropathological diagnosis of MSA.”

8. Introduction, first paragraph: The abbreviation “PD” is used, but it has not been defined previously. It could be defined in the Abstract (first paragraph): “… to distinguish from Parkinson’s disease (PD)”.

We have revised our manuscript accordingly.

9. Introduction, second paragraph: Are there North American data about the mean age at onset of MSA? These could be pertinent if the patient lived in the United States. The European data are pertinent too (Irish descent of the patient).

Unfortunately, data from the largest North American study of MSA has yet to be published so we referenced the European data.

10. Case Presentation, fourth paragraph, last sentence: “The child is currently five years old…”: To avoid any ambiguity with the word “currently” (there may be some delay between submission and publication of this report), this sentence may be re-written as “The child was five years old in 2011.”

We avoided providing dates to preserve patient confidentiality and since dates could potentially be used to identify her daughter. We instead chose to state that “At age five years, her daughter had developed normally…”

11. Case Presentation, seventh paragraph: Figure 1 (A-F) may be divided into Figure 1 (A-C, Microscopic and microscopic features) and Figure 2 (A-C, Alpha-synucleinopathy).

We divided the Figure 1 as suggested.

Editorial comments (minor issues not for publication):

12. Case Presentation, sixth paragraph:
“At age 37, she received” (no capital She)
“… she received bilateral subthalamic nuclei deep brain stimulation (STN-DBS)”

We have corrected the manuscript accordingly.

13. The use of ”#” (Abstract) versus “alpha” (text and figure legend): You may want to use one or the other.

We have revised our abstract accordingly.

14. Acknowledgments: There a few typos in this section.
We have corrected the Acknowledgment accordingly.

15. References (plural): This section should follow the JMCR reference style.

We have revised the reference accordingly.

16. Figure Legends:
Figure 1 (A-C): You may want to use a more precise title: e.g., “… features of patient’s brain (post-mortem)”.
There are a few typos in this section: e.g., use of full stop/period at the end of each subtitle; use of capital after each colon.

We have revised the figure legends accordingly.

In addition, the Editorial Team would also like to request for formatting changes required for your manuscript, as it does not conform to the journal style. Kindly address the following:
1. Please include the study design in your title, i.e. Case report. For example: A presenting with B in C: a case report.

We have changed the title to “Pregnancy in Multiple System Atrophy: A Case Report”

2. Please modify your manuscript, as the ethnicity of the patient in the Abstract is different in the Case Presentation Section of the manuscript.

We have corrected the ethnicity of the patient in the Abstract.

We appreciate the opportunity to revise this manuscript and hope that it is now acceptable for publication in The Journal of Medical Case Reports.

Sincerely,

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