Author's response to reviews

Title: Marchiafava-Bignami disease mimics motor neuron disease: Case Report

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Version: 2
Date: 4 December 2013

Author's response to reviews:

We are grateful for the positive evaluation of the manuscript and for the opportunity to revise the original manuscript. The following are our responses to the comments made by the reviewers.

Reviewer's report
Title: Marchiafava-Bignami disease mimics motor neuron disease: Case Report
Version: 1
Date: 5 November 2013
Reviewer: John CM Brust

Reviewer's report:

This case report has educational value and possibly unique features.

Major compulsory revisions: For a neurology journal, there is need for clarification and added detail.

1) The Introduction seems to use the term "bulbar palsy" to refer to weakness of muscles innervated by cranial nerves 5, 7, 9, and 10, whether upper or lower motor neuron in type. In conventional practice "bulbar palsy" usually refers to lower motor neuron weakness and "pseudo-bulbar palsy" to upper motor neuron weakness. This has bearing on the patient's "poor" palate elevation and gag reflex. Reduction or absence of these reflexes would more likely reflect lower motor neuron weakness than upper motor neuron weakness, arguing against "primary lateral sclerosis" as a plausible diagnosis. Might the authors clarify?

Reply: We are very grateful for the reviewer's comment. The present case showed dysarthria including poor gag reflex and palate elevation as lower motor neuron signs, and slurred speech, brisk jaw jerk reflex, and the snout reflex as upper motor neuron signs, which have been defined previously as mixed dysarthria that is not infrequently found in amyotrophic lateral sclerosis [20]. Other neurological examinations revealed muscle weakness of the lower face
and four limbs, as well as hyperreflexia in the bilateral upper limbs and the positive bilateral Babinski reflexes. Thus, it is suggested that the clinical presentation mimicked a motor neuron disease, especially amyotrophic lateral sclerosis but not primary lateral sclerosis. We have revised the 3rd paragraph of the Discussion section as follows:

Line 18, page 7: In particular, the dysarthria included a poor gag reflex and palate elevation as lower motor neuron signs, and slurred speech, brisk jaw jerk reflex, and the snout reflex as upper motor neuron signs, which have been defined as mixed dysarthria that is not infrequently found in ALS [20]. Other neurological examinations revealed muscle weakness of the lower face and four limbs, as well as hyperreflexia in the upper limbs bilaterally and positive Babinski reflexes bilaterally. Thus, the clinical presentation mimicked MND, especially ALS. Interestingly, recent studies have shown that hyperintense signal lesions on FLAIR of the subcortical precentral gyrus bilaterally, as seen in the present case, were consistent features of ALS, and that the corpus callosum was also involved in the pathogenesis of ALS [21-23].

2) The MMSE score on admission was 22. What cognitive domains were abnormal? Recent memory? Or was the admitting mental status more suggestive of Wernicke encephalopathy (ie, multi-domain)? There was no improvement in the MMSE score at discharge. Were the abnormalities at that time identical to those on admission? (Giving simply a numerical score is of little help in describing what was wrong with the patient.

Reply: We appreciate this comment. We apologize for this error: the MMSE score after vitamin B therapy was 26, not 22, points. As suggested by the reviewer, we have revised the manuscript to describe the results of MMSE in detail. Initial MMSE on admission was 22 points: orientation to time, -2 points, attention and calculation, -4; three word recall, -2. On admission day 14, the MMSE score had improved to 26 points: attention and calculation, -4 points. The present case gave precise answers in other categories of tasks in the initial and follow-up examinations of MMSE, which was not suggestive of Wernicke encephalopathy. We have added results of the MMSE in detail in the Case report section.

Line 22, page 4: Neurological examination revealed an alert patient with a mini-mental status examination (MMSE) score of 22 points (orientation to time, -2 points; attention and calculation, -4; three word recall, -2).

Line 8, page 6: On hospital day 14, the MMSE score had increased to 26 points (attention and calculation, -4), limb weakness had improved, and the patient could walk with a cane.

3) The tongue had neither atrophy nor fasciculations, but neither tongue movement nor dysarthria is mentioned. On the next page, the patient is described as speaking "in a clear voice." Does that represent improvement from an earlier dysarthria?

Reply: We thank the reviewer for this comment. On admission, his tongue could be protruded from the mouth and remained midline, and moved from side to side.
Although his speech was slurred on the initial examination, after vitamin B1 therapy the speech gradually improved until he could speak clearly. Therefore, we considered that his dysarthria was improved after therapy. We revised the manuscript as follows:

Line 6, page 5: The tongue could be protruded from the mouth and remained midline, and moved adequately from side to side.

4) Were the upper limb "incoordination" and "truncal instability" considered cerebellar in origin? Was cerebellar vermal atrophy seen on MRI? Were eye movements normal (including absence of nystagmus)?

Reply: Thank you. We appreciate this important comment. As suggested by the reviewer, the present case had upper limb incoordination, truncal instability, and gaze paretic nystagmus bilaterally. After vitamin B therapy, such symptoms were improved. Brain MRI did not show the atrophy of cerebellar vermis and hemispheres. So far, it is widely accepted that alcohol induces cerebellar degeneration as well as neuropathy. Therefore, it is suggested that chronic alcoholism and malnutrition might cause transient cerebellar degeneration, which was improved after vitamin B therapy in the present case. We have added the description regarding cerebellar ataxia in the revised Case Report section.

Line 11, page 6: Gaze paretic nystagmus and finger-to-nose incoordination were also improved.

5) Were tendon reflexes also increased in the legs?

Reply: The present case showed increased deep tendon reflexes in the jaw jerk and bilateral upper extremities but not lower extremities on admission. However, bilateral Babinski reflexes were positive.

6) DWI was positive, but ADC was not, consistent with the DWI signal reflecting simply shine-through. Do the authors agree? If they do, is there any point in displaying the DWI and ADC images? Might they comment?

Reply: Thank you. We agree with the reviewer’s comment. The present case showed hyperintense lesions in the bilateral precentral gyrus and corpus callosum on FLAIR of initial MRI. These lesions were also high on DWI and normal in ADC map, indicating that increased signal intensity in such lesions on DWI reflected T2 shine-through. We have deleted the last sentence of the 2nd paragraph in the Discussion section, stating that normal ADC lesions might be related to good outcome in this case from the Discussion section.

7) The notion that MBD might be related to products in red wine, originally proposed by Marchiafava and Bignami, has long been discredited, eg, by Ironside R et al (Brain 1961; 84: 212), who described MBD in whiskey drinkers.

Reply: We appreciate this comment. As suggested by the reviewer, we revised our manuscript as follows. We also referenced a paper by Ironside et al. as reference no. 6.

Line 23, page 6: MBD is most frequently seen in middle-aged or elderly chronic
alcoholic males [6-9,11]. MBD was first reported in 1903 by Marchiafava and Bignami, who originally described the symptoms in Italian men with increased consumption of inexpensively manufactured Chianti red wine [1]. Currently, however, MBD is known to occur in patients with chronic consumption of other sorts of alcohol including whisky and French liqueur [6,7]. MBD has also been found in severely malnourished people without a history of alcoholism [7,18]. In the present case, long-term consumption of beer and Japanese distilled spirits and malnutrition might have been related to the pathogenesis of MBD. Although the precise mechanisms underlying development of MBD remain unknown, effects of toxic agents present in alcohol, vitamin B complex deficiency, or osmotic disorders have been considered as potential causes [3-4,7]. In a report of an MR spectroscopic study, it was suggested that inflammatory reactions accompanying demyelination and micronecrosis and secondary axonal damage might occur in the acute stage of MBD [19]. Presence of cerebral microhemorrhage on susceptibility-weighted imaging was reportedly associated with cognitive dysfunction in MBD patients, and cytotoxic edema on DWI and the ADC map might predict poor outcome [8,11].

Reviewer's report
Title: Marchiafava-Bignami disease mimics motor neuron disease: Case Report
Version: 1 Date: 17 October 2013
Reviewer: Lewis P. Rowland

Reviewer's report:
In earlier times, Marchiafava-Bignami disease (MBD) could be diagnosed only by postmortem examination. Now it can be diagnosed in life by finding MRI evidence of degenerative changes in the corpus callosum, as the authors of this manuscript have done. I have numbered the pages, starting with the cover sheet as page 1.

Page# Par Line Comment
1 Spell out abbreviations with first usage.
Reply: Thank you. We have revised the manuscript accordingly, and have included a list of abbreviations used.

12 2 1 Authors do not give enough information to determine whether cranial nerve finding indicate dysfunction of lower motor neurons. Otherwise the disorder could be classified as primary lateral sclerosis, not "MND". Mention presence or absence of fasciculation in tongue.
Reply: We appreciate this important comment. As suggested by reviewer, it is essential to describe the patient’s neurological findings in detail for the initial diagnosis of primary lateral sclerosis, or “MND”. On admission, the present case showed, swallowing disturbance, poor gag reflex and palate elevation as lower motor neuron signs, and weakness of the bilateral orbicularis oris, slurred speech, brisk jaw jerk reflex, and a snout reflex as upper motor neuron signs. He did not have tongue fasciculation. Collectively, he showed mixed dysarthria on
admission. Mixed dysarthria was not infrequently found in patients with ALS [20]. Thus, his initial diagnosis was MND especially in ALS but not primary lateral sclerosis. We have added details of his neurological findings in the Case Report section as well as the Abstract, and stated the consideration regarding mixed dysarthria in the Discussion section. We also added the literature by Tomik & Guiloff as reference no. 20.

Line 8, page 2: On admission, the patient was alert with mild cognitive dysfunction. The facial expression was flat, and there was weakness of the orbicularis oris bilaterally. The patient’s speech was slurred, there was difficulty swallowing, and the gag reflex and palate elevation were poor. The jaw jerk reflex was brisk and the snout reflex was positive. Neither tongue atrophy nor fasciculation were found. Bilateral upper and lower limb weakness with increased bilateral upper limb reflexes and Babinski reflexes were found. Because he had progressive dysarthria and dysphagia with upper and lower motor neuron signs, the initial diagnosis was motor neuron disease.

Line 1, page 5: The facial expression was flat, and there was weakness of the orbicularis oris bilaterally. Weakness of the frontalis muscle and orbicularis oculi was not found. The speech was slurred, and there was difficulty swallowing; the gag reflex and palate elevation were poor. The jaw jerk reflex was brisk and the snout reflex was positive. Emotional lability was not found. Neither tongue atrophy nor fasciculation were found.

3 up Give vitamin B1 level.

Reply: We stated the vitamin B1 level in the Abstract.

Line 17, page 2: The vitamin B1 level was 14 ng/mL (normal: >24 ng/mL), and MRI revealed hyperintense lesions in the splenium of the corpus callosum and the primary motor cortices bilaterally.

1 up How long did it take before symptoms and MRI changes improved?

Reply: Follow-up MRI, which showed disappearance of hyperintense lesions in the splenium of the corpus callosum and the primary motor cortices, was done 17 days after admission. Thus, there were 17 days between initial neurological presentation and follow-up MRI.

Line 2, page 19: After vitamin B therapy for 17 days, the neurological disorders alleviated concurrently with disappearance of the lesions on MRI, which led to the definitive diagnosis of MBD.

Line 12, page 6: Repeat MRI 17 days after admission showed the disappearance of signal abnormalities in the splenium of the corpus callosum and the precentral gyrus on FLAIR and DWI (Fig. 2A-C).

13 1 Mention number of usual range of weeks or months for duration of symptoms.

Insert a short paragraph for set of consensus symptoms for diagnosis.

Reply: Thank you. Previous case reports demonstrated that it took a few weeks to half a year to recover from symptoms and have diminished MRI changes after
therapy in MBD patients. Also, patients with MBD showed a variety of neurologic features such as seizures, confusion, and deterioration of consciousness, which can be difficult to differentiate from symptoms of other alcoholic neurological disorders, including Wernicke encephalopathy. Interhemispheric disconnection syndromes caused by disorders of the corpus callosum may be characteristic symptoms in MBD patients. We revised our manuscript as follows. We also referenced new papers regarding interhemispheric disconnection and MBD as references no. 13 and 14.

Line 10, page 3: Over 90% of the patients with MBD exhibited a poor prognosis [10]. However, MBD patients can recover completely with disappearance of the callosal and adjacent white matter lesions on serial MRI after adequate therapy in a few weeks to half a year [7,9,11,12]. MBD includes a variety of neurologic features such as seizures, confusion, and deterioration of consciousness, which can be difficult to differentiate from symptoms of other alcoholic neurological disorders [3]. Interhemispheric disconnection syndromes caused by disorders of the corpus callosum may be included in characteristic symptoms of the diagnosis of MBD [13,14].

Instead of “bulbar palsy” mention upper and lower motor neuron signs.

Reply: We appreciate this comment. We have deleted “bulbar palsy” and use the term “upper and lower motor neuron signs” in the revised 2nd paragraph of the Introduction section, Case report section, and Discussion section. We also deleted “bulbar palsy” from the key words.

Key words: Marchiafava-Bignami disease, motor neuron disease, amyotrophic lateral sclerosis, upper motor neuron signs, lower motor neuron signs, chronic alcoholism

Line 19, page 3: Dysarthria and dysphagia can occur in various neurological disorders, including cerebrovascular disease, neurodegenerative disease, Guillain-Barré syndrome, and neoplastic disease [15-18], and are caused by disorders of cranial nerve motor nuclei in the lower brainstem resulting in lower motor neuron signs, as well as of the bilateral corticobulbar tracts resulting in upper motor neuron signs. In particular, progressive dysarthria and dysphagia are not infrequently found in patients with motor neuron disease (MND); 8% of patients with amyotrophic lateral sclerosis (ALS) present with progressive dysarthria and dysphagia as the initial symptoms [17].

Line 15, page 5: The initial diagnosis was MND because of the development of progressive dysarthria and dysphagia with upper and lower motor neuron signs, and the limb weakness with upper motor neuron involvement.

Line 18, page 6: Specific clinical characteristics of the present case are the development of dysarthria and dysphagia with upper and lower neurons signs, and limb weakness with upper motor neuron signs.

Line 11, page 8: In conclusion, MBD can mimic MND, and physicians should include MBD in the differential diagnosis for patients with progressive dysarthria and dysphagia and motor weakness.
History of alcoholism is good. The oropharyngeal symptoms were present for only 3 weeks, which can be considered "subacute".

Reply: Yes. The present case developed dysarthria and dysphagia in 3 weeks. His dysarthria and dysphagia were “progressive” and “subacute”, which mimicked motor neuron disease. Thus, our initial diagnosis was motor neuron disease.

When did he have subdural hematoma diagnosis? what happened to it (few sentences)?

Reply: When the present case was 44 years old, he developed left hemiparesis and apathy 1 month after a fall. Brain CT showed bilateral subdural hematoma, and he underwent burr-hole drainage for bilateral chronic subdural hematomas. After operation, he became independent in activities of daily living functions.

Line 18, page 4: At the age of 44, he underwent burr-hole drainage for bilateral chronic subdural hematomas. After surgery, he became independent regarding the activities of daily living.

Could you tell whether facial weakness was upper or lower motor origin?

Reply: The present case showed weakness of the bilateral orbicularis oris but not the frontalis muscle and orbicularis oculi, indicating that he had upper motor neuron disorder of bilateral facial nerve. We have revised our manuscript as follows.

Line 1, page 5: The facial expression was flat, and there was weakness of the orbicularis oris bilaterally. Weakness of the frontalis muscle and orbicularis oculi was not found.

Was there a snout reflex? emotional lability (pseudobulbar palsy)?

3 TRs were increased in arms. Hoffmann signs? Grasp reflex?

Reply: We thank the reviewer for these comments. The present case showed a snout reflex, but there was no emotional lability, Hoffmann signs, or forced grasp reflex. We have described those findings in the revised Case Report section.

Line 4, page 5: The jaw jerk reflex was brisk and the snout reflex was positive. Emotional lability was not found.

Deep tendon reflexes in the upper limbs were increased, and Babinski reflexes were positive bilaterally. Hoffmann reflexes and the forced grasp reflex were negative.

With both upper and lower motor neuron signs, why not ALS?

4up No LMN signs of denervation in tongue or limb muscles. Was this PLS?

Reply: Thank you. As suggested by the reviewer, the present case showed development of dysarthritis and dysphagia with upper and lower neurons signs, and limb weakness with upper motor neuron signs. Thus, the clinical presentation of this case mimicked ALS but not PLS. Now we have revised our manuscript in the Discussion section, and replaced referenced papers 21, 22, 23.
Line 24, page 7: Thus, the clinical presentation mimicked MND, especially ALS. Interestingly, recent studies have shown that hyperintense signal lesions on FLAIR of the subcortical precentral gyrus bilaterally, as seen in the present case, were consistent features of ALS, and that the corpus callosum was also involved in the pathogenesis of ALS [21-23].

16 2 4 When did vitamin therapy start? Give date. When did gradual improvement start?

Reply: In the present case, complex vitamin B therapy was started on the day of admission. After the second day of admission with therapy, he showed gradual improvement of his dysphagia, dysarthria, cognitive impairment, and gait disturbance.

Line 3, page 6: Complex vitamin B therapy, including 100 mg of thiamin, was started intravenously on the day of admission. After admission, the patient’s swallowing slowly improved, and gradually the speech became clear. On admission, only food of a pudding-like texture was tolerated, but 7 days after admission gruel-like foods were manageable, and 13 days after admission the patient was placed on a normal diet.

17 2 1up Spell out abbreviations with first usage.

Reply: We appreciate this comment. We spelled out MBD in the Introduction section. Now we spell out ADC as apparent diffusion coefficient in the Case report section.