Author's response to reviews

Title: Limb-Onset Amyotrophic Lateral Sclerosis Patients Visiting Orthopedist Show a Longer Time-to-Diagnosis since Symptom Onset

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Version: 4 Date: 11 January 2013

Author's response to reviews: see over
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**Version:**

**Author’s response to reviews:** see over
Reviewer's report

Title: Limb-Onset Amyotrophic Lateral Sclerosis Patients Visiting Orthopedist Show a Longer Time-to-Diagnosis since Symptom Onset

Version: 2 Date: 9 November 2012
Reviewer: Peter Berlit

Reviewer's report:
This is a retrospective study focussing on the delay of diagnosis of ALS. The described difference between patients with bulbar onset and limb onset has been published frequently. The significant delay caused by consulting the "wrong" specialist (i.e. orthopedics) in limb onset ALS is a new and relevant finding.
The first sentence of the results section of the abstract needs explanation: What is meant with the examination of 78 patients, when the total number of ALS cases is 202?

We have corrected this mistake in the results section of the abstract, as indicated by the reviewer.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Needs some language corrections before being published

We have requested language corrections and attached a “CERTIFICATE OF ENGLISH EDITING.”

Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests
Author’s response to reviews

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Version:
Author’s response to reviews: see over
Reviewer's report

Title: Limb-Onset Amyotrophic Lateral Sclerosis Patients Visiting Orthopedist Show a Longer Time-to-Diagnosis since Symptom Onset

Version: 2 Date: 10 December 2012

Reviewer: Friedhelm Sandbrink

Reviewer's report:
The authors describe a retrospective study in ALS patients to determine “how the choice of physician […] may affect the time it takes for a diagnosis of ALS to be made”. This appears to be a rather straight forward question. The authors answer this in the title of their study as that the ALS patients with limb-onset visiting an orthopedist initially “show a longer time-to-diagnosis since symptom onset”.

Major compulsory revisions:
1) A more extensive chart may greatly enhance the value of the study by making it more relevant, as the study in its current form leaves many questions unanswered. The reader is left with the impression that orthopedists may not be as aware as other specialists about ALS and thus miss to diagnose the ALS early on. This impression is supported by the authors who suggest the need for increased education of non-neurological physicians in their conclusion. This conclusion appears premature. The authors do not describe detailed clinical characteristics of the patients themselves, and whether the patients presenting to the orthopedist may actually have had a different presentation and course. The authors speculate that the increase in the diagnostic interval in limb onset patients visiting the orthopedist is because of lack of bulbar symptoms in the early stages of disease. It would be worthwhile to get more details from the patients' charts in this regard, if at all possible. It is conceivable that limb onset patients were heterogeneous and differed between the different specialties. We know that older age at onset predicts shorter survival. Did the patients who chose to see an orthopedist differ in their age from the patients presenting to other physicians? Did they have a slower progressive course at least initially? Did they present with symptoms resembling radiculopathy, lumbar or cervical spinal stenosis? If the data cannot be obtained from the chart, at least a more detailed discussion appears necessary. The discussion section may benefit from a more
detailed description of the prognostic factors in ALS in general and in particular as they relate to potential impact upon presentation to the different specialists.

We agree with your comments. We have checked the records of the LO patients who visited an ORTH first (Table 2) and added the following sentences to the Results section.

“We analyzed the characteristic differences between patients who were referred to a neurologist directly from an ORTH and those who were referred from an ORTH to other clinics before finally visiting a neurologist (Table 2). Three patients who were referred directly to a neurologist received spinal surgery. However, there were no differences in mean age, spinal spondylosis, or diagnostic interval between these 2 groups.”

In the Discussion section, we have also added these sentences, according to the reviewer’s comments:

“We also compared the characteristic differences between LO patients who were referred to a neurologist directly and those who were referred from an ORTH to other clinics before finally visiting a neurologist. Three patients directly referred to a neurologist received spinal surgery, but there were no differences between these 2 groups in mean age, spinal spondylosis, or diagnostic interval. A high incidence of spondylosis is reported in patients at the mean age of ALS onset, and about 4% of ALS patients undergo decompressive spinal surgery after the onset of retrospectively recognized symptoms of ALS [17]. Therefore, the possibility of ALS must be recognized in the evaluation of weakness, even in the presence of radiographic evidence of spinal spondylosis.”

2) Patients were stratified as bulbar onset vs limb onset, and correlation of the time to final diagnosis with type of practitioner seeing the patient initially was made. The final diagnosis was made in all patients by a neurologist. Thus any delay in diagnosis may be explained primarily as delay in referral or presentation to a neurologist, but this is not specifically measured or reported. The figure 2, labeled “diagnostic pathway”, appears rather simplistic. Referral to a specialist may come from the general practitioner, or initiated by the patient directly. For greater clarification in this regard, the figure 2 should be replaced with a more detailed figure outlining the number of patients along the different routes
including many that remain unlisted, if such data exist (such as GP to orthopedist). Did any of the patients who presented to and were diagnosed by a neurologist (62/202 patients) get seen initially by their GP prior to them presenting to the neurologist, possibly without a dedicated referral consultation (as not mandated by the health care system)?

Related: The authors state that “more than 50% of the patients with ALS were referred to an inappropriate clinic prior to final diagnosis”. This may be an overreach, as the authors themselves point out that many patients were not referred to the specialist by another provider but presented directly without referral.

We agree with your comment that “diagnostic pathway” appears rather simplistic. Actually, some patients with ALS visited more than 2 clinics before finally visiting a neurologist. Therefore, we have changed Figure 1 to show the pathway in more detail.

We have added the following sentences to the Results section, as indicated by the reviewer.

“The diagnostic pathway from the onset of symptoms to final diagnosis of ALS is summarized in Figure 1. Fourteen ALS patients visited 2 clinics before finally visiting a neurologist in the BO group. On the other hand, 24 patients visited 2 clinics and 5 patients visited 3 clinics in the LO group.”

We have also changed a sentence in the Discussion section as follows:

“In Japan, it is recommended that patients have their own primary care doctor; however, they can visit any clinic first freely and without a referral. Once they visit a clinic, the physician makes a referral to the specialist if needed.”

Therefore, we would like to suggest that many ALS patients were referred to an inappropriate clinic prior to final diagnosis.

Minor essential revisions:
4) The study is a retrospective analysis of the hospital records of ALS patients at Toho University Omori Medical Center from Jan 1 to July 31, 2011. It is not clear whether the 202 patients enrolled into this study represent all ALS patients during
this time period (as not explicitly stated so), and what are the reasons for exclusion, if any.

This sentence has been changed in the Methods section and now appears as follows:

“We reviewed the hospital records of all ALS patients who fulfilled the REE (definite, probable, or probable-laboratory-supported) at Toho University Omori Medical Center, Tokyo, Japan from January 1, 1990 to July 31, 2011. The diagnosis of ALS was made by consulting neurologists with extensive experience (OK, KI, and YI).”

5) The title states a “longer time-to-diagnosis since symptom onset” for patients visiting an orthopedist, but does not state the comparison specifically. Per the body of the text, the comparison is made specifically to neurologist (as the only specialist time shown to have a significantly different time to diagnosis).

We have now included the following sentence in the Results section, as the reviewer indicates.

“There were no differences between patients who visited a neurologist and those who visited any of the other physicians investigated.”

We have also included the following sentences in the Discussion section, as the reviewer indicates.

“Our results show that LO patients who visit an ORTH first have a longer diagnostic interval compared to those who visit a neurologist first. Furthermore, no difference could be seen between patients who visited a neurologist first and those who visited any of the other physicians investigated.”

6) The writing may benefit from a few corrections or changes in style, with some mentioned here. In the abstract, the “Results” section states that “A total of 78 ALS patients were examined”. This appears incorrect, as a total number of 202 patients were studied.

We have corrected this mistake, as indicated by the reviewer.
7) Patients seek medical attention for the initial symptoms of the disease (not signs, page 5).

This change had been made throughout the text, as indicated by the reviewer.

8) El Escorial criteria for ALS have been widely accepted (instead of singular).

This change has been made, as indicated by the reviewer.

9) The conclusion includes a sentence (beginning with “When looking at...”) that is not grammatically correct.

This mistake has been corrected.

Level of interest: An article of limited interest
Quality of written English: Needs some language corrections before being published
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I declare that I have no competing interests