Author's response to reviews

Title: Nemaline Myopathy and Heart Failure: Role of Ivabradine. A Case Report

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Author's response to reviews: see over
Carina Wallgren-Pettersson, MD

We are honored to receive a revision from you.

Below the point-by-point answers to the comments

Major clinical Comment:

This manuscript describes a patient who presented at the age of 33-34 years with subacute weakness mainly of the upper limbs. Dysphagia and rapidly progressive heart failure ensued within the following year. He was found to have a monoclonal gammopathy. What immediately comes to mind is the entity sporadic late-onset subacute nemaline myopathy, SLONM, despite the fact that heart failure has not been an early symptom in previously described patients. Because of the poor prognosis in SLONM, and because it is not clear to me from reading the manuscript how the patient is doing currently in terms of his skeletal muscle strength, I suggest that the patient be re-evaluated with this in mind without further delay, for appropriate treatment to be initiated if this diagnosis is confirmed.

Response:

We really thank you for your advice about our patient. We update the case report with a recent complication: aspiration pneumonia. Fortunately antibiotic therapy was sufficient for healing and a tracheostomy tube was inserted to protect airways from further aspiration. At the moment the patient is regularly doing physiotherapy (in particular chest physiotherapy) and is always on ivabradine.

We believe that continuing physiotherapy is fundamental for the patient. Please inform us if there is something new about nemaline myopathy therapy? We will be grateful.

Major Compulsory Revisions:

1) There are a number of publications on adult-onset nemaline myopathy, many of which explicitly describe SLONM, where the presence of a monoclonal gammopathy has been found to carry a poor prognosis. Other case reports, especially those preceding the 2005 paper by Chahin et al., have been less detailed. At least one report (Taglia et al 2012) introduces the use of ivabradine for heart failure. These publications should be cited and careful comparisons made with the patient described herein.

It is true that in some patients with mild nemaline myopathy, the diagnosis may have been delayed into adulthood, and the patient may present in adulthood with respiratory failure without a prior diagnosis of myopathy. In these cases, a careful history may reveal a childhood-onset weakness previously overlooked, or findings on physical examination suggesting a congenital onset, and a genetic cause is then likely to be found to underlie the symptoms.

If, however, the onset of weakness is truly in adulthood, and subacute, and especially if a monoclonal gammopathy is present, the diagnosis of SLONM is more likely.
Response:

We cited more publications about adult-onset nemaline myopathy, included some case reports with monoclonal gammopathy (Eymard 1993, Keller 2006).

We cited the interesting report by Taglia et al. However there are some differences. In the report by Taglia et al beta-blocker was substituted with ivabradine after about 12 years of follow up, likely because of the severe respiratory insufficiency due to the paralysis of the diaphragm, also requiring continuous ventilatory support. Conversely instable hemodynamics and hypotension were predominant in our patient and requiring early therapeutic countermeasures to obtain a better hemodynamic compensation. Moreover beta-blocker was not suspended.

No history of childhood-onset weakness was traceable in our patient.

2) 

All articles reporting cardiac involvement in nemaline myopathy should be cited, since this is so rare.

Response:


3) 

Did the patient’s postural symptoms amount to camptocormia, reported in a few of the SLONM cases? Would the authors have a profile picture that would be more informative than the dorsal one, in terms of the posture of the spine?

Response:

We are sorry but we have no profile picture of the patient: we have a frontal picture if you think may be interesting we can include in the text

4) 

Regarding the histological findings, essential details are whether the patient had type 1 fibre hypotrophy or whether it was atrophy, and whether, in addition to this, there was type 1 fibre predominance.

Response:

Histological findings: mainly atrophic fibres with type 1 predominance.
Minor Essential Revisions:

The language requires minor revision. The word nemaline is misspelt in the Title, and the first sentence of the Abstract implies that a wide spectrum of phenotypes is present in the muscle fibres.

Response:

We adjust the word Nemaline in the title and the first sentence (with the word “clinical”).
Hisashi Kawashima, MD

We are honored to receive a revision from you.

Below the point-by-point answers to the comments

**Major:**

This manuscript is written about a case who had IVABRADINE recovered dramatically. The case is interesting and worthwhile to publish to decide beta-blocker. However there are a few case and very preliminary, since the diagnosis is limited. And also the course is short. No biopsy of heart is done.

Response:

Thank you for your revision. It's true, few cases have been reported. Our patient is still alive. In most reported cases only the autopic study confirmed heart involvement and no heart biopsy was available before exitus. The clinical and pathological findings of our patient were similar to those of previously described cases of adult-onset nemaline myopathy including proximal muscle weakness, dysphagia, lack of familiarity involvement or preceding symptoms and monoclonal gammopathy.

At the present time unfortunately we have no heart biopsy to further confirm the diagnosis but we believe the diagnosis of cardiac involvement is likely.

**Minor:**

The authors should add similar report of the effectibenes in neuromusclare diseases in discussion. The authors should add the figure of nemaline body.

Response:

We cited an unique case report (Taglia et al) in which is described the efficacy of ivabradine in nemaline myopathy with cardiac involvement.

We add the figure of nemaline bodies.