

## Manuscript Title

Use of 4-aminopyridine for Motor Weakness Due to Charcot- Marie - Tooth Hereditary Motor Sensory Neuropathy

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## Summary

*The manuscript was received on August 22, 2017 and was peer reviewed by two reviewers and an editor.*

*The initial recommendation of Major Revision was made on October 13, 2017.*

*The first revision was submitted on November 8, 2017 and was re-evaluated by the editor.*

*The manuscript was accepted for publication on November 13, 2017.*

## Peer Review Comments

### Reviewer 1

The authors describe a single patient with a diagnosis of CMT treated over a period of 12 months with 4-AP. When evaluated on the ASIA scale, motor strength increased from 3.6 to 4.2 in the upper limbs and 3.9 to 4.5 in the lower limbs. There was also a mild decrease in the perception of pain and report of considerable increase in walking endurance, decreased falls and no longer using a cane. The authors hypothesise that 4-AP improves conduction through demyelinated axons.

I think the manuscript requires several clarifications:

1. The patient is genetically unclassified. It is not clear if the individual has had any genetic testing, even for the most common genetic forms of CMT. The nerve conduction tests are not reported and his clinical profile is very atypical for CMT. It is uncommon for CMT to initially present with severe dysaesthesia of both hands and feet, and then there be a 14 year gap to the development of weakness. The need for intrathecal morphine to control pain is again very very atypical of CMT. There is no family history of CMT (of course this does not exclude non-autosomal dominant forms of CMT. Most forms of CMT are length-dependent with the lower limbs affected more severely when compared with the upper limbs, but this patients pre-treatment ASIA scores show more severe weakness in the upper limbs. This raises the possibility that the patient may have an inflammatory neuropathy where pain and non-length dependent weakness are more common.

2. It appears that the ASIA scale is a spinal cord injury scale. Outcome measure like the CMTNS V2 (adults) and CMTPedS are validated for use in CMT. The authors need to provide references for their statement on page 3 that 'Use of these standardized measures has been endorsed throughout the rehabilitation community', especially for CMT. Similarly, assessment on a standardised validated test like 6MWT would better characterise improvement in walking endurance.

3. 4-AP is thought to improve conduction delay and block in demyelinated segments of nerves, which may explain the improvement in GBS, and possibly in MS. However the pathology in CMT is not conduction block, but axonal loss (secondary to demyelination). Was there conduction block in the nerve conduction studies?

4. it would be important to provide a detailed table showing which muscle actually became stronger. If there was an actual improvement in nerve conduction, then it should be the distal denervated muscles that improved the most.

5. The phenotype being atypical for CMT makes it difficult to compare the improvement with pre-treatment progression. A 12 month assessment of progression pre-treatment, or deterioration after stopping the drug may have provided a control.

**Reviewer 2:**

The authors describe a single case of CMT who appeared to respond to 4-aminopyridine.

Although interesting, I have several concerns with the case.

1. The diagnosis of CMT is not clear. The patient is in the older age group and pain and other positive symptoms appear to be prominent. The latter is unusual in inherited neuropathies – have the authors considered an acquired form of neuropathy?
2. There was no other supportive history to suggest that the patient has CMT
3. There was no neurophysiology data that one could review to support the diagnosis
4. The side-effects of the medication needs to be included in the Introduction rather than the discussion
5. The outcome measures were poor – the authors utilised MRC grading as far as I can tell which is insensitive. Hand dynamometry may have been a more objective tool or repeat nerve conduction study
6. A single patient that is not blinded to treatment with no controls make for a poor observation – there is no way of ascertaining placebo effect in this case
7. There was also no mention if the authors obtained Ethics approval prior to reporting the case

Minor comments:

The structure could be improved and more clearly delineated.

The discussion is superficial and does not address the shortcomings of the report

Recommendation: major revision