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Can serum neurofilament light chain be used as a biomarker for treatment monitoring in subacute combined degeneration?

Jannis Müller*; Anna Stenik; Anneza Panagiotou; Özgür Yaldizli

***Corresponding Author: Jannis Müller**

Neurologic Clinic and Policlinic, Department of Medicine, University Hospital Basel and University of Basel, Basel 4031, Switzerland.

Email: jannis.mueller@usb.ch

Keywords

Subacute combined degeneration; Vitamin B12 deficiency; Inverted V sign; Pair of binoculars sign; Neurofilament light chain.

Clinical Case Description

A 45 year old non-vegetarian project manager presented to our emergency department with a 2-weeks history of unsteadiness and diffuses numbness in both legs. He also reported having intermittent heartburn. Otherwise, the medical and family history was unremarkable. The patient did not smoke or consume alcohol regularly. Examination revealed symmetric spastic paraparesis, ataxia and dysdiadochokinesia in arms and legs. Deep tendon reflexes in the legs were brisk and Babinski's sign positive on both sides. He could not discriminate sharp and dull in the legs. Moreover, the vibration sense in the feet was markedly reduced. His gait was severely spastic-atactic. Romberg's sign was positive. Otherwise, the neurological and internal medical examination was normal.

Full Blood Count (FBC) showed leukopenia (3.31 x 10^6/µL [ref.: 4.5-11]) and hyporeactive, hyperchrome macrocytic anemia (hemoglobine 116 g/L [ref.: 120-150]; MCV 119 fL [ref.: 76-100]; MCH 41.9 pg [ref.: 27-33]; reticulocytes 7% [ref.: 4.8-16.4]). Serum vitamin B12 was markedly decreased (<111 pmol/L [ref.: 200-900]), methylmalone acid was increased (25.94 µmol/L [ref.: <0.4]). Anti-parietal-cell and anti-intrinsic-factor-IgG were positive. Serum neurofilament light chain (sNfL) was markedly elevated (79 pg/mL; 99th percentile compared to 485 age-matched healthy controls) indicating severe neuroaxonal loss [1]. Motor evoked potentials showed prolonged central latencies to the lower limbs (central motor conduction time to anterior tibial muscle: right 20.9 msec, left 20.5 msec [ref.:<20 msec]). Somatosensory evoked potentials (SSEP) exhibited markedly prolonged central latencies from the arms (N20 of median nerve: right 24.6 msec, left 23.4 msec, respectively (ref.: <22.3 msec). SSEPs from the legs were not detectable.

Brain MRI was unremarkable whereas the spinal cord MRI showed bilateral T2w hyperintense dorsal ("inverted V sign") and lateral columns ("pair of binoculars sign") throughout the whole spinal cord indicating subacute combined degeneration (SCD) [2,3]. Gastroduodenoscopy was macroscopically unremarkable. Antrum biopsy revealed intestinal metaplasia with mucosal atrophy. Immunhistochemistry showed hyperplasia of enterochromaffine-like cells suggesting an atrophic autoimmune gastritis. Helicobacter pylori staining was negative.

We started cyanocobalamin 1 mg intramuscular twice per week. Here upon, the ataxia ameliorated within the following 4 weeks of inpatient rehabilitation. After 5 months of vitamin B12 supplementation, the gait had markedly improved. FBC, vitamin B12 and methylmalone acid had normalized and sNfL had significantly decreased, but was still markedly elevated compared to 485 age-matched healthy controls (decrease from from 79 pg/mL at baseline (99^{th} percentile) to 10 pg/mL (85^{th} percentile) after 5 months).

At month 9, the neurological examination showed residual impairment of vibration sense and mild gait ataxia, but was otherwise normal. MRI after 12 months showed reduction of hyper intensity of the lateral column but still hyper intense dorsal columns.

We found this case instructive, particularly for the following reasons: (1) Long extending spinal cord lesions have classically been described as pathognomonic signs of Neuromyelitis Optica Spectrum Diseases (NMOSD). However, one has to be aware of other differential diagnoses, such as metabolic myelopathies. The "inverted V" and the pair of "binoculars" are MRI signs that are suggestive of SCD, whereas NMOSD lesions preferentially include the grey matter of the spinal cord. (2) SCD is classically known as a demyelinating disorder, however, the highly elevated NfL (a neuronal cytoskeleton protein that is released into the blood following neuroaxonal injury) in our case indicate a substantial axonal loss. (3) Although the clinical improvement was remarkable following vitamin B12 substitution, spinal cord affection was still visible after 12 months on MRI. The incomplete recovery was also reflected by the ongoing elevation of NfL: After 5 months of vitamin B12 substitution, NfL levels have still not normalized suggestive of ongoing neuroaxonal loss. This finding emphasizes the importance of the long-term therapy and monitoring of patients with SCD.

Further studies are warranted to investigate whether or not sNfL can be used as biomarker for treatment monitoring in SCD.

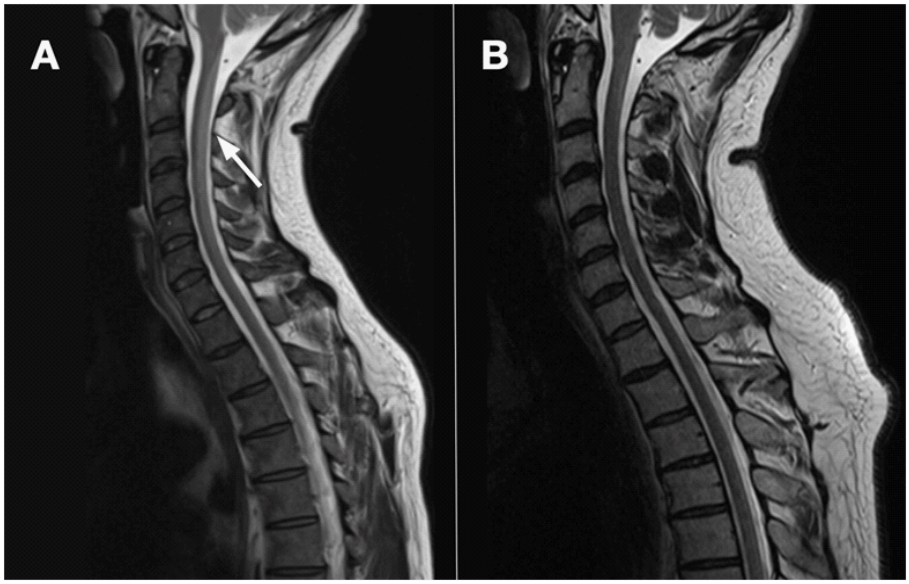

Figure 1: Sagittal T2 weighted images of the cervical spinal cord in subacute combined degeneration. Long extending spinal cord lesion (white arrow) in subacute combined degeneration two weeks after symptom onset (A) that markedly resolved after 12 months of vitamin B12 supplementation (B).

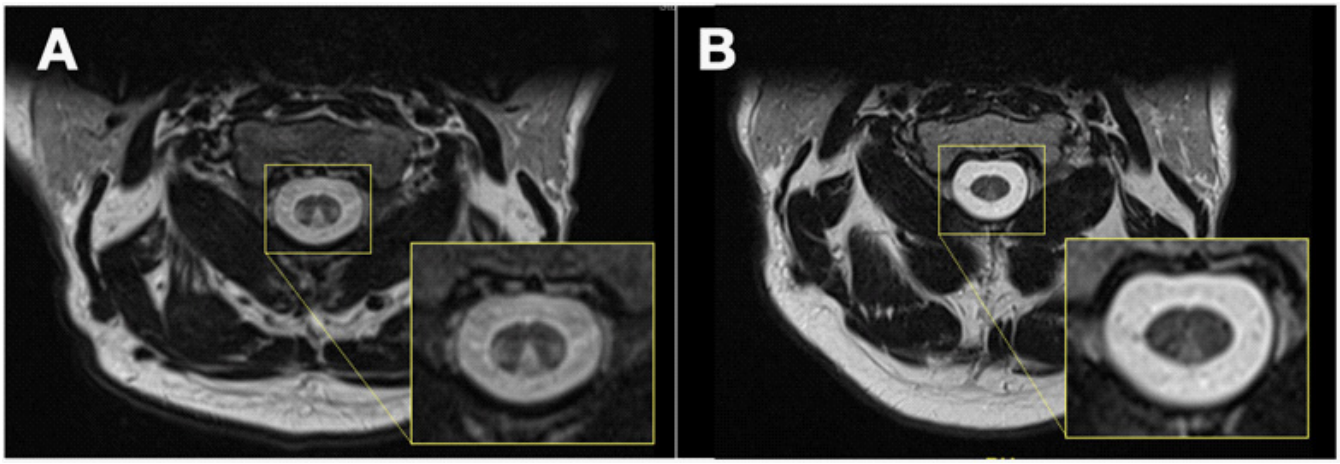

Figure 2: Axial T2 weighted scans of the spinal cord at level C2 in subacute combined degeneration. T2w hyperintense dorsal ("inverted V sign") and lateral columns ("pair of binoculars sign") at baseline (A) and after 12 months of vitamin B12 supplementation (B).

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Authors Information: Jannis Müller[1]; Anna Stenik[1]; Anneza Panagiotou[2]; Özgür Yaldizli[1]
[1]Neurologic Clinic and Policlinic, Department of Medicine, University Hospital Basel, Basel, Switzerland.
[2]Internal Medicine, Department of Medicine, University Hospital Basel, Basel, Switzerland.

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