Conventional MRI for diagnosis of Subacute Combined Degeneration (SCD) of the spinal cord due to vitamin B12 deficiency

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Running title: Conventional MRI in diagnosing SCD due to vitB12 deficiency

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ABSTRACT
Subacute combined degeneration of the spinal cord (SCD) is often found in vitamin B12 deficiency and typically shows hyperintensity on T2-weighted images of the lateral and posterior columns. The purpose of the study was to evaluate the use of conventional magnetic resonance examination in diagnosing SCD. Thirty-six patients were clinically confirmed and retrospectively analyzed; conventional spine MRIs were available for all patients and eight of them had contrast enhancement MRIs. The patients were followed for a minimum period of 4 weeks by telephone or clinically and 2 of them had follow-up MRIs after vitamin B12 treatment. 19 out of 36 patients showed abnormal signal intensity on T2 weighted images with a sensitivity of 52.8%, among which 18 in the posterior aspect of the spinal cord and 1 in the anterior horn of the thoracic spinal cord. The spinal cord abnormalities were seen at the cervical spine in 12 patients (33.3%) and at the thoracic spine in the other 7 patients (19.4%). Axial T2-weighted images showed symmetric linear T2-hyperintensity as an “inverted V” at the cervical spinal cord in 5 patients, which has been reported as a typical sign of SCD. For patients with thoracic spinal cord abnormalities, the bilateral paired nodular T2-hyperintensity looked like "binoculars" at the thoracic spinal cord. Only one out of the eight patients showed slight enhancement after injection with contrast agent. All the 36 patients reported clinical improvement after appropriate vitamin B12 treatment. The two follow-up spine MRIs showed a decreased extent of the lesion. Therefore, conventional MRI is useful in the diagnosis and management of SCD caused by vitamin B12 deficiency.

Key Words: conventional magnetic resonance imaging, subacute combined degeneration of the spinal cord, vitamin B12, deficiency, nutrition

INTRODUCTION
Vitamin B12 has a fundamental role in central nervous system function at all ages, its deficiency can present with brain, optic nerve, spinal cord, and peripheral nervous system disorders. Vitamin B12 deficiency is common in both developed and developing countries. As China is entering an ageing society, there are more old people who cannot get enough vitamin B12 whether due to gastrointestinal disease or inadequate dietary intake. In western countries, subacute combined degeneration of the spinal cord due to vitamin B12 deficiency mainly happens among vegans, and especially strict vegetarians. The lack of vitamin B12 can be clearly seen by examining the serum concentration of vitamin B12 and methylmalonic acid (MAA).
Subacute combined degeneration is characterized by posterior and lateral column damage of the spinal cord, which causes loss of proprioception and vibration sense in the feet, legs and hands, paresthesiae in the extremities, and corticospinal signs such as spasticity, hyperreflexia and the Babinski sign. The most consistent MRI finding is a symmetrical abnormally increased T2 signal intensity limited to posterior or posterior and lateral columns in the cervical and thoracic spinal cord, and on axial T2-weighted images “inverted V” sign can be seen. The cervical and upper thoracic cord is most commonly and severely affected. Studies on SCD had been done retrospectively or prospectively. Some suggested that conventional MRI had low sensitivity in diagnosing SCD when prospectively studied, but their sample size was small which limits their conclusion. We aimed to assess conventional MRI features and clinical characteristics of Asian patients in this study, to assess the value of conventional MRI in diagnosing SCD of spinal cord.

MATERIALS AND METHODS

Patients
The institutional ethics committee approved the study. A total thirty-six patients (20 males and 16 females, the median age=50 years, and age range=26 to 76 years) with biochemically proven vitamin B12 deficiency (<189 pg/mL) and abnormal clinical manifestations were included in the study. Written informed consent was obtained from all subjects after the purpose of the study was explained to them. The duration from onset of paresthesia of the distal limbs varied from half a month to eight years. In this study, 14 patients had a history of gastrointestinal disorders and 5 had psychiatric manifestations, and positive Romberg signs could be seen in 9 patients.

Clinical evaluation
Serum vitamin B12 level was measured by electrochemiluminescence (COBAS e411) [Roche diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim, Germany] method. Neurological examination was performed by a neurologist independently to define the severity of impairment in these patients with vitamin B12 deficiency.

Conventional MRI protocol
Conventional MRI data were acquired on a 3 T Simens Verio and a 1.5T Simens Avanto MRI scanner, performed on a 12-channel head-neck-spine coil by using T1 fluid attenuated inversion recovery (FLAIR) and T2 fast recovery (FSE) in the sagittal and axial planes.
Imaging parameters for T1 FLAIR in sagittal plane were TR=2400 ms, TE=25 ms, TI=1000 ms, NEX=1, slice thickness=3 mm, flip angle=90°, acquisition matrix=384 × 256, FOV= 280 mm, reconstructed matrix=512×512. T2 FS in sagittal plane had the following parameters TR=6000 ms, TE= 100 ms, NEX=2, slice thickness=3 mm, flip angle=90°, acquisition matrix=384 × 256, FOV=320 mm, reconstructed matrix=512 × 512. Imaging parameters for T2 FS in axial plane were TR=3500 ms, TE=120 ms, NEX=2, slice thickness=3 mm, flip angle=90°, acquisition matrix=320 × 224,FOV = 180 mm, reconstructed matrix=512 × 512. The cervico-dorsal and thoracic spine was performed to look for the B12 deficiency-related changes in the spinal cord. The flow velocity of the contrast agent was 2 mL per Kg through the vein.

Treatment and follow-up
All the 36 patients were administered 1000 μg of vitamin B12 intramuscularly for several days after clinically diagnosed as SCD, followed by orally taken vitamin B12 and folate at home for months depending on their condition. The activity was supervised by a neurologist with maintenance of record to assess the compliance. All the patients were followed for a minimum period of 4 weeks, and only two were re-evaluated on MRI imaging.

Data analysis
The MRI scans were reviewed independently by two experienced radiologists with one having more than 4 years’ experience in the field of neuroradiology and the other more than 25 years. There was no inter-observer disagreement in the MRI findings. The sensitivity of conventional MRI in diagnosing SCD was calculated.

RESULTS
19 out of 36 patients showed abnormal signal intensity on T2 weighted images with a sensitivity of 52.8%, among which there were 18 in the posterior column of the spinal cord and 1 in the anterior columns of the thoracic spinal cord; lateral column involvement was not apparent. The spinal cord abnormalities were seen at cervical spinal in 12 patients (33.3%) and at thoracic spine in the other 7 patients (19.4%) (Table 1). MRIs also demonstrated adjacent involvement of multiple segments of the cord. For the five patients with cervical spinal cord abnormalities, axial T2-weighted images showed symmetric T2-hyperintensity that appeared as an “inverted V” sign in the posterior column of the cervical spinal cord (Figure 1). For patients with thoracic spinal cord abnormalities, the bilateral paired nodular T2-hyperintensity looked as “binoculars” at axial thoracic spinal cord (Figure 2). Only one out of the 8 patients who had
enhanced MRI examinations showed slightly enhanced after injected with contrast agent.

All patients presented insidious neurological abnormalities such as tingling sensation in distal extremities, joint position and vibration, impaired sensation of fine touch, paresthesia, numbness, and difficulty in walking. 9 patients had positive Romberg signs, 14 patients had a history of gastrointestinal disorders and 5 suffered abnormal psychiatric conditions. After appropriate supplementation of vitamin B12, out of 36 patients, clinical signs and symptoms persisted in 11 patients, there was complete clinical improvement in 16 patients, while 9 patients lost contact with us. The lesion extent of the two patients decreased on follow-up MRI images.

DISCUSSION

Causes of vitamin B12 deficiency
Vitamin B12 acts as a coenzyme in the methyl malonyl-CoA mutase reaction, which is required for myelin synthesis. Its deficiency therefore results in defective myelin synthesis, leading to several central and peripheral nervous system dysfunctions. Vitamin B12 deficiency is often ignored and may cause several hematological, gastrointestinal, psychiatric and neurological manifestations, which is usually caused by pernicious anaemia, congenital or acquired malabsorption conditions (achlorhydria in elderly patients, long-term alcoholism, gastric or ileal resection, coeliac disease, chronic pancreatic insufficiency, Zollinger Ellison syndrome, Crohn's disease), medications (colchicine, neomycin, and p-aminosalicylic acid), disorders of intracellular cobalamin metabolism (methylmalonic aciduria and homocystinuria), increased requirement (in hyperthyroidism and alpha thalassemia), or inadequate intake (e.g. vegetarian diet). Determination of methylmalonic acid and homocysteine are particularly recommended in cases of diagnostically unclarified vitamin B12 deficiency.

Clinical manifestation and MRI findings
Vitamin B12 deficiency due to malabsorption syndrome is frequent in elderly people. In this study 14 patients had gastrointestinal disorders, and 5 had psychiatric manifestations. Subacute combined degeneration is clinically characterized by symmetric dysesthesia, disturbance of position sense and spastic paraparesis or tetraparesis, which may be caused by the involvement of the posterior and lateral columns of the cervical and upper thoracic parts of the spinal cord. The first abnormality is usually sensory impairment, most often presenting as distal and symmetrical paraesthesiae at lower limbs frequently associated with ataxia. Almost all patients have loss of vibratory sensation, often associated with diminished cutaneous sensation and
proprioception and nine of them had positive Romberg signs. Corticospinal tract involvement is common in the more advanced cases, with abnormal reflexes, motor impairment and, ultimately, spastic paraparesis.\textsuperscript{6,7} Only 16 out of 36 patients had completely clinical recovery and we lost contact with 9 patients which may be explained by the poor compliance of the patients and the different disease course of the patients.

Conventional MRI in diagnosing SCD has a relatively high sensitivity of 52.8\% in our retrospectively study. Patients with cervical spinal cord abnormalities showed symmetric linear T2-hyperintensity as an “inverted V” sign at cervical spinal cord on axial T2-weighted images. While for patients with thoracic spinal cord abnormalities, bilateral paired nodular hyperintensity looked as “binoculars” on axial T2-weighted images. Follow-up MRIs after vitamin B12 treatment showed decreased abnormalities in the two patients. Symmetric T2-hyperintensity within dorsal column of spinal cord is commonly seen in SCD patients with a linear pattern in the cervical spine and a nodular pattern in the thoracic spine. The residual patients who showed no abnormal signal intensity on MR images might be explained by the fact that the lesions may gradually increase when serum levels of vitamin B12 are low for prolonged periods of time.

**Treatment and diagnosis**

It is important to distinguish B12 deficiency from other causes of myelopathy, as it is treatable. Early detection is necessary for full clinical recovery as it is critical in the pursuit of improved quality of life and health care cost savings. The present report provides a renewed and more recent rationale for clinicians to use definitions of B12 deficiency that include homocysteine or MMA. By identifying and treating a B12 deficiency earlier, it may be possible to prevent some of the functional disabilities common to individuals as they age but possibly responsive to improved nutrition.\textsuperscript{8} Andrès suggested a dose of 1000 μg of oral cyanocobalamin for pernicious anemia (during the entire lifetime) and a mean daily dose of 250 μg for food-cobalamin malabsorption.\textsuperscript{9}

In the present study, MRI of the spine showed spinal cord signal abnormality in 19 out of 36 patients with a high sensitivity of 52.78\%. Classic posterior column involvement was seen in 16 patients, posterior and lateral columns involvement in two patient and involvement of anterior column in one patient each. Cervical or cervico-thoracic cord with predominant involvement of posterior columns is usually observed in patients with vitamin B12 deficiency related SCD and may be more specific for this condition as reported in the literature.\textsuperscript{10} Our data is in agreement with the literature with respect to the posterior column involvement, and it is
seen in a slightly large percentage of all the patients. In a recently published review of observational studies, it was mentioned that MRI findings at the time of diagnosis could have a prognostic value in SCD.\textsuperscript{11,12}

It is important to distinguish subacute combined degeneration from copper deficiency myelopathy (CDM) due to vitamin B12 deficiency and methotrexate-induced myelopathy where the abnormalities of the dorsal and/or lateral columns of the spinal cord are consistent with those described for SCD. Thus, specific laboratory studies are required.\textsuperscript{13,14}

\textbf{Conclusion}

Conventional MRI may be a useful tool for the diagnosis of SCD as it has a relatively high sensitivity. The diagnosis of SCD should be based on clinical features and serum vitamin B12 levels combined with conventional MRI examination.

\textbf{CONFLICT OF INTEREST}

We don’t have any conflict of interest.

\textbf{REFERENCES}


Table 1. MRI features and abnormal distribution of the patients

<table>
<thead>
<tr>
<th>MRI Findings</th>
<th>Dorsal-cervical spine</th>
<th>Thoracic spine</th>
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<tbody>
<tr>
<td></td>
<td>“Inverted V”</td>
<td>Patchy</td>
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<tr>
<td>T2-hyperintensity</td>
<td>5</td>
<td>7</td>
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<tr>
<td>52.8% (19/36)</td>
<td></td>
<td></td>
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<tr>
<td>No abnormal signal change</td>
<td>47.2% (17/36)</td>
<td></td>
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<tr>
<td>Enhancement</td>
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<tr>
<td>Follow-up MRIs</td>
<td>2/36</td>
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Figure 1. MR findings baseline as well as follow-up in a 44-year-old man with vitamin B12 deficiency. (A) T1W-FLAIR sagittal image did not show any alteration in signal intensity. (B, C) T2-weighted sagittal images show increased signal intensity in the cervical spinal cord extending from C1 to C6 level. (D) T2-weighted axial image shows abnormal signal involving the posterior columns of cervical cord with inverted V sign. On 4 weeks follow-up, while patient was receiving treatment, partially resolution of abnormal cord hyperintensity was observed in T2-weighted sagittal, T1-FLAIR sagittal and T2-weighted axial images (E, F, G, H).
Figure 2. MR findings in a 47-year-old woman with symmetric dyesthesia in the lower extremities for half a month. (a) T1-weighted sagittal image did not show any alteration in signal intensity. (b, c) T2-weighted sagittal images show increased signal intensity in the cervical spinal cord extending from T7 to T11. (d) The abnormal signal intensity looked bilateral paired nodular T2-hyperintensity as "binoculars" at thoracic spinal cord on axial T2 weighted images through the 7th thoracic spinal cord level.