A retrospective study of 23 cases with subacute combined degeneration

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Purpose: To study retrospectively the diverse presentations, ancillary tests and neuroimaging in patients with subacute combined degeneration (SCD). Methods: Twenty-three Chinese patients with SCD were included in this study. The clinical presentations and laboratory data including comprehensive metabolic panel, serum folic acid, vitamin B12 levels, gastroscopy and images of spinal cord on magnetic resonance imaging (MRI) were evaluated. Rating scales for localizations of lesions and functional disabilities were used to define the severity of neurological impairment. Results: No difference was found between men and women in the age of disease onset. For most of the patients, sensory symptoms, oftentimes as initial symptoms, occurred earlier than motor symptoms. The signs of the disease were more obvious than the symptoms. Six patients had sensory deficit levels mimicking transverse myelopathy. Anemia was not always detected in our patients with SCD. Normal or even elevated serum levels of vitamin B12 were found in seven patients. Spinal cord lesions on MRI were observed in six patients and the clinical and neuroimaging findings were not necessarily consistent. Conclusions: The sensory symptoms occur earlier than the motor symptoms in SCD patients. SCD patients may have sensory deficit level. Normal or even elevated serum levels of vitamin B12 may occur in patients with SCD.

KEYWORDS: subacute combined degeneration, clinical features, sensory deficit level, hemoglobin, vitamin B12

Introduction

Subacute combined degeneration (SCD) is a neurodegenerative disease caused by vitamin B12 deficiency. The patients usually present with neurological, psychiatric, hematological and gastrointestinal symptoms [1]. Because of the low incidence of SCD and variable clinical presentations, the diagnosis is oftentimes challenging. Early diagnosis and treatment of SCD are important because the neurological symptoms usually progress continuously without treatment, which may result in irreversible damage to the nervous system and even death. Full recovery is possible if the patients receive treatment within three months after the onset of the disease [2]. In this retrospective study, we evaluated the clinical and laboratory data of 23 Chinese patients with SCD, who were hospitalized at our hospital between January 2010 and June 2013. We focused on the atypical symptoms and signs of the disease which are helpful for differential diagnoses, in an attempt to help the clinicians be aware of the possibility of SCD and initiate the treatment early.

Methods

The retrospective study included 23 patients who were diagnosed with SCD and treated in an inpatient setting at our hospital between January 2010 and June 2013. All the patients met the diagnostic criteria for SCD with modification [3]: clinical symptoms and signs of posterior and lateral columns or peripheral nerve impairment, low serum levels of vitamin B12 or clinical improvement...
after cobalamin treatment in patients with normal or elevated levels of vitamin B12 level, and no other spinal cord or peripheral nerve disease.

Comprehensive metabolic panel, serum folic acid, vitamin B12 levels, gastroscopy and spinal cord magnetic resonance imaging (MRI) were performed on all patients. Folic acid (normal range 4.2–19.9 ng/ml) and vitamin B12 levels (normal range 240–900 pg/ml) were measured by using immunochemistry luminescence method (ARCHITECT B12 Reagent Kit, Abbott Laboratories Ltd, America). Sagittal and axial T1 and T2 weighted images of the spinal cord were obtained with 1.5T MRI (Magneton impact, Siemens, Germany).

Two rating scales were used in our study. A simple rating scale was used to define the localizations of lesions, including lateral column, posterior column, peripheral nerves, autonomic nervous system and brain. One score was given to a patient with one location involved and maximum score was 5, if all the locations were involved. Disability rating scale described by Healton et al. [4] was used to evaluate the clinical symptoms, including gait disturbance, sensory disturbance, mental impairment, peripheral nerve injury and pyramidal tract damage. The maximum score of 16 points indicated most severe damage.

Statistical analysis
Continuous data were expressed using mean ± standard deviation and categorical data using number and percentage. When two groups were compared, independent samples t test for continuous data and chi-square test for categorical data were used. Correlation analysis was performed by using the Spearman rank correlation. p < 0.05 was chosen as significant level. All statistical analyses were performed by using SPSS (version 13.0; SPSS Inc., Chicago, IL, USA).

Results
Patients' profile
The age of the 23 SCD patients ranged from 40 to 85 years (mean age 60.39 ± 13.09). Fifteen patients were male and eight patients were female. No difference was found between men and women in the onset age of the disease (59.67 ± 12.02 vs. 61.75 ± 15.69, p = 0.725). For the patients’ past medical history, the potential risk factors for vitamin B12 deficiency were gastric ulcer or gastrectomy (n = 7, 30.43%), alcohol abuse (n = 3, 13.04%), vegetarian diet (n = 2, 8.70%), long-term anorexia (n = 3, 13.04%) and anemia (n = 6, 26.09%). No hepatic diseases, renal insufficiency or cancer was identified in our patients. Six patients had a history of irregular usage of B12 or folic acid oral preparations before admission (26.09%). However, the retrospective nature of this study may result in the difficulty to find out other identifiable causes of B12 increase.

Clinical features
The shortest period from the onset of symptoms to the initiation of treatment was 0.3 months, and the longest was 120 months with an average of 24.99 months. The clinical features were described in Table 1. On admission, 60.87% (14/23) of the patients complained of walking instability, while 78.26% (18/23) of the patients showed positive Romberg signs (p < 0.05). 43.48% (10/23) of the patients complained of limb weakness, while 60.87% (14/23) of the patients had positive Babinski sign (p < 0.05). 52.17% (12/23) of the patients complained of numbness of limbs, while 65.22% (15/23) of the patients had peripheral sensory disturbances (p < 0.05). Six of the patients (6/23, 26.09%) were found having sensory deficit levels in thoracic or lumbar segments.

For the initial symptoms, 52.17% (12/23) of the patients reported limb numbness, while 21.74% (5/23) patients complained of limb weakness (p < 0.05) and 13.04% (3/23) patients had walking instability (p < 0.05).

Laboratory examinations
Hemoglobin
Eleven patients had reduced levels of hemoglobins (HGB) and twelve patients had HGB levels within normal limit. The difference of HGB levels between the two groups was statistically significant (98.36 ± 13.01 vs. 137 ± 11.55, p < 0.001). The number of patients with gastritis or gastric ulcer confirmed by using endogastroscopy in low-HGB group was more than that in normal-HGB group (6/11 vs. 1/12, p = 0.016). No differences were found between low-HGB group and normal-HGB group in the mean corpuscular volume (MCV, 100.47 ± 14.40 vs. 92.99 ± 7.15, p > 0.05), neurological functional disability scale (5.45 ± 2.25 vs. 5.00 ± 2.7, p > 0.05) and the score of lesions (2.82 ± 0.75 vs. 2.33 ± 1.30, p > 0.05).

Serum vitamin B12 levels
Reduced levels of vitamin B12 were detected in 16 patients (Table 2). Interestingly, two patients with normal vitamin B12 levels and five patients with elevated levels of vitamin B12 were found. No difference in the number of patients with risk factors (anorexia, vegetable diet and gastritis or gastric ulcer) and spinal lesions on
Table 1. Clinical features of SCD patients in number (%) of 23 patients.

| Chief complaints       | Signs                          | Initial symptoms               | Other symptoms               |
|------------------------|-------------------------------|--------------------------------|------------------------------|
| Walking instability    | 14(60.87)                     | 18(78.26)*                     | 12(52.17)#                   |
| Limb weakness          | 10(43.48)                     | 14(60.87)*                     | 5(21.74)                     |
| Limb numbness          | 12(52.17)                     | 15(65.22)*                     | 6 (26.09)                    |

Compared with the number of chief complaints, *p > 0.05; Compared with the number of motor symptoms (limb weakness or walking instability), #p < 0.05.

Table 2. The comparison between low group and no-low group of vitamin B12.

|                | Anorexia or vegetable diet (n) | Gastritis or gastric ulcer (n) | Hb (g/L) | MCV (FL) | Folic acid (n) | Spinal lesions (n) | Scale of disability | Score of lesions |
|----------------|-------------------------------|--------------------------------|----------|-----------|----------------|---------------------|---------------------|------------------|
| No-low group   | 7                             | 2                              | 1        | 125.71 ± 23.03 | 99.81 ± 14.62 | 4                   | 2                   | 5.57 ± 2.37 | 2.71 ± 0.95 |
| Low group      | 16                            | 3                              | 6        | 115.88 ± 23.86 | 95.15 ± 10.22 | 7                   | 4                   | 5.06 ± 2.14 | 2.50 ± 1.15 |
| p              | 0.599                         | 0.266                          | 0.385    | 0.526     | 0.554          | 0.858               | 0.518               | 0.592            |

Gastritis or gastric ulcer = gastritis or gastric ulcer found by gastroscope; Folic acid = the level of folic acid higher than normal. Spinal lesions = spinal lesions found on MRI; Scale of disability = neurological functional disability scale; Score of lesions = score of localization lesions.
MRI were found in low vitamin B12 group and no-low vitamin B12 group.

**Correlation analyses of SCD course and serum tests with nervous system damage**
The correlations of the SCD course, HGB, MCV and vitamin B12 levels with neurological deficits (including neurological functional disability scale and score of lesions) were analyzed and no significant correlation in statistics was found.

**Responses to intramuscular vitamin B12 therapy**
The symptoms and signs of all the patients improved significantly after the therapy with intramuscular injection of vitamin B12 (North China Pharmaceutical Limited Company, China) at a dose of 1–1.5 mg per day for two-to-four weeks before discharge. Serum B12 levels in 16 SCD patients were re-examined and within normal range one month after treatment. Six (6/23, 26.09%) patients had spinal lesions on MRI, and three of them had repeated MRI showing resolution of the lesions at three months follow-up after discharge. However, the retrospective nature of the study and the impossibility to directly evaluate the neuroimaging data are one of the limitations of our study.

**Discussion**

In this retrospective study, we found that the sensory symptoms, oftentimes as initial symptoms, occurred earlier than motor symptoms, and the signs of the disease were more obvious than symptoms. We observed some patients had sensory deficit levels. In addition, we found that normal or even elevated serum levels of vitamin B12 and spinal cord lesions on MRI in some patients.

The typical features of SCD myelopathy are described as follows: sensory disturbances are mostly symmetrical with no obvious level; the neurological damage was composite (bilateral, multitracts and multisite); slow progression and the lack of volatility [5]. However, six of our patients were found having sensory deficit levels in the thoracic or lumbar segments. It indicated that the lesions of lateral columns were severe and spread to superficial sensory conduction bundle (spinothalamic tract).

Normal or elevated vitamin B12 levels were found in the patients with SCD in our study even though one of the typical SCD diagnostic criteria is reduced serum B12 levels. Recently SCD cases with normal serum B12 levels have been reported [6–8]. Copper deficiency can lead to similar clinical manifestations as vitamin B12 deficiency. A serum copper level should be tested in the SCD patients with normal serum B12 levels or without response to vitamin B12 supplementation [9]. In this retrospective study, copper levels were not available for our patients. However, the patients’ symptoms and signs improved significantly after intramuscular injection of vitamin B12. The therapeutic efficacy makes the diagnosis of SCD very likely in our patients.

The phenomenon that SCD patients have normal or elevated serum B12 levels is termed “functional vitamin B12 deficiency”. It has been reported that SCD patients with normal or elevated serum B12 levels had abnormal transcobalamin (TC), a factor promoting cellular uptake of B12 by TC receptor-mediated endocytosis [2]. A normal or increased serum vitamin B12 level does not accurately reflect the underlying tissue availability of vitamin B12 and may be misleading. Serum methylmalonic acid or homocysteine levels are more accurate reflection of vitamin B12 functional statuses [10]. SCD patients with normal or elevated serum B12 concentration may respond to repeated high-dose injections of B12 [11], which were confirmed in our cases.

Vitamin B12 deficiency is often associated with megaloblastic anemia in Chinese [12]. Megaloblastic anemia is the earliest common symptom and the reason for patients visiting doctors. However, neurological symptoms may occur prior to those of the blood system. Patients with SCD may have long courses of neuropathy in the absence of hematological abnormalities [1,13]. In our study, the difference of mean HGB concentration in low-HGB group and normal-HGB group was statistically significant, while the anemia was generally mild in our patients. The number of patients with gastritis or gastric ulcer found by using gastroscope in low-HGB group was more than that in normal-HGB group. It indicated that stomach diseases might affect patients’ intake of other nutrients in addition to vitamin B12 malabsorption. This may affect the hematological system more than the nervous system [14].

In our study, we found the course of SCD and MCV had a trend of positive correlation with the extent and localization of nervous system damage, but the correlation did not reach the statistical significance. Longer course and higher MCV are associated with more severe neuropathy, as indicated in the study by Healton et al. [4]. The small sample size and applying the two scales to the retrospective study are the limitations of our study.

There was no significant gender difference between men and women in our study as well as in the previous report [6]. The onset of SCD is mostly in middle age or older. Average age of onset in our study was 60 years, which is consistent with the majority of studies and case reports [3,15,16]. Lin et al. [17] reported three SCD patients with the onset around 20 years of age and they all had clear history of nitric oxide inhalation. In
our study, seven patients had gastritis or gastric ulcer and five patients were on a vegetarian diet or had long-term anorexia. These potential causes of vitamin B12 deficiency often occur in the elderly. Probably it may explain the late onset of SCD.

Vitamin B12 storage capacity is large (2000–5000 μg in the whole body) while demand is small (1–2.8 μg per day), so that the onset of SCD is usually insidious and the disease is slowly progressive with the symptoms worsening overtime [2]. In our study, the shortest time from the onset of the disease to the initiation of treatment was 0.3 months and the longest was 120 months with an average of more than 1 year. When the body's deficiency of vitamin B12 develops to a certain extent, most of the patients start to present sensory abnormalities such as limb numbness, and motor symptoms occurred eventually. In our report, more than half of the patients (52.17%) had sensory impairments as an initial symptom. All patients gradually displayed limb weakness, gait ataxia, mental disorders or cognitive impairment, blurred vision, defecation abnormalities or impotence and other symptoms. Our data showed that the patients’ chief complaints and corresponding neurological signs were not entirely consistent and the neurological signs may be more obvious than symptoms. This pattern of clinical manifestations may be helpful for the diagnostic consideration.

26.09%(6/23) of our patients were found having spinal cord lesions on MRI, which is more than 14.8%(8/54) reported by Jain et al. [18] but far less than 82.00% reported by Locatelli et al. [19]. Possible reasons are as follows: first, MRI changes may lag behind the onset of clinical symptoms [20,21]. Second, conventional MRI may not be a useful tool to diagnose SCD because of its low sensitivity, while diffusion tensor imaging is a good alternative [18]. Third, some clinicians and radiologists are not familiar with SCD, which may result in misdiagnoses as cervical spondylosis, multiple sclerosis or even MRI artifacts. Lastly, as reported by Hemmer et al., MRI damages of SCD are not present in every patient. Clinical and imaging findings are not necessarily consistent [2,18,19,22,23].

Conclusion

For Chinese SCD patients, most of them may first have sensory abnormalities and motor symptoms often occur later. The neurological objective signs may be more obvious than subjective symptoms. Sensory deficit levels may exist in some patients. SCD cannot be completely excluded in patients without anemia or with normal or even elevated serum vitamin B12 levels. Lesions on MRI are not observed in every patient. Clinical and imaging findings are not necessarily consistent [2,18,19,22,23]. The limitations of this paper may stem from the small sample size and the retrospective nature of this study.

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Supplementary Material

Supplementary material available online

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