Common variable immunodeficiency leading to spinal subacute combined degeneration monitored by MRI

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Abstract
A patient is reported on with a common variable immunodeficiency syndrome (CVID), in whom chronic gastritis with antibodies against parietal cells and a cytomegalovirus associated enteritis led to vitamin B12 deficiency with consecutive subacute combined degeneration of the spinal cord. The resulting medullary changes, most probably representing demyelination, were visualised with MRI. The effects of treatment were also monitored over three years by MRI and clinical examination. The resolution of the MRI changes correlated with clinical improvement of the patient’s signs. In the medical literature only five cases of vitamin B12 related spinal cord changes have been identified by MRI; none was caused by a CVID syndrome.

Keywords: magnetic resonance imaging; common variable immunodeficiency syndrome; vitamin B12

Common variable immunodeficiency syndrome (CVID) is a rare disease of unknown origin that can lead to a vitamin B12 deficiency. Subacute combined degeneration of the spinal cord is a sequela of vitamin B12 deficiency, which can cause various central and peripheral neurological disorders.1 2

We report a rare case of CVID. The patient presented with a subacute combined degeneration of the spinal cord due to vitamin B12 deficiency. The degeneration was monitored for three years by MRI.

Case report
A 54 year old man was admitted to our hospital with complaints of numbness and paraesthesia in both arms, legs, and around the umbilicus. These symptoms had begun in his feet six months earlier and had steadily progressed. He additionally had gait disturbances and weakness of the arms, especially the legs. He reported a weight loss of 11 kg over the previous six months, minor depression, and a mental slowing.

Neurological examination disclosed a loss of superficial sensation below the segmental level of T 9 and the sense of vibration. The sense of position was disturbed in all four limbs (right>left, arms>>legs). The Romberg sign was positive, and a prominent sensory ataxia of the arms and a gait ataxia were detected. The reflexes of the right knee, left ankle, and upper limbs were reduced.

Neuropsychologically, the patient exhibited emotional instability, irritability, minor depression, and a slight intellectual deterioration.

Electrophysiologically, the visual evoked potentials showed bilaterally reduced amplitudes and prolonged latencies. The N30 and P40 amplitude of the somatosensory evoked potentials of the tibial nerve could not be reproducibly recorded at the time of admission (fig 1). The somatosensory evoked potentials of the median nerve and the motor cortex stimulation were normal. Electromyography and nerve conduction studies provided evidence of a demyelinating polyneuropathy.

Neuroradiological examination showed a hyperintense band on MRI on the T2 weighted sequence, extending from the cervical to the lumbar level (fig 2). After application of Gd-DTPA, no enhancement was detected.

Laboratory investigations disclosed a prominent macrocytic anaemia (haemoglobin 8.2 g/dl, packed cell volume 23.5%, red blood cell count 1.87 T/l, mean corpuscular volume 109 cm3 ) and leukaopenia (white blood cell count 3.5 G/L). The cobalamin concentration (radioisotopic assay) was<<100 pg/ml (normal concentration>200 pg/dl). There was a high serum concentration of antibodies against parietal cells.

The Schilling test without intrinsic factor was too low (0.4%, normal values>10%). The rate of cobalamin absorption increased to 2.65% after adding the intrinsic factor. These findings were compatible with a reduced production of intrinsic factor in association with a malabsorption.

Biopsy of the gastric mucosa disclosed a massive chronic atrophic gastritis with Helicobacter infection. The biopsy of the ileum showed a cytomegalovirus associated enteritis. An HIV test was negative.
These findings suggested that the patient had subacute combined degeneration of the spinal cord, chronic atrophic gastritis, and enteritis associated with cytomegalovirus, caused by HIV negative syndrome with an antibody deficiency (CVID or idiopathic CD4 lymphocytopenia).

The patient was treated with cobalamin, iron, folic acid, and immunoglobulins. Follow up evaluations, performed at two, six, and 12 months, and at three years showed a considerable improvement of the neurological deficit as well as the visual and somatosensory evoked potentials (fig 1). The values for laboratory tests returned to normal.

Follow up MRI was performed at three and six months and at three years after the initial investigation. The hyperintensity of the dorsal parts of the myelon in the T2 weighted sequence also returned to normal (fig 2).

Discussion

To the best of our knowledge, this is the first case of an HIV negative immunodeficiency syndrome causing a vitamin B12 deficiency, which led to a subacute combined degeneration of the spinal cord documented by MRI.

CVID is a rare, acquired disease of unknown cause, with heterogeneous clinical manifestations. In some reports it is characterised by recurrent respiratory and gastrointestinal infections. The hallmark of CVID is the formation of defective antibodies in HIV negative subjects. These patients are prone to various autoimmune disorders, including pernicious anaemia. The detection of parietal cell antibodies and of enteritis associated with cytomegalovirus in the patient we present is in line with these autoimmune disorders.

Vitamin B12 deficiency may result from insufficient ingestion or impaired intestinal absorption of vitamin B12. Insufficient ingestion can be due to insufficient uptake—namely, chronic conditions resulting from alcoholism, anorexia nervosa, or an extremely imbalanced diet. Impaired absorption is mainly caused by one of the following: (1) relative or absolute intrinsic factor deficiency due to parietal cell atrophy, gastric carcinoma, or partial or total gastrectomy; (2) antibody production against vitamin B12, intrinsic factor, or parietal cells; (3) malabsorption due to ileitis terminalis, colitis ulcerosa, intestinal tuberculosis, resection of the ileum, pancreas insufficiency,
amyloidosis, and collagenosis. The peak incidence is in the sixth and seventh decades.\(^1\) Vitamin B12 deficiency has been reported to occur in HIV infected patients with chronic diarrhoea.\(^8\)

The clinical picture associated with vitamin B12 deficiency is determined by the resulting pernicious anaemia, atrophy of the upper intestinal tract mucosa, and involvement of the central and the peripheral nervous systems.

One of the most prominent neurological effects is the subacute combined degeneration of the spinal cord, also termed “funicular myelosis”. Here the cervical and thoracic medullary white matter, especially the posterior and lateral columns (funiculi), are primarily affected. The white matter tracts involved show demyelination with degeneration of myelin sheaths and axonal loss. Involvement of the posterior columns (70%-90%) leads to paraesthesia (80%-85%), impaired proprioception (70%-90%), and loss of vibration sense, whereas involvement of the lateral column leads to paresis (55%-80%).\(^1\)

The described medullary changes can be visualised on MRI. This was shown in our patient as well as five other published case reports.\(^9\)-\(^13\) The age of these patients (one woman and five men) ranged from 10 to 69 years (mean 46.3 years). All showed an intramedullary hyperintensity on the T2 weighted images, which is thought to be mainly due to demyelination. By contrast, axonal loss is thought to occur later and to a lesser degree.\(^13\) This demyelination was located in the cervical spinal cord in two patients,\(^9\)\(^10\) in the cervical and thoracic spinal cord in three patients including the one we report on,\(^11\)\(^12\) and only in the thoracic spinal cord in the remaining patient.\(^13\) In all but one patient,\(^9\) multiple levels were affected. The posterior columns were the site of maximal signal intensity change.

![Image of MRI scans showing hyperintensity in the spinal cord](image-url)
in our patient and three others.\textsuperscript{11–13} These MRI findings are compatible with histopathological findings, mainly demyelination. Gd-DTPA was administered twice; one patient showed mild enhancement.\textsuperscript{11}

It is important to recognise these changes on spinal MRI. As MRI becomes more accessible, the MRI examination can be performed before the results of laboratory tests are available. As the clinical picture of vitamin B12 deficiency or CVID can be puzzling, changes on MRI can help to establish the diagnosis. Although extensive changes within the spinal cord have also been reported in multiple sclerosis, they are unusual.\textsuperscript{14}

Follow up studies performed at 10 weeks,\textsuperscript{13} four months,\textsuperscript{9} five and 10 months,\textsuperscript{12} six months (our patient), and at three years (Berger and Quencer\textsuperscript{10} and our patient) always disclosed a reduction or resolution of the intramedullary hyperintensity after treatment with vitamin B12. Thus the effect of treatment can be successfully monitored with MRI. As the therapy leads to a remyelination of the affected white matter tracts, their signal intensity on the T2 weighted sequence returns to normal in parallel with improvement of the clinical picture. If improvement begins as early as 10 weeks after therapy, the main reason for the clinical picture and the MRI changes cannot be ascribed to axonal loss.

In conclusion, MRI can be used to diagnose subacute combined degeneration of the spinal cord as well as to monitor its treatment, especially in such rare cases as the one presented here.

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