Case Report - An interesting case of reversible myelopathy with megaloblastic anemia due to tropical sprue

KRUPA SHANKAR
Department of General Medicine, PSG INSTITUTE OF MEDICAL SCIENCE & RESEARCH

Abstract: Vitamin B12 deficiency is common, with most patients lacking classical features of advanced, severe deficiency. Early diagnosis and treatment can prevent severe anemia and irreversible damage to the nervous system. We describe a 31-year-old with megaloblastic anemia who presented with clinical and radiological features of early myelopathy and low serum levels of vitamin B12. Further evaluation led to a diagnosis of tropical sprue causing megaloblastic anemia and treatment with cyanocobalamin injections led to rapid resolution of clinical manifestations and magnetic resonance imaging abnormalities. We have reviewed the literature of magnetic resonance imaging in vitamin B12 deficiency myelopathy and discussed the issues related to diagnosis and early treatment of this potentially reversible condition.

Keyword: MRI - magnetic resonance imaging, SCD - subacute combined degeneration, MMA - methylmalonic acid.

INTRODUCTION

Vitamin B12 deficiency can cause a wide range of neurological disorders, including myelopathy, neuropathy, neuropsychiatric disturbances, and less often, optic neuropathy(1). A survey of the literature revealed many cases of vitamin B12 deficiency myelopathy with documented magnetic resonance imaging (MRI) abnormalities(2-11). Some of these cases included a description of the temporal relationship of MRI findings to the neurological symptoms and changes in response to therapy. Most reported cases respond well to cobalamin treatment if it is instituted early, although residual neurological and radiological abnormalities can occur if therapy is delayed. We report resolution of clinical and MRI abnormalities in a patient with vitamin B12 deficiency myelopathy following cyanocobalamin supplementation and discuss the approach to diagnosis and early recognition of this treatable and reversible condition.

REPORT OF A CASE

A 31-year-old man got admitted with the chief complaints of loss of weight & appetite, nausea for the past 18 months, memory disturbances for the past 9 months, weakness of all 4 limbs for the past 7 months (upper limbs > lower limbs) & urinary / fecal incontinence for the past 3 months. These symptoms were insidious in onset and slowly progressive. His recent and immediate memory were impaired but remote memory was intact.

Initially, he had weakness of both lower limbs with difficulty in walking. He also had difficulty in gripping his chappals while walking. His weakness gradually progressed to a stage where he was not able to walk without support. He had difficulty in walking in the dark and negotiating narrow pathways. He used to sway minimally to either side while walking & also had 2-3 episodes of trivial falls.

Now for the past 2 months, he has been totally bedridden and at the time of admission, he was not even able to move his toes. He had mild weakness of the upper limbs and difficulty in performing fine activities like buttoning his shirt / combing his hair & holding objects. He had difficulty in flexing his neck & turning and getting up from bed. He was able to feel his bladder sensation, but could not control his voiding of urine.

He had significant weight loss of 12 kilograms over the past 1 year. He also had excessive hair loss (figure 1) over the same period. He also had mild abdominal pain in the epigastric region for the past 3 months.

He did not have any symptoms suggestive of cranial nerve involvement / behavioural, sleep or speech disturbances / involuntary movements / raised intracranial pressure / root pain. He did not have any history of positive or negative sensory symptoms. He did not feel any electric shock-like sensation on flexing his neck (Lhermitte's sign). There was no history of giddiness / excessive or reduced sweating. He was a vegetarian by diet. He was not a smoker / alcoholic. He had no prior exposure to any toxic chemicals nor chronic intake of any drugs.

He was born of non-consanguinous marriage and he is unmarried. There was no history of pre-marital exposure / similar illness among family members. He did not have any respiratory or cardiovascular symptoms. This 31-year-old male presented with progressive symptoms of quadriaparesis (pyramidal weakness), sensory ataxia and memory loss along with gastrointestinal symptoms of 18 months duration.

General physical & CNS examination

On general examination, he was conscious, co-operative and obeying commands. He weighed 45 kilograms. His height was 164 centimetres and body mass index was 17. He was afebrile at the time of admission. His vitals were stable and all peripheral pulses were well felt. On general physical examination, he had alopecia & brown coloured hair (figure 1). He also had evidence of knuckle hyperpigmentation (figure 2).
There was no evidence of any neurocutaneous markers and peripheral nerves were not palpable. There were no trophic changes / muscle tenderness.

Mini-mental status examination revealed a score of 22/30. His pupils were 3 millimetres in size and equally reacting to light. There was no ptosis. His extra-ocular movements & field of vision were normal. Examination of his fundus did not reveal any abnormality. Sensations over the face were normal. He did not have any evidence of facial palsy. His gag reflex was normal. He had weakness of both the sternocleidomastoids. Examination of the tongue did not reveal any abnormality.

On examination of the motor system, the posture of his legs was found to be externally rotated. There was mild wasting of the inner aspect of both the thighs (right > left). There was evidence of disuse atrophy. There was no wasting of the small muscles of hands / feet. Examination of the tone showed mild spasticity of both the lower limbs. He had mild weakness of the extensors of elbow and wrist joint as evidenced by a power of 4. His handgrip was slightly weak on both the sides. He had neck muscle & truncal weakness.

He had weakness of the hip joint as evidenced by a power of 3 on both sides. He also had weakness of the knee and ankle joint on both sides as evidenced by a power of 2. His deep tendon reflexes and knee jerk on both sides were brisk as evidenced by a grading of 3. His ankle jerk was absent on both sides. He also had an absent abdominal reflex. His plantar reflex was equivocal on both sides. His sphincteric reflexes were sluggish and no primitive reflexes were elicited. His pain, touch & temperature sensations were normal. Vibration sense was grossly impaired in both lower limbs and upper limbs up to spinous process of first cervical vertebra(C1). Joint position sense was lost in the toes and ankles of both lower limbs and up to fingers of both upper limbs. He was able to stand only with support.

Examination of the spine & cranium was normal. Examination of other systems did not reveal any abnormalities. This patient had features of progressive non-compressive myelopathy (upper level – first cervical vertebra(C1), involving pyramidal and posterior columns) and peripheral neuropathy with mild dementia & malnutrition.

Investigations & Treatment

This patient's complete blood count showed macrocytosis as evidenced by a mean corpuscular volume of 131, a haemoglobin of 11.3 gm/dl, hematocrit of 34%, a platelet count of 1,39,000 and an elevated erythrocyte sedimentation rate of 103 mm. Peripheral smear showed the presence of macro-ovalocytes and hypersegmented neutrophils(figure 3) & macrocytic anemia. The patient's reticulocyte count was 4.2 which was well above the normal range. Lactate dehydrogenase levels were within the normal range. His liver function tests & renal function tests did not reveal any abnormalities.

Vitamin B12 levels were 64 pg/ml which was well below the normal range and serum folate level was normal. Bone marrow aspiration revealed erythroid hyperplasia and an increase in eosinophilic precursors. Both hyper and hypolobated megakaryocytes with few giant band forms, megaloblasts and giant metamyelocytes(figures 4,5) were seen which was suggestive of megaloblastic anemia. Bone marrow trephine biopsy showed few haemopoietic cells with megaloblastic erythroid precursors(figure 6)
MRI cervical spine showed evidence of mild cervical & proximal thoracic cord enlargement with abnormal uniform T2 hyperintensity within dorsal & lateral columns of cervical spinal cord extending superiorly from cervicomedullary junction and inferiorly into thoracic cord(figures 7-11) which was suggestive of SCD. MRI scan of the brain was essentially normal.

Oesophago-gastro-duodenoscopy revealed the presence of a lax lower esophageal sphincter and erosive gastritis. Deep duodenal biopsies were taken, which showed fragments of duodenal mucosa with focal villous blunting & an increased cellularity of lamina propria(figures 12,13) & lymphoid aggregates. Brunner glands were seen extending into lamina propria. Nucleomegaly of the crypt epithelium(figure 14) was also seen. Based on these findings, a diagnosis of tropical sprue was made.

A final diagnosis of tropical sprue with nutritional deficiencies including vitamin B12 deficiency with subacute combined degeneration of the spinal cord with peripheral neuropathy & mild dementia was made. This patient was treated with injections of vitamin B12, 1000 micrograms once daily for 1 week followed by 1000 micrograms once weekly for 1 month followed by once monthly thereafter. He was also treated with tablets of folic acid 5 mg once daily and tablets of tetracycline 500 mg thrice daily for 6 months as treatment for tropical sprue and he was also put on a high protein and vitamins diet. Within 1 month of initiation of therapy, the patient's symptoms had resolved and neurological examination revealed an improvement in power & memory and he was discharged in a well condition.

DISCUSSION
This patient had megaloblastic anemia with resultant vitamin B12 deficiency myelopathy. Despite an obvious cervical cord signal abnormality on T2-weighted MRI(figures 7-11), replacement of vitamin B12 early in his illness resulted in resolution of symptoms, signs, and MRI abnormalities.

The specific spinal cord lesion caused by vitamin B12 deficiency is known as subacute combined degeneration (SCD). Neuropathologic studies of SCD show spongiform changes with foci of myelin and axonal destruction mainly in the posterior and lateral columns, but also involving anterior columns in a few advanced cases(1). The point at which SCD becomes irreversible is poorly understood. Cases of resolution of clinical manifestations and radiological abnormalities indicate that early treatment can lead to reversal of pathologic changes.
Delay in the diagnosis and/or initiation of therapy may result in permanent irreversible injury to the spinal cord with little or no improvement on treatment. Complete recovery is more likely after early intervention. Paresthesia’s often resolve within weeks, possibly because of a peripheral nerve involvement or reversible impairment of central sensory conduction. Objective signs of spinal cord dysfunction, including weakness, spasticity, and proprioceptive deficits, may require months to improve(12). With early recognition, patients may resume a normal lifestyle with limited impairment of gait. Relapses may occur because of non-compliance with long-term supplementation(12).

A review of reported cases of MRI’s in patients with vitamin B 12 deficiency myelopathy revealed variable MRI abnormalities(3-11). The most common finding was increased T2-weighted signal in the posterior columns of the cervical and/ or thoracic spinal cord. Swelling of the cervical cord on T1-weighted imaging(10,11), enhancement of posterior columns and lateral columns on post-contrast T1-weighted imaging(9), and increased signal on T2-weighted imaging in the posterior columns with variable involvement of the lateral and anterior columns(6,10), have also been described in vitamin B12 deficiency. Atrophy of the thoracic cord has been reported in patients with long-standing symptoms (>20 months)(2).

Complete resolution of MRI abnormalities has been described in a few patients; all had symptoms of less than 12 months duration and follow-up MRI scans were done 18 days to 36 months after initiation of treatment(3,4,7,8,9). Improvement in imaging findings was reported in most of the patients with follow-up scans(5,8,11). In some cases, only partial resolution of clinical symptoms occurred despite complete disappearance of MRI abnormalities, suggesting the presence of irreversible axonal degeneration. An associated peripheral neuropathy could also account for this observation, but in many cases there was no evidence of diffuse peripheral neuropathy on electrodiagnostic studies(4,11).

Clinical manifestations of patients described in the literature with MRI evidence of myelopathy varied in severity, type and distribution. Severity of symptoms and signs ranged from mild, with minimal or no disability to severe disability with loss of ambulation. Symptoms and signs in increasing order of severity included Lhermitte phenomenon, paresthesia’s of the hands and feet, loss of sensation (often with a cervical sensory level), sensory ataxia (with mild to absent vibration and proprioception) that resulted in inability to walk in some patients, and upper motor neuron distribution of weakness (with spastic paresis in 1 patient)(2-11).

Although from our review of the literature it would appear that less severe clinical manifestations and early institution of therapy correlated with more rapid and complete recovery, some patients have severe and progressive symptoms that improve notably despite severe initial disability(2-11,13).

Patients with vitamin B 12 deficiency may have overt neurologic disease in the absence of hematological findings(14). Pernicious anemia caused by defective intrinsic factor production by parietal cells accounts for most cases of vitamin B12 deficiency. A variety of auto-antibodies are detected in patients with pernicious anemia, including antibodies to gastric parietal cells and to the intrinsic factor (14).

Despite being present in 85% of affected patients, parietal cell antibodies are nonspecific, often being detected in other organ-specific autoimmune diseases and in 3% to 10% of healthy persons. The anti-intrinsic factor antibody test is highly specific for pernicious anemia but relatively insensitive, being positive in approximately half of the patients(15).

Elevated serum or urinary levels of MMA and homocysteine are sensitive for the diagnosis of vitamin B12 deficiency and usually precede the development of hematological abnormalities and reductions in the serum vitamin B12 level(16). Measurement of these metabolites is especially useful in those with low-normal serum vitamin B12 levels in the range of 200 to 350 pg/ml (14,16).

Timms et al(5), described a patient who developed unsteady gait and burning dysesthesia of his hands and feet, 2 weeks after receiving nitrous oxide during general anaesthesia. Initial cervical spine MRI was normal. Subsequent MRI, 3 months after disease progression revealed T2-weighted signal abnormality in the posterior columns of the cervical and thoracic cord. Laboratory studies at that time revealed findings consistent with vitamin B 12 deficiency. Thus, symptoms may precede the MRI abnormalities, and a normal MRI early in the disease does not exclude the diagnosis(5).

Differential diagnosis for an abnormal MRI signal in the cervical or cervico-thoracic cord include infection (eg. tubercular, human immunodeficiency virus, herpes zoster) or postinfectious myelitis (eg. viral or mycoplasmia), sarcoidosis, multiple sclerosis, acute transverse myelitis, lymphoma and other neoplasms, paraneoplastic myelopathy, cervical spondylosis with cord compression, toxins (eg. n-hexane, hexanedione, nitrous oxide), radiation myelitis, arterial or venous ischemia, vascular malformations of the dura and spinal cord, and syringomyelia. Many of these diagnoses can be excluded on clinical grounds or with appropriate diagnostic testing.

Although MRI findings in these diseases are nonspecific, the findings of increased T2-signal intensity in the cervical cord, in conjunction with the clinical examination findings and laboratory testing, can help make the diagnosis of vitamin B12 deficiency myelopathy. In addition, MRI can be used in conjunction with clinical and laboratory testing to assess response to treatment.

This case illustrates the importance of considering vitamin B12 deficiency in any patient who presents with myelopathy, even when serum vitamin B 12 levels are in the lower range of normal. The importance of early diagnosis and treatment in the prevention of irreversible neurological injury secondary to SCD is also emphasized. Since most patients with early neurological symptoms secondary to vitamin B12 deficiency present initially to primary care physicians, it is important that all primary caregivers become familiar with this entity, since delay in diagnosis or treatment can result in permanent neurological injury and reduce responsiveness to therapy.

REFERENCES