CASE REPORT

Helicobacter pylori associated vitamin B₁₂ deficiency, pernicious anaemia and subacute combined degeneration of the spinal cord

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SUMMARY

A 23-year-old man presented with weakness in the lower limbs, numbness in hands and feet over past 6 months. Examination revealed a combination of absent ankle jerk, extensor plantar response and reduced sensations in a glove and stocking distribution. MRI of the spinal cord was distinctive of subacute combined degeneration (SACD) of the spinal cord. Serum vitamin B₁₂ was low and anti-intrinsic factor antibodies were positive. A biopsy of the stomach revealed intense inflammatory infiltrates in lamina propria with grade III *Helicobacter pylori* infection. Other work-up for the cause of vitamin B₁₂ deficiency was unremarkable. *H pylori* infection triggers autoantibodies by a mechanism of molecular mimicry. This case report highlights *H pylori* as a causative agent in vitamin B₁₂ deficiency and culminating in SACD of the spinal cord. *H pylori* treatment reverses the underlying pathogenesis and corrects vitamin B₁₂ deficient state in selected individuals.

BACKGROUND

Vitamin B₁₂ deficiency is one of the potentially treatable causes of dementia and demyelination. Early diagnosis is essential as neurological symptoms become irreversible if treatment is delayed. Hence early treatment is essential. Vitamin B₁₂ absorption occurs in the ileum and is mediated by intrinsic factor secreted by gastric parietal cells. *Helicobacter pylori* are ubiquitous organisms invading the gastric mucosa and are a global burden. It causes superficial gastritis, destruction of the gastric parietal cells and atrophic gastritis, resulting in reduced availability of intrinsic factor for vitamin B₁₂ transport.

This causes an interference with vitamin B₁₂ absorption, thus leading to vitamin B₁₂ deficiency and its clinical manifestations. This case report highlights *H pylori* as a causative agent in vitamin B₁₂ deficiency. This is crucial, as anti-*H pylori* treatment can potentially reverse the underlying pathogenesis and could correct vitamin B₁₂ deficiency overtime. This case report provides further evidence to treat *H pylori* infection in selected cases of vitamin B₁₂ deficiency.

CASE PRESENTATION

A previously healthy 23-year-old man presented with abnormal sensations in his hands and feet for the past 6 months, which he described as 'numbness in hands' and 'perceiving ground as a feeling of walking on sand'. These symptoms were associated with difficulty in walking, swaying to either

side and were pronounced on closing eyes. He also had difficulty in gripping his footwear and a difficulty in getting up from the squatting position. These symptoms started insidiously and gradually progressed to an extent of affecting his daily activities. He did not have any bladder disturbance. Dietary assessment was normal. There is no history of alcohol consumption or drug misuse.

On examination moderate pallor, mild icterus and knuckle pigmentation were present and body mass index was 22.5 kg/m². Ophthalmoscopic examination was unremarkable. A neurological examination showed normal higher psychiatric functions, cranial nerves and speech. Motor system examination showed weakness in lower limbs with distal muscle weakness greater than proximal. A combination of absent ankle jerk with an extensor plantar response was noted bilaterally. Vibration, joint position senses were impaired in upper and lower limbs. Pain and temperature sensations were intact. Gait was broad based with positive Romberg's sign, suggesting involvement of posterior columns of the spinal cord.

INVESTIGATIONS

Haemoglobin 6.5 g/dL, mean corpuscular volume 104 fL, mean corpuscular haemoglobin 27.4 pg, mean cell haemoglobin concentration 29.7% and reticulocyte count 1.2%. Corrected reticulocyte count 0.52, white cell count 4000 cells/mm³, platelet count 2.78 lakh/mm³ and erythrocyte sedimentation rate 80 mm/h. The peripheral blood smear was suggestive of a macrocytic blood picture with hypersegmented polymorphonuclear neutrophils. Serum lactate dehydrogenase 3294 U/L. Total bilirubin 1.9 mg/dL, direct bilirubin 0.78 mg/dL, total proteins 6 gm/dL, serum albumin 3.8 gm/dL, albumin/globulin ratio 1.7, alanine aspartase 27 U/L and alanine transaminase 34 U/L. The bone marrow examination revealed a hypercellular marrow with predominantly megaloblastic hyperplasia (figure 1).

Serum iron 104 µg/dL, total iron binding capacity 379 µg/dL and serum ferritin 24 ng/dL. Serum vitamin B₁₂ level was reduced 88 pg/mL (normal range 180–800 pg/mL). Stool examination did not reveal any abnormality. Serum folate and copper levels were normal. HIV ELISA was non-reactive; Thyroid function tests were within normal limits.

In view of the underlying clinical picture MRI of the spinal cord was considered which demonstrated an abnormal hyperintense signal in the posterior aspect of the spinal cord at the cervical and thoracic regions from level C1–T12 (figure 2).

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Figure 1 Bone marrow examination showing evidence of megaloblasts and megaloblastic hyperplasia.

Transverse T2-weighted MRIs obtained at these levels showed an abnormal hyperintensity within the posterior spinal cord corresponding to the dorsal column (figure 3) and a hypointense signal on T1-weighted MR images. This distinctive pattern of abnormal signal intensity is characteristic of subacute combined degeneration (SACD) of the spinal cord.

Antibodies to intrinsic factor were positive. As a workup for pernicious anaemia and vitamin B₁₂ deficiency, gastrointestinal endoscopy and gastric biopsy were performed. Upper gastrointestinal endoscopy showed evidence of corpus and antral gastritis. Biopsy from corpus of stomach revealed marked infiltration of lamina propria with polymorphonuclear neutrophils and mononuclear cells (figure 4). A magnified image of the specimen showed altered gastric gland morphology and evidence rod-shaped organisms within the gland (figure 5). Giemsa staining of the specimen showed marked *H pylori* colonisation (figure 6). Rapid urease test was positive.

Figure 2 Sagittal T2-weighted MRI of the cervical spinal cord demonstrating an abnormal hyperintense signal in the posterior aspect of the spinal cord (indicated by arrows) extending from the level of C1 to the level of C6.

Absorption of vitamin B₁₂ occurs in the terminal ileum, a process mediated by intrinsic factors. Ileal pathologies like ileal Koch's, Crohn's disease, tropical sprue, ileitis and intestinal diverticulosis, intestinal stagnant loop syndrome could result in vitamin B₁₂ deficiency overtime. These were ruled out in our case as colonoscopy and the distal ileal biopsy were normal.

TREATMENT

The patient was treated with anti *H pylori* regimen and 1000 µg of hydroxocobalamin intramuscular injections daily for 2 weeks, followed by weekly maintenance injections. This was supplemented with a 5 mg daily oral folic acid tablets.

OUTCOME AND FOLLOW-UP

Over 4 months the patient showed substantial improvement in gait and neurological signs with a disappearance of icterus and normalisation of haemoglobin and serum bilirubin.

DISCUSSION

Gastric parietal cells secrete intrinsic factor and thereby aid vitamin B₁₂ absorption. Autoimmune destruction of these gastric parietal cells results in pernicious anaemia. Peak onset of age in pernicious anaemia is 60 years. It has higher incidence in women, common in Northern Europe and relatively uncommon among Asians. Juvenile pernicious anaemia is an entity occurring in older children and resembles pernicious anaemia in adults. Most of these individuals have either associated vitiligo or underlying endocrinopathy such as type 1 diabetes mellitus or autoimmune thyroiditis.

H pylori causes antral gastritis, peptic ulcer and gastric atrophy. It can stimulate an autoimmune process against the gastric parietal cells¹ and α , β subunits of the proton pump² by a mechanism of molecular mimicry. *H pylori* triggers antibody production against intrinsic factor in genetically susceptible individuals³ and eventually progresses to vitamin B₁₂ deficiency and pernicious anaemia. There is considerable evidence suggesting a positive correlation between *H pylori* and pernicious anaemia³

Figure 3 Transverse T2-weighted MRI obtained through the cervical spinal cord showing an abnormal bilaterally symmetrical signal hyperintensity within the posterior spinal cord corresponding to the dorsal column (indicated by arrows).

Figure 4 Gastric biopsy specimen with marked infiltration of lamina propria with neutrophils, lymphocytes and plasma cells suggesting active gastritis (indicated by arrows).

and also *H pylori* itself as a causative agent in vitamin B₁₂ deficiency.⁴ Kursad *et al*⁴ successfully treated vitamin B₁₂ deficiency in significant number of individuals with anti-*H pylori* therapy alone, strongly suggesting *H pylori* role in the pathogenesis of vitamin B₁₂ deficiency.

Other causes of vitamin B₁₂ deficiency include malnutrition, gastrointestinal malabsorption and abnormalities affecting the metabolism of vitamin B₁₂. Most common causes include simple atrophic gastritis, chronic alcohol ingestion, gastric bypass surgery, gluten induced enteropathy, jejunal diverticulosis, tropical sprue, intestinal stagnant loop syndrome, Crohn's disease, infestation with fish tapeworm and HIV infection. *H pylori* is a novel causative agent in vitamin B₁₂ deficiency.⁴

Vitamin B₁₂ is an essential component for both neuronal integrity and haematopoiesis. Source for vitamin B₁₂ in humans is mainly food of animal origin like meat, fish and dairy products. Strict vegans have problem of inadequate supply of vitamin B₁₂ unless there is bacterial contamination of the food stuffs.¹ The average daily requirement of vitamin B₁₂ is 1–3 µg. Content of normal dietary cobalamin is 5–30 µg. If supplies are cut-off, body stores of 2–3 mg are sufficient for 3–4 years.⁵

Clinical manifestations of vitamin B₁₂ deficiency include pallor, glossitis, knuckle pigmentation, peripheral neuropathy, demyelination of the dorsal column, pyramidal tracts in the spinal cord and rarely optic atrophy and cerebral symptoms.

Figure 5 Magnified image of the gastric biopsy specimen showing altered gastric gland morphology and evidence of rod-shaped organisms within the gland (indicated by an arrow).

Figure 6 Giemsa staining showing marked *Helicobacter pylori* colonisation of the gastric biopsy specimen.

The earliest manifestation and also the first to disappear with initiation of treatment is peripheral neuropathy, presenting with paraesthesias and absent reflexes.⁵ Eventually ataxia, distal limb weakness and sensory loss may develop. An extensor plantar response is the first clue of underlying spinal cord involvement. Our patient had distal sensory loss, impairment in joint position and vibration sense, ataxia and combination of absent ankle jerk with an upgoing plantar response, all are pathognomic of SCD of the spinal cord.

MRI of the spinal cord in SCD would show an increase in T2-weighted signal intensity (figure 2) as a result of demyelination and gliosis, which were also seen in this patient. These findings in the background of normal vitamin B₁₂ level should arouse a suspicion of copper deficiency.

Haematological manifestations in vitamin B₁₂ deficiency include macrocytic anaemia. Vitamin B₁₂ is closely linked to support DNA synthesis along with folic acid. Lack of either vitamin interferes with DNA synthesis and ineffective erythropoiesis. Ineffective erythropoiesis is associated with intramedullary haemolysis, causing an elevated serum lactate dehydrogenase and indirect bilirubin levels.⁶ Our patient had icterus, high lactate dehydrogenase levels and indirect hyperbilirubinaemia, this may lead to a false diagnosis of autoimmune haemolytic anaemia.

Variations in clinical presentation among individuals infected with *H pylori* may be related to the genotype and phenotype of infecting strain.⁴ Diagnosis of vitamin B₁₂ deficiency in our case was confirmed by peripheral blood smear examination, bone marrow findings and low serum vitamin B₁₂. Our patient had positive antibodies against the intrinsic factor (pernicious anaemia) with a severe *H pylori* infection, thus resulting in impaired vitamin B₁₂ absorption and its deficiency.

Learning points

- ▶ Vitamin B₁₂ deficiency and its neurological manifestations are potentially reversible if prompt replacement therapy is initiated.
- ▶ Ineffective erythropoiesis due to vitamin B₁₂ deficiency results in intramedullary haemolysis and this may lead to a false diagnosis of haemolytic anaemia.
- ▶ Eradication of *Helicobacter pylori* could correct this deficiency overtime in selected individuals.

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