CASE REPORT

Pitfalls in the diagnostic evaluation of subacute combined degeneration

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Accepted 24 April 2015

SUMMARY

We report a case of a 43-year-old man presenting with a 2-week history of painless ascending sensory disturbances, suspected to be suffering from acute inflammatory polyneuropathy. On clinical examination, deep tendon reflexes were preserved and muscle strength was 5/5 everywhere. Gait was ataxic with positive Romberg test. Lumbar puncture was normal and electroneurography demonstrated demyelination. With spinal cord involvement centred on the posterior tracts on MRI, differential diagnosis focused on cobalamin deficiency. Initial laboratory work up showed nearly normal holotranscobalamin (43 pmol/L, normal >50) suggesting no vitamin B₁₂ deficiency. Surprisingly, further testing including methylmalonic acid (3732 nmol/L, normal <271) and homocysteine (48.5 µmol/L, normal <10) showed an impairment of vitamin B₁₂-dependent metabolism leading to the diagnosis of subacute combined degeneration. Only after repeated history taking did the patient remember having taken tablets containing cobalamin for 3 days before hospitalisation. In case of B₁₂ deficiency, holotranscobalamin can rapidly normalise during supplementation, whereas methylmalonic acid and homocysteine might help to detect B₁₂ deficiency in patients who recently started supplementation.

BACKGROUND

Acute ascending sensory deficits constitute a neurological emergency and require a thorough clinical evaluation and diagnostic work up. The differential diagnosis of this clinical picture is broad, and some underlying disorders require close monitoring and immediate treatment. This is especially true for acute inflammatory demyelinating polyneuropathy, as it may rapidly progress and lead to respiratory failure, and severe autonomic disturbances.¹ This disorder needs to be distinguished from other potential causes of ascending sensory deficits, including toxic and malnutrition-related neuropathies, and transverse myelopathy. Polyneuropathy due to cobalamin (vitamin B₁₂) deficiency, which can be accompanied by spinal cord and brain demyelination, is treatable by vitamin B₁₂ substitution and is potentially reversible when treated early.²

In the present case, we lead through the diagnostic work up for acute ascending sensory deficits, and discuss potential pitfalls in the laboratory diagnostics of vitamin B₁₂ deficiency.

CASE PRESENTATION

A 43-year-old man presented with a 2-week history of painless ascending sensory disturbances affecting

his legs and arms. The patient had no cognitive symptoms or visual disturbances. On initial history taking, no toxic exposure or drug intake was reported (especially no use of acid-suppressing medication). The patient stated frequent consumption of meat products. He had no history of gastric surgery. Family history for neurological disorders was negative. On clinical examination, impaired touch and pain sensation (reaching up to the elbows and knees) was reported, and position sense and vibration sense were strongly reduced at the feet. There was also impaired sensation for touch below dermatome Th7 bilaterally. Deep tendon reflexes (including the Achilles tendon reflex) were weak but symmetric. Babinski sign was negative and muscle tone was normal. Muscle strength was 5/5 everywhere. A Romberg test showed increased sway, and gait was broad-based/ataxic. Cranial nerves were normal; no cerebellar deficits were noted. Later, during hospitalisation of the patient, we learned he had undergone intramuscular B₁₂-substitution 2 years before hospitalisation due to vitamin B₁₂ deficiency, without clinical symptoms detected in a routine screening as part of a health check-up (serum-B₁₂ level May 2012: 120 pmol/L, normal: >180).

INVESTIGATIONS

Lumbar puncture was normal (including normal cell count, glucose, lactate and negative syphilis serology) except for slightly elevated total protein (0.56 g/L, normal <0.5). Electroneurography showed increased distal motor latencies and reduced nerve conduction velocities, and slightly increased F-wave latencies at the legs (table 1), while electromyography was normal. Noteworthy, except for moderately reduced amplitude of the compound muscle action potential of the median nerve, no axonal changes were seen. These findings were consistent with sensorimotor demyelinating polyneuropathy of the legs.

With normal median and ulnar nerve measurements, the upper extremity sensory deficits remained unexplained. We therefore obtained spinal cord imaging, demonstrating non-enhancing T2-hyperintensities (figure 1A, B) on the posterior columns (C2–C5), which is characteristic of subacute combined degeneration. Cerebral MRI showed no abnormalities and neuropsychological testing demonstrated no cognitive deficits. Differential diagnosis now focused on cobalamin deficiency. However, initial laboratory work up showed almost normal holotranscobalamin (43 pmol/L, normal >50) levels not typical for clinically relevant vitamin B₁₂ deficiency. Surprisingly, further laboratory testing

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To cite: Ulrich A, Müller D, Linnebank M, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-208622

Table 1 ENG findings (6 days after symptom onset)

Nerve	Motor nerve conduction velocity (m/s)	Distal motor latency (ms)	Temporal dispersion	F latency (ms)	Sensory nerve conduction velocity (m/s)	cMAP (mV)/sNAP (μ V)
L median N	Distal 50 (n>48) Proximal 62 (n>48)	4.1 (n<4.0)	None	29.4 (n<31)	Distal 52 (n>49) Proximal 51 (n>52)	3.0/20.6
R median N	Distal 46 (n>48) Proximal 65 (n>48)	4.2 (n<4.0)	None	NA	Distal 56 (n>49) Proximal 50 (n>52)	7.7/23.0
L ulnar N	NA	3.0 (n<3.2)	None	29.0 (n<32)	Distal 50 (n>41) Proximal NA	8.7/22.9
R ulnar N	Distal 53 (n>44) Proximal 69 (n>45)	2.5 (n<3.2)	None	29.9 (n<32)	Distal 48 (n>41) Proximal 61 (n>46)	7.9/19.6
L peroneal N	Distal 38 (n>42) Proximal 59 (n>41)	5.8 (n<4.9)	None	59.9 (n<56)	NA	5.6 (n>2.6 mV)/NA
R peroneal N	Distal 26 (n>42) Proximal 46 (n>41)	5.2 (n<4.9)	None	66.7 (n<56)	NA	4.1 (n>2.6 mV)/NA
L tibial N	29 (n>40)	4.8 (n<5.5)	None	65.5 (n<58)	NA	12.6 (n>5.8 mV)/NA
R tibial N	19 (n>40)	5.1 (n<5.5)	None	71.1 (n<58)	NA	8.7 (n>5.8 mV)/NA
L sural N (orthodrome, needle ENG)	NA	NA	NA	NA	38 (n>48)	NA/12.3
R sural N (orthodrome, needle ENG)	NA	NA	NA	NA	40 (n>48)	NA/19.5

cMAP, compound muscle action potential; ENG, Electroneurographic; NA, not available; sNAP, sensory nerve action potential.

demonstrated strongly increased methylmalonic acid (MMA; 3732 nmol/L, normal<271) and plasma total homocysteine (48.5 μ mol/L, normal<10) levels, showing an impairment of vitamin B₁₂-dependent metabolism. Folate, zinc and copper levels were normal. These findings supported the diagnosis of cobalamin-associated subacute combined degeneration and peripheral polyneuropathy. Only after repeated history taking did the patient remember having taken cobalamin-containing tablets for 3 days before hospitalisation. We additionally analysed total cobalamin (133 ng/L, normal range 180–914) from the initial blood sample, which also showed only a moderately reduced level.

During the course of hospitalisation, the patient developed shortness of breath and chest pain. With underlying pulmonary embolism confirmed by chest CT, he was started on rivaroxaban.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis was driven by the initial presentation of ascending sensory disturbances and demyelinating neuropathy, while deep tendon reflexes were preserved and lumbar puncture was normal except for slightly elevated total protein levels. This combination made acute inflammatory demyelinating polyneuropathy unlikely and re-enforced a diagnostic work up. In view of myelopathy, ischaemia, metabolic-toxic causes and malnutrition/malabsorption were considered. With very high MMA and homocysteine levels, cobalamin deficiency became the most likely cause despite almost normal holotranscobalamin levels. Low iron serum levels supported the hypothesis of malnutrition/malabsorption. The supplementation of cobalamin a few days before hospitalisation explains why holotranscobalamin and total cobalamin levels were only slightly decreased on admission.

TREATMENT

Treatment with subcutaneous cyanocobalamin (1000 μ g) given every other day was initiated (intramuscular application was contraindicated due to pulmonary embolism treated with therapeutic heparin). Folic acid was supplemented as well.

OUTCOME AND FOLLOW-UP

Under treatment with cyanocobalamin, MMA and homocysteine levels continuously decreased, and were normal again after 1 month (figure 2). Clinically, the patient reported significant improvement of sensory disturbances and gait ataxia. Follow-up MRI after 2 months showed significant regression of the dorsal column hyperintensities (figure 1C, D). Upper gastrointestinal endoscopy revealed several duodenal ulcers, while no *Helicobacter pylori* was found on biopsy, and anti-intrinsic factor and antiparietal cell antibodies were negative. To what extent these duodenal ulcers reduced cobalamin absorption remains unclear. The patient is now under oral cobalamin and folic acid supplementation and received proton pump inhibition

Figure 1 MRI of the spinal cord before (A and B) and 2 months after (C and D) initiating cobalamin supplementation. T2-weighted axial (A and C) and sagittal (B and D) cuts are presented, demonstrating marked T2-hyperintensity along the posterior columns of the cervical spinal cord (as indicated by the black and white arrows) in axial and sagittal sections, referred to as subacute combined degeneration. On follow-up, these changes were markedly reduced (C) or even disappeared (D).

Figure 2 Methylmalonic acid (MMA; black circles) and holotranscobalamin (black squares) levels before and during the first month of supplementation with cyanocobalamin relative to cut-off values for MMA (normal range <271 nmol/L) and cyanocobalamin (normal range >50 pmol/L).

treatment for 6 weeks. On follow-up examination 4 months after symptom-onset, his sensory disturbances were greatly reduced with slight residual deficits in touch and pain sensation at the feet, while vibration and position sense had normalised.

DISCUSSION

This case highlights the possible diagnostic pitfalls in patients presenting with subacute ascending sensory disturbances and demyelinating neuropathy. First, it shows that history taking and laboratory work up with holotranscobalamin (or total cobalamin) alone can be misleading. Second, it underlines the importance of detailed and repeated drug history taking, including asking about recent use of supplementary substances, especially if diagnostic tests are suggestive of a malnutrition-related disorder. In this case, holotranscobalamin levels were probably almost back to normal due to cobalamin supplementation initiated a few days before hospitalisation. However, strongly elevated blood levels of MMA and homocysteine proved the ongoing metabolic deficiency, and the decrease of MMA and homocysteine levels under appropriate supplementation with cyanocobalamin further supported this diagnosis (see ref. 3 for a detailed review). Thus, this case emphasises the assessment of metabolites of cobalamin, including MMA and homocysteine, to increase sensitivity for cobalamin deficiency, especially since total cobalamin and holotranscobalamin levels may still be normal or borderline normal while increased metabolites (MMA, homocysteine) already indicate cobalamin deficiency.^{4 5} With only 0.1% of a middle-aged control group having MMA concentrations above 750 nmol/L,⁶ a positive MMA just by chance seemed very unlikely in our patient. Especially as it was accompanied by severe homocysteine elevation in the presence of normal folate levels, also strongly suggesting vitamin B₁₂ deficiency. Upper gastrointestinal endoscopy is part of the standard diagnostic work up in patients with cobalamin deficiency to identify those cases with autoimmune or *H. pylori*-associated gastritis and to distinguish them from those with malnutrition or other causes of gastrointestinal malabsorption, such as gluten-induced enteropathy, gastric bypass surgery or chronic alcohol ingestion. In our patient, however, the isolated duodenal ulcers with negative anti-intrinsic factor antibodies may not be sufficient to link cobalamin deficiency with gastrointestinal malabsorption. Also, long-term use of acid-suppressing medication

(proton pump inhibitors and histamine 2 receptor antagonists) needs to be considered as an underlying cause of vitamin B₁₂ malabsorption. Gastric acid is essential to cleave vitamins from nutritional proteins; and intrinsic factor, which is required for absorption of vitamin B₁₂ in the ileum, is produced by the same cells that produce gastric acid.⁷

With regard to the differential diagnosis, a distinction from acute inflammatory demyelinating polyneuropathy is essential—especially due the very recent symptom onset (about 2 weeks ago). However, lack of cytoalbuminological dissociation and preserved deep tendon reflexes both speak against an inflammatory cause of the polyneuropathy. While the majority of cobalamin deficiency-associated polyneuropathies are axonal or combined axonal-demyelinating, about 10–25% are purely demyelinating.^{8 9} This may make distinction from an inflammatory cause of the neuropathy more difficult, especially if symptom onset is very recent. Importantly, possible spinal cord involvement has to be addressed if clinical findings are not satisfactorily explained by peripheral neuropathy. T2-hyperintensive myelopathy on MRI, being most prominent at the posterior columns accompanied by clinical signs of damage to the posterior columns (impaired position-sense, vibration-sense, decreased touch), is characteristic of subacute combined degeneration^{10 11} and must initiate an intense search for cobalamin deficiency, while the clinician must also be aware of the differential diagnosis including syphilitic myelopathy (tabes dorsalis) and copper deficiency (if cobalamin metabolites are normal).¹² To the best of our knowledge, no similar cases with almost normal holotranscobalamin levels but severe MMA increases due to short-term supplementation have been published in the literature.

The pulmonary embolism found in our patient is possibly linked to the cobalamin deficiency, especially since high homocysteine levels are associated with an increased risk for venous thrombosis.¹³

Learning points

- ▶ While acute/subacute ascending sensory deficits must initiate an urgent diagnostic work up for acute inflammatory demyelinating polyneuropathy, normal protein levels and cell count on spinal tap, preserved deep tendon reflexes and electroneurographic measurements falling short of explaining all sensory deficits sufficiently make this diagnosis unlikely, shifting the focus to metabolic-toxic and malnutrition-related neuropathies that can have combined spinal and peripheral nerve involvement.
- ▶ Laboratory work up for the evaluation of possible cobalamin deficiency should include holotranscobalamin, homocysteine and methylmalonic acid (MMA), since a single parameter—holotranscobalamin in this case—may be almost normal despite severe deficiency as indicated by very high MMA serum and homocysteine levels.
- ▶ Drug history, especially long-term use of acid-suppressing medication, is essential for evaluation of vitamin B₁₂ deficiency. We strongly recommend routinely evaluating for the intake of supplementary substances, including vitamins.
- ▶ Prompt cobalamin supplementation and regular monitoring of cobalamin metabolites under supplementation are essential, as cobalamin-induced (neurological) deficits are potentially reversible if treated early.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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