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Clinical case

Reversible dementia and seizures due to metformin-induced vitamin B12 deficiency

Démence réversible et des crises épileptiques secondaires à un déficit en vitamine B12 induit par la metformine

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1. Introduction

Vitamin B12 is an essential cofactor for multiple enzymatic reactions involved in erythropoiesis, myelin sheath synthesis, signal neurotransmission, neuronal integrity and other crucial processes [1]. Besides classical hematological consequences, its deficiency can have serious repercussions on both the peripheral and central nervous system. The latter manifests clinically in various neuropsychiatric symptoms, such as delirium, memory impairment, subacute combined degeneration and rarely optic neuritis. They rarely represent the initial complaint or the sole manifestation of vitamin B12 deficiency, leading to a possible diagnostic delay, serious complications and sequelae. Therefore, treatment should be instaured as early as possible when the diagnosis is suspected to ensure the reversibility of the neurological damage, along with searching for and treating its potential cause.

2. Case report

A 64-year-old woman with a history of hypertension and type 2 diabetes mellitus under metformin for 30 years at a daily dose of 1700 mg, and insulin for 5 years, was admitted after developing frontal headaches with progressively worsening gait disturbances over 2 months. Two weeks prior to her consultation, the family noticed a sudden onset of visual hallucinations, memory impairment with an important impact on her daily activities, intermittent resting tremor, urinary incontinence and stereotyped episodes of lapses of consciousness during which the patient stared into space for a few seconds. The neuropsychological evaluation revealed a frontal syndrome, a visuospatial skills impairment, an aphaso-apraxo-agnosic syndrome and attention and concentration deficits (Table 1) (Fig. 1a). Bilateral grasping reflex and intermittent resting tremor were also noted.

Slow waves in the fronto-parietal region were detected on electroencephalogram (Fig. 2). Referring to the ILAE 2017 classification, our patient presented non-motor epileptic seizures with

Table 1
Initial neuropsychological evaluation showing memory, attention and concentration impairment, an aphaso-apraxo-agnosic syndrome and their improvement after treatment.

	Before treatment	After treatment
Mini Mental Status Examination	3/30	21/30
Attention–concentration	Severe deficit	Improvement
Verbal memory (5 words test)	Altered free recall	Improved free recall with cues
Direct digit span	Not assessable	4/7
Backward digit span	Not assessable	2/7
Clock drawing test	0/7	5/7
Language		
Denomination (DO30)	0/30	28/30
Sementic/phonemic fluence	Severe alteration	Improvement

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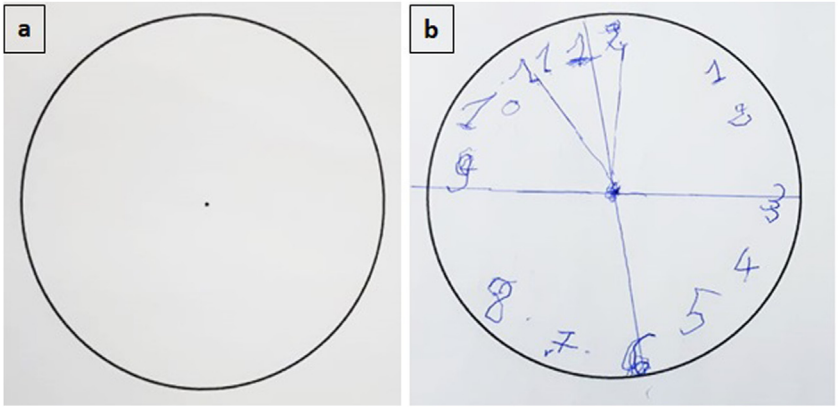

Fig. 1. Clock drawing test showing visuospatial skills impairment and apraxia (a) and their improvement after treatment (b).

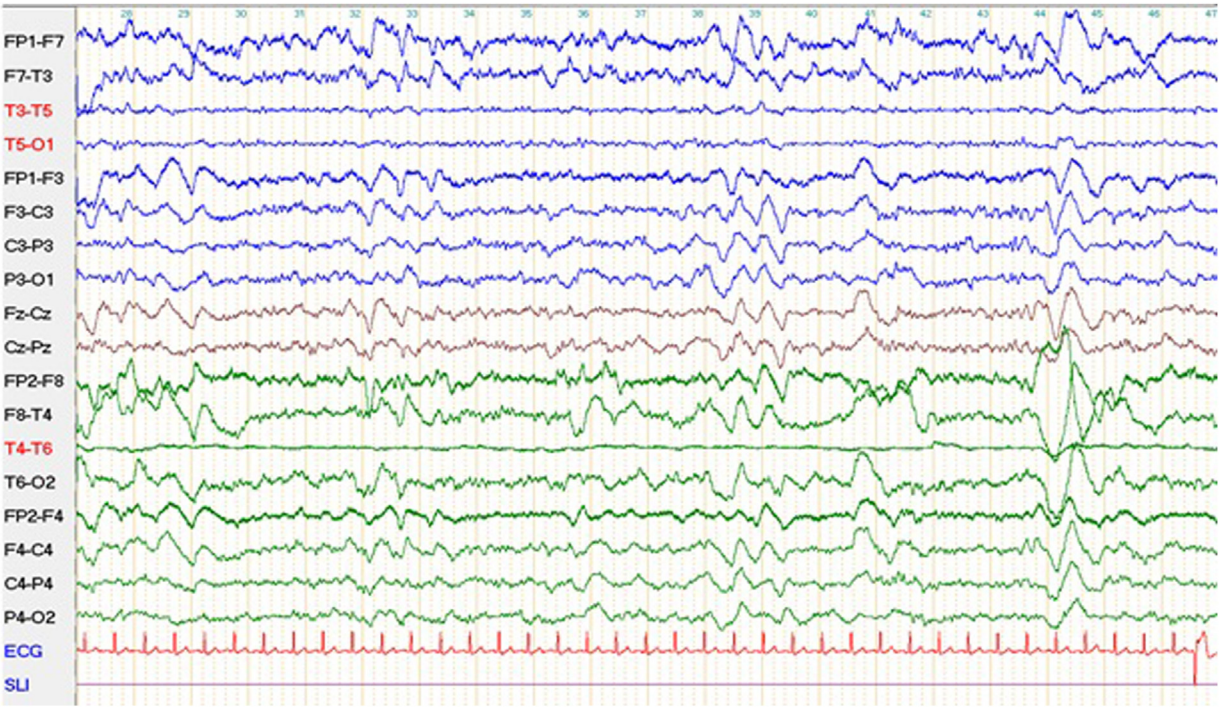

Fig. 2. Electroencephalogram showing slow waves in the fronto-parietal region.

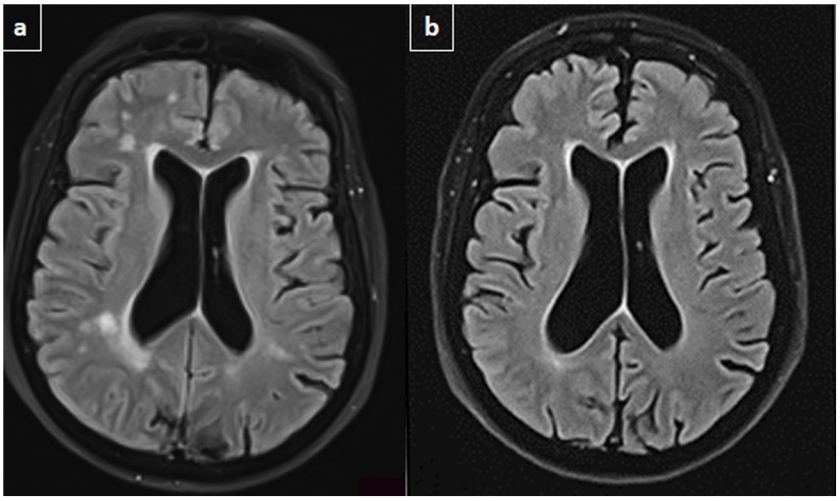

Fig. 3. Axial FLAIR-T2 images showing initial white matter hyperintensities (a) and their disappearance after treatment (b).

unknown onset [2]. Cerebral magnetic resonance imaging revealed white matter hyperintensities (WMH) on T2 and T2 FLAIR weighted images (Fig. 3a). Blood count showed microcytic anemia. Cerebrospinal fluid analysis and iron level were normal. Serum vitamin B12 level was low at 50 pg/mL (normal range between 200 and 700 pg/mL). Anti-intrinsic factor and parietal cell antibodies were negative, and the upper gastrointestinal endoscopy was normal. The diagnosis of metformin-induced vitamin B12 deficiency was made after excluding other causes of dementia and vitamin B12 deficiency, such as the use of other medications (proton-pump inhibitors, H2-receptor antagonists, etc.), vegetarian diet, exocrine pancreatic insufficiency, tumor, infection and inflammatory bowel disease.

Therefore, metformin was switched to a GLP-1 agonist and vitamin B12 injections were prescribed at the dose of 1000 μg twice daily for 2 months, then 1000 μg daily for two additional months with cessation of seizures and drastic cognitive and motor improvement (Table 1) (Fig. 1b). A cerebral MRI performed 4 months after treatment showed the disappearance of the WMH (Fig. 3b).

3. Discussion

Here, we reported a rare case of acute-onset reversible dementia with seizures due to metformin-induced vitamin B12 deficiency. Vitamin B12 is a cofactor in essential biochemical processes. Among the mechanisms explaining the neurological symptoms, alteration in one-carbon metabolism, genetic vulnerability, and alteration in folate metabolism are cited [3]. In fact, vitamin B12 deficiency impairs myelin sheath synthesis, signal neurotransmission and neuronal integrity, resulting in neurocognitive symptoms which have rarely been reported as the revealing symptom as in our case [1,4]. Another particularity of the clinical presentation for our patient in comparison to the literature is the acute onset, which is usually insidious followed by progressive worsening. Moreover, our patient presented a severe attention and concentration deficit, which is an infrequent feature and a part of frontotemporal dementia-like manifestations [5]. Epileptic seizures in vitamin B12 deficiency are also rare. As far as we know, our case represents the first report of non-motor seizures due to vitamin B12 deficiency. The mechanism involved in epileptogenesis is unclear and seizures are usually reversible after vitamin replacement. On MRI, different aspects can be found ranging from a normal MRI to cerebral atrophy, lacunar infarcts and WMH [5,6]. Although the evolution of brain signal abnormalities after treatment was not described in the literature, a particularity of spinal cord signal abnormalities is their possible reversibility [7,8]. This was also confirmed in our case for the WMH. As for the etiology, a gastrointestinal cancer and an autoimmune disease need to be considered as well as an iatrogenic origin, especially in elderly who have multiple comorbidities and prescribed therapies.

In fact, metformin is the most frequently prescribed medication in type 2 diabetes and can lead to anemia and vitamin B12 deficiency in long-term use. Previous studies have shown that the prevalence of metformin-induced vitamin B12 deficiency varied greatly and ranged between 5.8% and 52% [9]. Although the exact cut-off varies between 1000 mg [10] and 1500 mg daily [11] between the different reports, metformin dosage seems to be the major and the most strongly associated factor with vitamin B12 deficiency [11–13]. However, results from different studies are still controversial regarding its duration use, between those who did not find any affect of duration on the occurrence of vitamin B12 deficiency [11], and those who found a significant association between the two after a 4-year metformin use period [14].

With the lack of consensus, some authors suggest measuring homocysteine or methylmalonic acid as well to help analyze the significance of vitamin B12 deficiency, compared to assessing the clinical presentation based on serum vitamin B12 measurement alone. Although few studies reported no change in homocysteine concentrations [15], the majority found an associated increased homocysteine level, which suggests true tissue deficiency [16].

The mechanism is still quite intriguing. Multiple hypotheses were suggested to explain its interference with vitamin B12 absorption in the ileum. First, it was stated that it alters small bowl motility, which affects bacterial flora and glucose, as well as vitamin B12 absorption. Other studies reported that its use decreases total cobalamin, total haptocorrin and haptocorrin-bound cobalamin plasma levels [15]. Metformin can also cause the deficiency by altering bile acid metabolism and reabsorption, resulting in impaired enterohepatic circulation of vitamin B12 and reduced intrinsic factor secretion by gastric parietal cells [17]. Finally, the major mechanism is thought to be through its calcium-antagonist action on the calcium-dependent membrane. As a matter of fact, calcium is necessary for the binding of the complex intrinsic factor-vitamin B12 to the receptor on the membrane, and therefore metformin alters the complex's absorption [17,18].

After diagnosing vitamin B12 deficiency, starting treatment is crucial. Although no protocol has been established, vitamin B12 injections need to be administered with a regimen varying from 1000 μg per day for 6 weeks to 3 months. Improvement depends on the severity of the initial presentation, the rapidity of diagnosis and appropriate treatment. As metformin seems to interfere with vitamin B12 absorption, administering it through intramuscular or sublingual routes may theoretically be superior to oral supplementation. Yet, high-dose oral supplementation may be as effective [17]. Moreover, increasing oral calcium intake has shown to reverse vitamin B12 malabsorption caused by metformin [18].

In regard to prevention, the 2021 American Diabetes Association Standards of Medical Care in Diabetes recommends a periodic assessment of vitamin B12 levels in metformin-treated patients, particularly in case of peripheral neuropathy or anemia (level B) [19]. Other reports suggest vitamin B12 screening even in asymptomatic patients in the presence of one or more risk factors or particular conditions [17]. According to the British Society for Haematology guidelines for diagnosis and treatment of vitamin B12 deficiency, no recommendations can be currently given on prophylactic administration with oral vitamin B12 in patients using metformin [20].

This case illustrates that psychiatric symptoms, reversible dementia, seizures can be dissociated from the classic textbook hematological and neurological signs associated with vitamin B12 deficiency. Searching for and treating the cause is important to ensure good prognosis and recovery.

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Disclosure of interest

The authors declare that they have no competing interest.

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