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Case report

Apathetic encephalopathy in thyreotoxicosis: an unsual cause of Wernicke Encephalopathy and osmotic demyelinating syndrome

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Abstract

Non-alcoholic Wernicke Encephalopathy (WE) is an overlooked complication of malnourishment in all its forms including undernutrition, inadequate vitamine intake and endocrinological diseases. Both delay in treatment and overtreatment can lead to severe neurological life-long consequences. Inadequate management in patients with chronic malnutrition may cause abrupt osmolytes unbalance and subsequent osmotic demyelination syndromes. We describe a 65-year old man with apathetic encephalopathy caused by thyreotoxicosis and associated with malnutrition and severe thiamine depletion.

Keywords: Apathetic Encephalopathy, Thyrotoxicosis Wernicke encephalopathy, osmotic demyelination syndrome

Background and Aim of the Work

Wernicke Encephalopathy (WE) is a severe but reversible form of subacute encephalopathy due to thiamine deficiency described by Campbell and Russell in 1941 and historically associated with alcohol-abuse. The pathognomonic triad of WE (ophthalmoplegia, ataxia and altered consciousness) is recognizable in around 1/3 of cases, mostly among alcoholic patients (1). However, non-alcoholic ethiologies of WE, including malnourishment and endocrinological diseases, exist and are still dramatically under-diagnosed. Diagnosis of WE is commonly achieved post-mortem, with less than 20% of cases recognized during lifetime (2). The missed acknowledgement of WE in chronically malnourished patients may end up with inadequate nutrition that can degenerate in life-threatening iatrogenic complications such as osmotic demyelination syndrome (ODS), including both central pontine and extrapontine myelinolisis (3). Apathetic encephalopathy (AE) represents an unusual manifestation of hyperthyroidism, historically named '*de-activated hyperthyroidism*', in contrast with its more typical '*activated*' counterpart (4), generally involving individuals from their middle age. The core clinical features of AE include weakness, tiredness, apathy and depression (5). We report the case of a non-alcoholic patient who developed AE with anorexia during autoimmune thyreotoxicosis complicated by WE and iatrogenic ODS.

Clinical Vignette

A 65 year-old Italian man, brilliant and highly performing in everyday social and working life, without prior history of alcohol abuse, developed subacute AE featured by behavioral changes including apathy,

forgetfulness, abulia and mild cognitive impairment leading to serious malnutrition and progressive weight loss. In the range of a few weeks he underwent remarkable changes in his daily life habits, interrupting hobbies and interests, being apparently aware of his mood alterations.

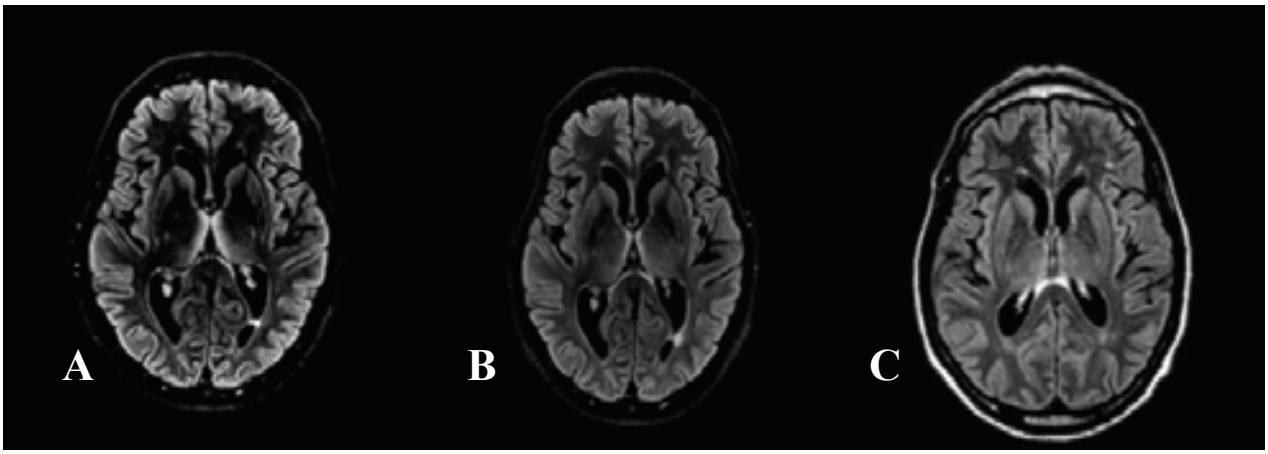
At admission to our hospital (Parma, Northern Italy), he was apiretic but markedly sarcopenic, his routine blood examination showed normal values (except for hypoalbuminemia and mild sideropenic anemia), he had low blood pressure, sinusal tachycardia, difficulty swallowing and was dehydrated. He had lost approximately 20 kg in the previous two months and appeared considerably older than his stated age. He immediately received support with total parenteral nutrition. A complete diagnostic work-up excluded organic causes of dysphagia and occult neoplasm. A 3T brain MRI showed bilateral and symmetrical FLAIR and T2-hyperintense lesions diffused along periaqueductal area, tectal plate, thalami, mamillary bodies, highly suggestive of WE. Thyroid function tests showed suppressed TSH level, high levels of thyroid hormones (FT3= 12.90 pg/mL, FT4= 5.09 ng/dL), high positive values of anti-thyroid receptor antibodies (antiTSH-R=35.55 uU/L). Thyroid ultrasonography pointed out a solitary thyroid nodule and thyroiditis. Parenteral vitamin supplementation, high doses of steroid therapy and metilmazole determined rapid neurological improvement and normalization of TSH values. Brain MRI follow-up, performed one month later, showed a partial regression of the T2-hyperintense lesions together with the presence of a high-T2-signal in the pons, suggesting a central pontine myelinolisis. The patient still suffered from dysphagia, asthenia and developed mild cerebellar ataxia, while his behavioral changes and cognitive disabilities were slightly improved. Serum sodium, potassium and phosphorus levels were never altered during the entire hospitalization period. In the following months the patient received supervised parenteral nutrition enriched with multivitamins and minerals.

The last brain MRI follow-up, carried out 4 months after admission, demonstrated almost complete resolution of the signal intensity changes in the brainstem (Fig. 1). The patient underwent intensive neurological rehabilitation for several months and, at the last follow-up, around 24 months after the discharge, he entirely recovered from his psychiatric and focal neurological symptoms even if he was still dependent in the activities of daily living as a result of being bedridden for long time and persistence of cerebellar ataxia.

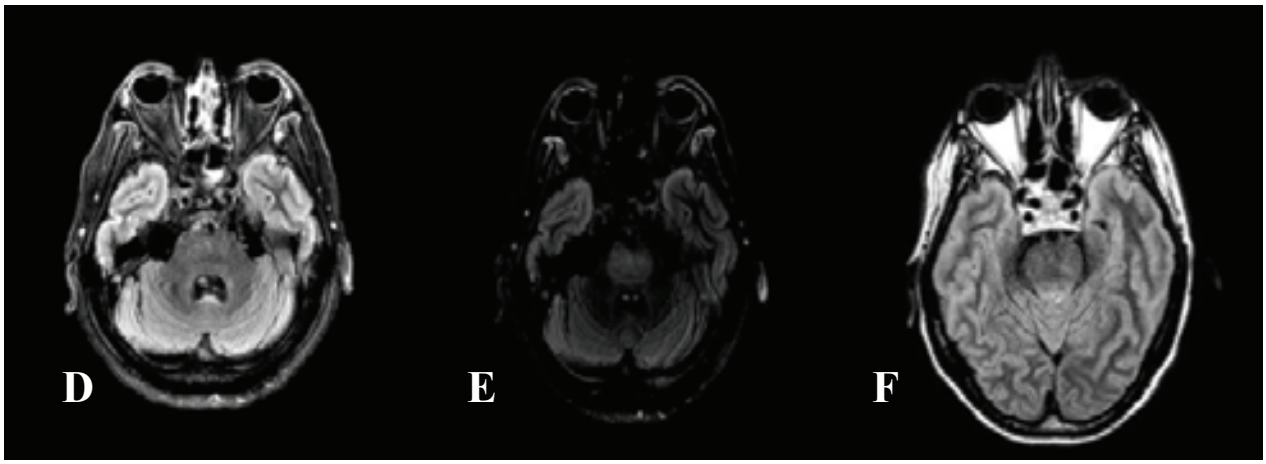
Conclusion

Our case is a classical example of 'de-activated hyperthyroidism' (alias 'apathetic encephalopathy') in a middle-age man with autoimmune thyreotoxicosis. Compared to the better-known 'activated hyperthyroidism', this frequently overlooked variant is more common among the elderly and the core clinical features are low basal metabolism rate, dry skin, apathy, abulia, weakness, depression and anorexia (4). Hence misdiagnosis with hypothyroidism or depression is common. In these patients weight loss is usually progressive and severe starvation and, if untreated, may lead to vitamine depletion (5).

Although alcohol abuse represents the most common risk factor, in WE patients it is of paramount importance to consider also non-alcoholic ethiologies including malnutrition, psychiatric disorders, anorexia nervosa, terminal malignancies, systemic infectious disease, hyperemesis gravidarium, bariatric surgery, gastrointestinal cancer, allogenic stem cell transplantation, haemodialysis, pancreatitis, starvation and thyrotoxicosis (1, 6). The typical clinical features of WE (ophthalmoplegia, ataxia and altered consciousness) are not always present and sometimes the disease presentation may be misleading, making the diagnosis significantly challenging for the clinician (1, 7). A broad range of brain MRI findings are potentially associated with WE and T2-w, FLAIR and DWI are considered the most useful MRI sequences for diagnosis (8). Brain MRI typically depicts bilateral symmetrical reversible cytotoxic edema with hyperintense T2 lesions around the aqueduct and third ventricle as well as within the medial thalamus, tectal plate and mammillary bodies (9). In these areas, the maintenance of cellular osmotic gradients is considered to be strictly related to thiamine levels (10). In pediatric patients, putamen involvement is a characteristic feature, probably due to the thiamine-dependent metabolism in this area in children (11).



3T Flair MRI: Evolution of bilateral talamus hyperintensity at time point 0 (A), one month later (B) and four months later (C)



3T Flair MRI: Evolution of pons hyperintensity at time point 0 (D), one month later (E) and four months later (F)

Atypical findings include signal hyperintensity in the dorsal medulla, pons, cerebellar nuclei, red nuclei, midbrain, cranial nerve nuclei, corpus callosum, fornices, caudate nucleus and fronto-parietal cortex, overall more frequent in non alcoholic patients (1). Contrast-enhancement can be seen in almost 50% cases and mamillary bodies enhancement are sometimes the only radiological sign in chronic alcoholics (12).

Untreated AE can end up with severe behavioral changes together with anorexia and malnourishment (13). Furthermore starvation in these patients may determine thiamine deficiency and consequent neurological damage. If under-rated, WE can evolve to Wernicke-Korsakoff syndrome with irreversible damage in the thalamus and mamillary body, yielding severe antero-retrograde amnesia and confabulation (14). Finally, incorrect management of parenteral nutrition could induce abrupt osmolytes changing in the brain and subsequent osmotic demyelination syndrome, comprehensive of central pontine myelinolisis or extrapontine myelinolisis, the latter frequently involving thalami, basal ganglia, cerebellum, lateral geniculate bodies and cerebral cortex (15).

Even if the first description dates back to 1931, 'de-activated thyretoxycosis' is still widely under-recognized. This insidious encephalopathy could end up with progressive malnutrition and vitamin depletion, worsened by irreversible neurological consequences. Clinicians must be aware of the diagnosis and should always consider both AE and WE in elderly patient with subtle or subacute encephalopathy and physical signs of malnourishment. It is mandatory to be extremely

careful in the management of parenteral nutrition to avoid iatrogenic complication such as ODS.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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