Case report

Akathisia superimposed to Hashimoto's encephalopathy in an old lady

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Abstract. *Background and aim:* Hashimoto's encephalopathy (HE) is a rare clinical entity that is associated with encephalopathy with alteration of consciousness, presence of high levels of antithyroid antibodies, and exclusion of other suspected etiologies. *Methods:* We describe a 60-year old lady who had been followed up for about 5 years for possible Alzheimer's disease plus Parkinson's disease and presented with akathisia overlapping a progressive encephalopathy compatible with the diagnosis of HE. *Results:* Initial steroid therapy had shown no clinical benefit, whereas a mild to moderate improvement in clinical condition was observed after a 5-day course of plasmapheresis. *Conclusions*: Given this case, it is clear that this challenging yet treatable clinical syndrome should be considered even in older patients. Furthermore, side effects such as akathisia should also be considered when starting antipsychotic treatment, particularly in patients with an unclear diagnosis. The patient is noteworthy due to the extremely rare occurrence of HE presenting with akathisia, especially in the elderly. (www.actabiomedica.it)

Key words: antithyroid antibody, Hashimoto's encephalopathy, elderly, akathisia, plasma exchange

Introduction

Hashimoto's encephalopathy (HE) is a rare heterogeneous clinical syndrome that is generally seen in young women and is known to have distinctive features of encephalopathy and high antithyroid antibody titers and respond to corticosteroid therapy (1). It may have a relapsing-remitting or progressive course, with rich symptomatology, including encephalopathy, seizures, neuropsychiatric disturbances, stroke-like events, myoclonus and tremor. Therefore, diagnosis requires a series of studies to exclude other suspected etiologies (2). On the other hand, HE is a rarer condition in older adults. Here, we report an old woman, who had been followed up for about 5 years for possible Alzheimer's disease (AD) plus Parkinson's disease (PD), presented with akathisia superimposed to HE.

Case report

A 60-year-old female patient was admitted to our clinic with a 2-month history of gait and balance problems, frequent falls (4-7 per day), posture change and a 1-month restlessness, agitation, insomnia, crying spells, slurred speech, hallucinations and a marked decrease in all activities of daily living.

Her husband said that she, applying to the emergency room at the beginning of her complaints, was thought to have had an ischemic brain attack. In addition to her daily sertraline and donepezil treatments, acetylsalicylic acid was prescribed, which was ceased by her husband due to inefficiency after 7 days. Later, levodopa, carbidopa entacapone combination and domperidone were started because of PD, but the patient could not use anti-PD drugs effectively due to significant

deterioration within two weeks. Then, olanzapine 10 mg/day and mirtazapine 15 mg/day were prescribed for 15 days before she was admitted to our Unit. In her past medical history, she was diagnosed with AD and PD 5 and 4 years ago, respectively; however, she received anti-PD drugs irregularly. In her family history, we observed that her mother had dementia. In the first physical examination, blood pressure was 107/73 mmHg (lying down) and 118/72 mmHg (standing), pulse was 72 beats/minute, and meaningful speech could not be managed with the patient due to the serious decrease in speech output, humming, crying spells, shouting episodes and disorientation. She was very restless; her head and trunk were in an anteflexed posture, with her head flexed laterally similar to dystonia while trying to walk or stand (Figure 1). With help, she could stand and walk only 1-2 meters. It was found out that she had paroxysmal dystonic contractions in the upper extremities and myoclonic movements dominant in the left upper extremity, rigidity in the upper extremities, brisk deep tendon reflexes, clonus in all extremities and neutral bilateral plantar response. Laboratory tests were within normal limits, except for low serum vitamin B12 and vitamin D levels shown in Table 1. Her brain imaging revealed no acute pathology (Figure 2).

Figure 1. The posture of the patient. Her head and trunk were in an anteflexed posture, with her head flexed laterally similar to dystonia while trying to walk or stand. She could stand with help.

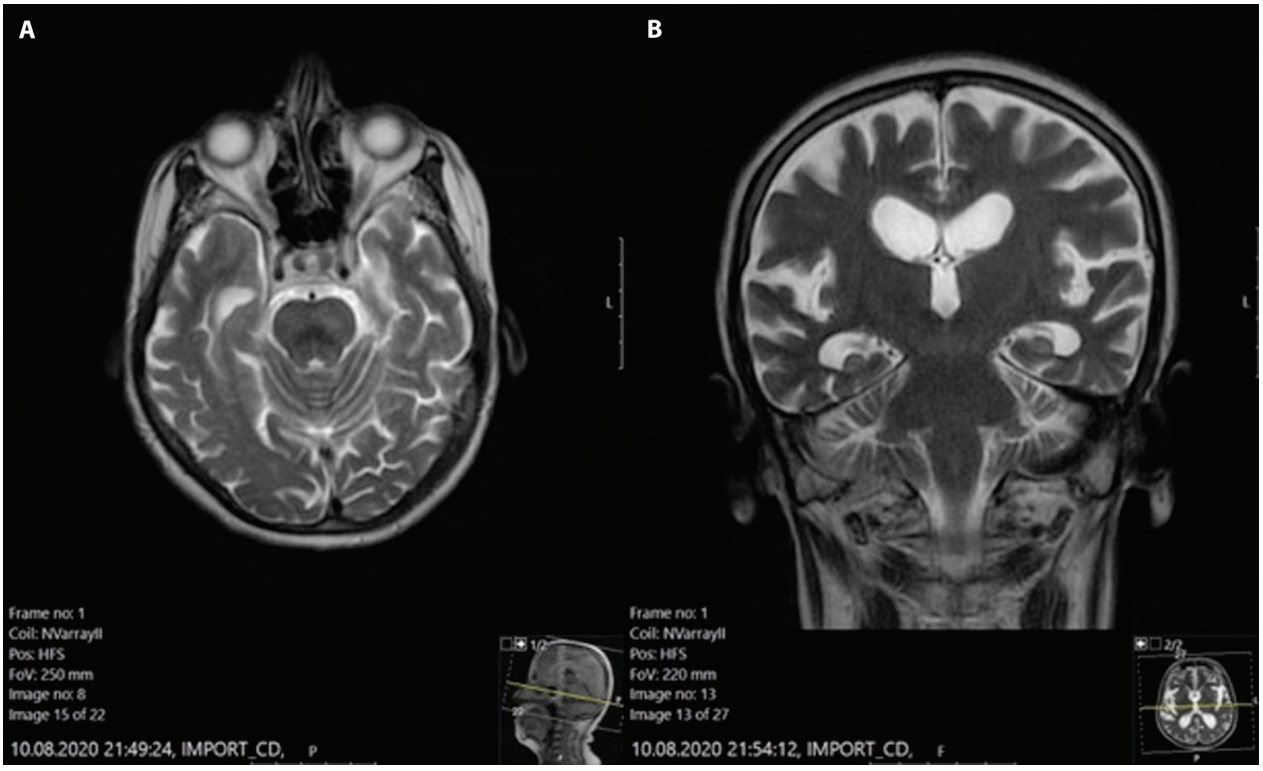

Figure 2. Magnetic resonance imaging of the brain. A. Axial T2 image reveals no focal abnormality. B. Coronal T2 image reveals diffuse global atrophy.

All her medicines (sertraline, domperidone, olanzapine and donepezil) were discontinued. According to the clinical findings, clonazepam 2 mg/day, mirtazapine 15 mg/day and propranolol 20 mg/day were started considering that the patient had akathisia (3), but no significant clinical improvement was observed in her condition. In addition, in the following days, we observed a generalized myoclonic seizure in which sodium valproate was initiated. In order to maintain adequate nutrient intake, enteral tube feeding was placed, vitamin B12 and D replacement therapy was also given, and Fosfomycin was started for urinary tract infection according to urine analysis. Her electroencephalogram (EEG) revealed a generalized slowing with no focal abnormalities (Figure 3) and her cerebrospinal fluid (CSF) analysis showed 2-3 white blood cells with protein, 56.3 mg/dl, and 73 glucose, mg/dl.

Given the patient's clinical presentation, initially acute-subacute and then progressive encephalopathy, neuropsychiatric symptoms, stroke-like event, and myoclonic seizures, the patient was suspected of having HE and further studies revealed antibodies to thyroperoxidase (TPO) (>1300 U/mL) and thyroglobulin (TG) (278.4 U/mL) were elevated, whereas free triiodothyronine, free thyroxine, and thyroid-stimulating hormone were in the normal range. Oral prednisone 80 mg/day was started immediately, with oral tenofovir due to possible occult Hepatitis B (Table 1) as long as she received steroid over 20 mg/day for at least one month (4). Meanwhile, CSF testing for herpes simplex virus 1 and 2 DNA, Anti-T pallidum immunoglobulin (Ig) M, IgG, and autoimmune encephalitis antibody panel were negative. Following the steroid therapy, the anti-TG-Ab titer decreased, plasmapheresis was initiated. After a 5-day course of plasmapheresis, a mild to moderate improvement in clinical condition was observed simultaneously with a remarkable decrease in Anti-TPO levels. She was turning her head towards the sound, her axial dystonia improved, myoclonic jerks decreased significantly. Because she was able to eat sufficiently, the feeding tube was removed. She was also able to sit in bed for a very short time with assistance. Her steroid was tapered. She remained clinically stable 2 months after discharge and her anti-TPO-Ab titer was 452.7 U/mL, while two months after the last visit she was re-hospitalized because we observed myoclonic jerks, agitation, and restlessness. The anti-TPO-Ab titer was 1163.4 IU/mL, and figure 4 shows the antithyroid antibody levels. Following 5 days of plasmapheresis cure, anti-TPO-Ab titer was decreased, so her clinics returned to her previous stable state and azathioprine therapy was initiated. After three months of azathioprine therapy, anti-TPO-Ab titer was 190 IU/mL (Figure 4) and she was clinically stable.

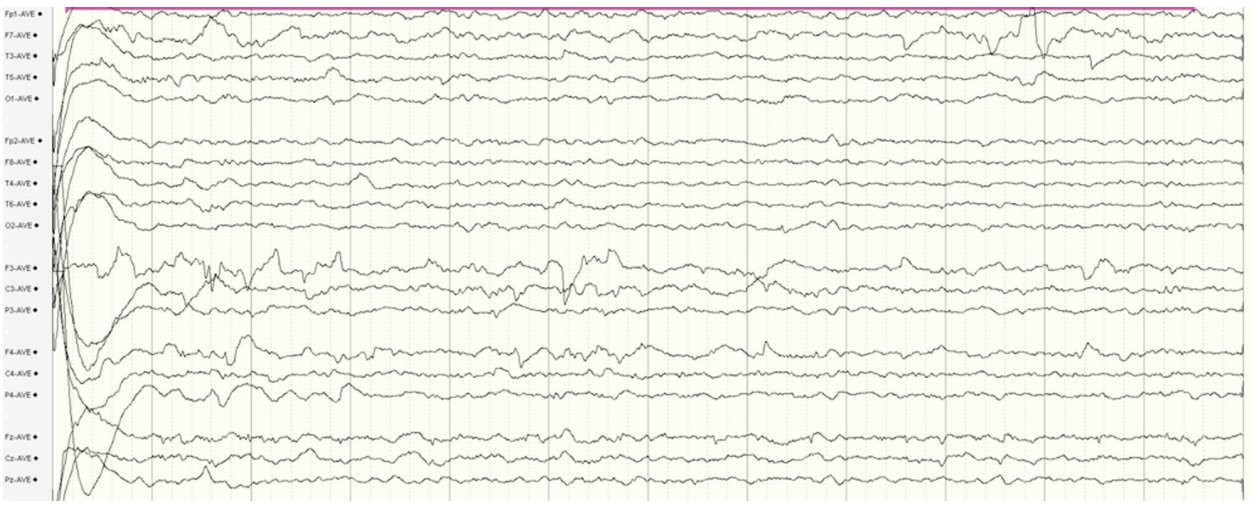

Figure 3. Electroencephalogram (EEG) of the patient demonstrating a generalized slowing.

Table 1. Laboratory Data

	Patient	Reference Range
Biochemistry		
Hemoglobin (g/dL)	13,8	12 - 16
Erythrocyte Sedimentation Rate (mm/h)	13	0 - 20
CRP (mg/L)	1,5	0,2 - 5
Glucose (mg/dL)	132	70 – 100
eGFR (mL/min/1.73 $m^{2)}$	99	> 90
ALT (U/L)	25	0 – 35
Vitamin B12 (pg/mL)	151	126,5 - 505
Ferritin (ng/mL)	102	11 - 306,8
25-OH Vitamin D (ng/mL)	22,92	30 -100
TSH (mIU/L)	4,22	0,38 - 5,33
FreeT4 (ng/dL)	0,68	0,5 -1,51
Free T3 (pg/mL	2,86	2,5 - 3,9
Anti-TG (U/mL)	278,4 - 331	64
Anti-TPO (U/mL)	> 1300 - > 1300	
TRAB (IU/L)	< 0.10	
Serology		
ANA	negative	
Ceruloplasmin	0,329	0,2 - 0,6
Tissue transglutaminase IgA	1,59	0 - 10
HIV Ag/Ab	negative	
Anti T.pallidum IgM and IgG	negative	
Hbsag	negative	
Anti-Hbs	positive	
Anti Hbc Total (IgG)	positive	
Anti HCV	negative	
Cerebrospinal Fluid (CSF)		
Glucose (mg/dL)	73	40 - 70
Total Protein (mg/dL)	56.3	15 - 40
Sodium (mmol/L)	151.3	136 -150
WBC (UL)	2	
RBC	0	
Aβ (1 – 40) (pg/ml)	6054	
Aβ (1 – 42) (pg/ml)	516.35	
Total Tau Protein (pg/ml)	436.94	> 375
Phospho Tau Protein (pg/ml)	64.7	> 60
Aβ42 Tau index	0.68	< 0,8
Aβ42/pTau Ratio	7.98	< 9

Table 1. (*Continued*)

	Patient	Reference Range
AMPA1 (Glu1)	negative	negative
AMPA (Glu2)	negative	negative
ANTI-CASPR2	negative	negative
ANTI-LGI1	negative	negative
ANTI-GABA B (GABABARB1/B2)	negative	negative
ANTI-DPPX	negative	negative
NMDA ANTIBODY (NMDAR Ab)	negative	negative

ANA, Anti Nücleer Antibody; ALT, Alanine aminotransferase; AMPA, anti-alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; Aβ: amyloid beta; ANTI-CASPR2: anti-contactin-associated protein-like 2 antibody; ANTI-GABA B: anti-gamma-aminobutyric acid-B receptor antibody; ANTI-LGI1: anti-leucine-rich glioma-inactivated 1 antibody; Anti-TG, anti-thyroglobulin antibody; Anti-TPO: antithyroid peroxidase antibodies; CRP, c reactive protein; DPPX, dipeptidyl-peptidase-like protein-6; FT4, free thyroxine; FT3, free triiodothyronine; GFR, glomerular filtration rate; HIV, human immunodeficiency virus; IG, immunoglobin; NMDAR, N-methyl-D-aspartate receptor; pTau, phospho tau; RBC, red blood cell; TSH, thyroid-stimulating hormone; TRAB, thyrotropin receptor-stimulating blocking antibody; WBC: white blood cell

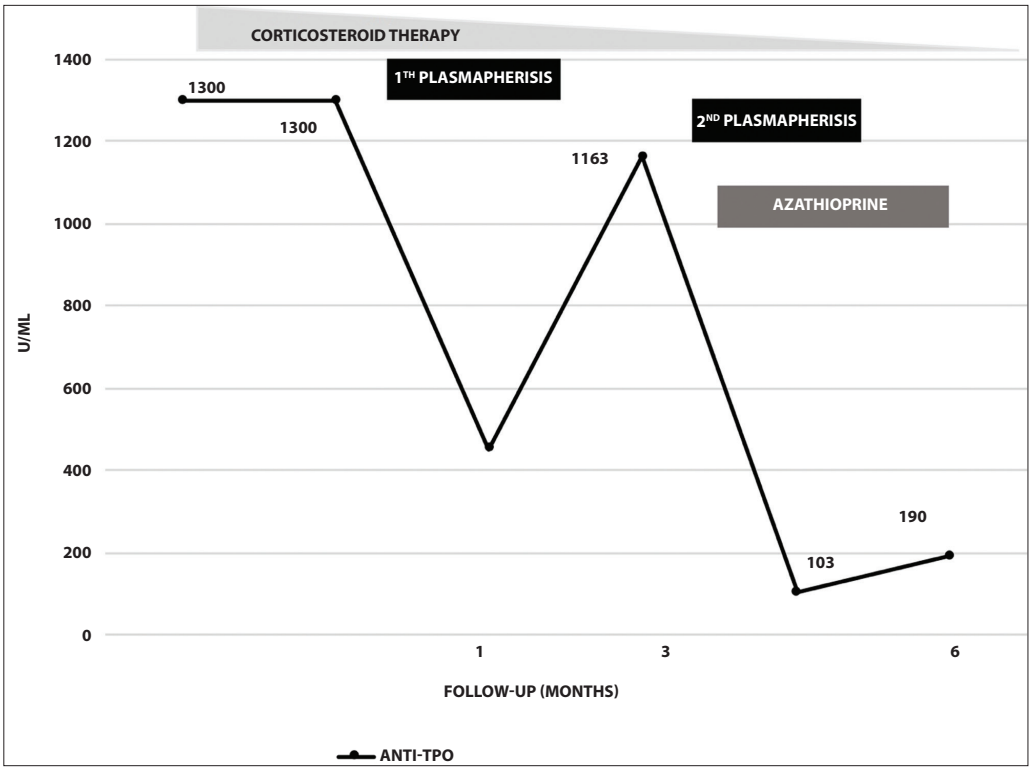

Figure 4. Summary of the patient's data regarding serum titers of thyroid autoantibodies and treatment regimens.

Discussion

In this unique case, as far as we are concerned, an old lady with symptoms of akathisia overlapping a progressive encephalopathy was presented. Akathisia was very prominent in her presentation, leaving her main symptoms in the background, which in turn could have resulted in missing her primary diagnosis, HE, an entity already overlooked in itself.

Akathisia is a condition that is often underdiagnosed because not all patients meet the diagnostic criteria such as the presence of motor restlessness in

regions other than the legs, and their symptoms can be attributed to other causes such as our patient who could not tell about inner restlessness (5). Accordingly, in our case, her restlessness had been misdiagnosed as a behavioral and psychological symptom of dementia. In addition, akathisia is a motor syndrome that usually occurs in the early days of antipsychotics, including olanzapine, which is also associated with dystonia (6). Therefore, physicians should be aware that such side effects associated with antipsychotics can be very distressing for patients, which may lead to confusion during the diagnosis process and the prescribing cascade. Moreover, it may be better to perform rating scales for extrapyramidal side effects such as akathisia, dystonia, dyskinesia in clinical practice, especially in geriatric practice, before starting these drugs.

On the other hand, our patient is noteworthy due to the extremely rare occurrence of HE especially in the elderly. HE can be encountered with an acute-subacute onset progressive course, a positive outcome may not be obtained from corticosteroid treatment, plasmapheresis may be required and permanent disability may result, as in our case. In fact, the response may be unpredictable as the pre-treatment characteristics of the disease, such as high anti-TPO titers, magnetic resonance imaging, EEG, or CSF findings, are not specific; thus, a very recent study concluded that only one-third of patients with suspected HE have shown complete clinical response to steroids (7). Therefore, a reliable biomarker is required to evaluate treatment response in HE. Additionally, the progression of HE according to the collateral history may have led to the lack of response to steroid treatment in our case.

Another point to be emphasized is the CSF findings of the patient. Patients with HE are usually reported to have elevated CSF protein, as in our case, a mild lymphocytic pleocytosis, and elevated IgG synthesis. Since she was diagnosed with dementia, biomarkers of AD in CSF have also been measured as part of the diagnostic process. Interestingly, the CSF profile of the patient could not exclude AD in which decreased amyloid-beta 42, increased tau and phosphotau concentrations are seen. However, we could not define the patient as HE accompanying AD due to lack of further evidence. Nonetheless, taking into account fluctuating consciousness, neurological signs, and seizures, as well as high Anti-TPO levels in patients with long-standing dementia is of great importance for HE with its progressive deteriorating course (8).

In conclusion, we presented akathisia superimposed to HE in an old lady. Although HE is still a diagnosis of exclusion, this challenging yet treatable clinical syndrome should be considered in older patients. Furthermore, side effects such as akathisia, dystonia, and dyskinesia should also be considered when starting antipsychotic treatment, especially in patients with an unclear diagnosis.

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

Informed consent: The informed consent was obtained from the next of kin.

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