HASHIMOTO’S ENCEPHALOPATHY

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Hashimoto’s encephalitis (HE), encephalitis which responds to steroids and is associated with auto-immune thyroiditis, was described by Brain et al. in 19661. Since then, about 100 cases have been described1-10. It is probably under diagnosed as it is not well known1. It presents with acute or sub-acute encephalopathy, tremor, myoclonus, ataxia, fits, psychosis or stroke like events, progressive or relapsing, high titres of anti-thyroid antibodies but independent of thyroid function2,4,10. Its two sub-types can co-exist: multiple stroke like events, and diffuse progressive, with dementia and psychiatric symptoms1.

Diagnostic criteria are encephalopathy with elevated anti-thyroid antibodies in the absence of infection, tumour or alteration in the cerebral vascular system. A good response to corticosteroids is typical2,4.

CASE

A 42 years old woman, white, secondary school education, married, from São Paulo, was admitted in Hospital in January 2007 with an acute febrile condition. She has universal alopecia which started when she was 13. There followed a period of three years with difficulties at school. She had three pregnancies with normal gestation, last 9 years ago. Eight years ago she developed hypothyroidism due to Hashimoto’s thyroiditis, and has been taking 125 mcg levothyroxine daily.

Her mother, 2 sisters and a daughter have Hashimoto’s thyroiditis, one sister also has vitiligo.

She had a 2 years history of feeling progressively tired, insomnia, cramps, tremors, arthralgia, paraesthesia in her hands and back pain. She had a 6 month history of behavioral changes and agitation, resulting in psychiatric treatment of estazolam 2 mg, bupropion 150 mg, carbamazepine 600 mg and duoxetine 30 mg daily.

Over the proceeding 2 months she had lost the nails of her right hand and had lesions on her back and face compatible with excoriation.

Five days prior to admission she had a high fever (41°C), body pain, tremors, cold extremities and pins and needles in her legs.

On admission, axillary temperature was 41°C. Normotensive, pulse 120 bpm, she had universal alopecia, cyanosis and pale pale alternating in the extremities, growing nails of the right hand and scars on her back and face. She was histrionic with disturbed thought. Ataxia, low amplitude high frequency action and postural tremors and myoclonus were observed in the four limbs. On the second day her temperature fell to 34°C. She was stable, suggesting a hypothalamic dysfunction.

Serology, cultures and diagnostic imaging did not indicate an infectious process. ESR was normal (7 mm) and CRP slightly elevated (2.23 mg/dL). ANCA, anti-DNA and ANA were negative. Biochemical results showed raised aminotransferases (AST >2× ALT >3×), hypocalcemia and hyperphosphatemia. Anti-thyroid peroxidase antibodies (anti-TPO) was 1.100 U/mL with normal TSH and free T4.

Cerebral MRI, electroencephalogram (EEG) and single photon emission computed tomography (SPECT) were all normal. Lumbar puncture was clear, 1 cell/mm3, mild hyperproteinorrachia (51 mg/dL); bacteriology, cultures and immunologic reactions for cysticercosis, syphilis, toxoplasmosis, cytomegalovirus, varicella-zoster, herpes simplex 1 and 2 and anti-TPO were negative. Oligoclonal bands were absent.

Pulse therapy with methyl-prednisolone 1g/IV/day for 3 days gave excellent results. She was maintained on oral prednisolone. To minimize the side effects of steroid therapy, in the second month the dose was reduced and azathioprine added, but due to hepato-toxicity this was suspended. The dose of thyroxine was reduced to 100 mcg.

The dose of steroid was gradually reduced. Episodes of sinus tachycardia of 140 bpm followed, with normal cardiac investigations. These were considered to be an autonomic dysfunction and well controlled with atenolol 50 mg/day. The hypocalcemia and hyperphosphatemia continued, despite calcium supplements with a reduction of PTH, consistent with hypoparathyroidism, compounding a picture of auto-immune polyglanular disease. There was a reduction in anti-TPO which co-related with the clinical picture. With the reduction of corticoids doses anti-TPO increased again, without clinical symptoms but with TSH elevation.

Now, two years later, she is well and is on prednisolone 2.5 mg on alternate days, and daily levothyroxine 112 mcg, atenolol 50 mg, calcium 1g and calcitriol 0.75 mg.

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DISCUSSION

There must be suspicion of HE patients with diverse neuro-psychiatric manifestations and a history of Hashimoto’s thyroiditis. It is a diagnosis of exclusion in a clinical picture of encephalitis with negative investigations\(^2,4,7,9\). The differential diagnosis includes incurable, degenerative diseases, like Creutzfeldt-Jacob disease, thus justifying a trial of steroids in selected patients\(^3\).

Little is known about the pathogenesis. High titres of anti-TPO are common markers of an auto-immune process but it is unlikely that they have a pathogenic role\(^6\). It is thought that there is an immune mediated cerebral vasculitis, with or without deposits of immune complexes, or an anti-neuronal mechanism mediated by anti-bodies\(^8\). Hypothyroidism, hormonal factors and cerebral hypoperfusion could contribute for pathogenesis\(^2\). Evaluation of pathological anatomy revealed discrete venous or perivascular changes but not a true vasculitis\(^4,8\).

HE occur predominantly in women (4:1), average age of 44 years, 20% under 18 years old\(^2\). Besides behavioral problems and cognitive decline, there may be fluctuating symptoms, tremor, transitory aphasia, myoclonus, ataxia, convulsions, sleep abnormalities, motor or sensory deficits and psychosis.

Patients can have normal TSH and hypo or hyperthyroidism\(^2,4,8\). Antibodies anti-TPO are present in 95–100% and antithyroglobulin in 73% of patients with HE. However, they can also be present in 10% of the adult population\(^8\).

The main change in the CSF is the increase in total protein, that was mild in this case, and rarely some lymphocytic pleocytosis\(^2,4\).

There are EEG changes in most cases, mainly generalized slowing\(^2,4,8\). MRI and cerebral angiography are normal in the majority of cases\(^2\). The most common abnormality is diffuse increased signal in the white substance\(^2\). SPECT can be normal but usually shows focal hypoperfusion\(^8\). All are reversible.

Treatment is based on the use of immunosuppressants, chiefly corticosteroids (intravenous methyl prednisolone in high doses (1 g/day/3 to 5 days) or oral prednisolone (50–150 mg/day)). The clinical improvement can occur on the first day, like in this case, but generally occurs within a week and up to 6 weeks\(^8\). The majority of patients return to their normal neurological state. Some symptoms may persist, such as tremors and loss of memory. It is recommended to reduce the dose of steroids over several months. Some patients need to stay on low doses or a new course of high dose of prednisolone is necessary\(^2\). Like other autoimmune disease improvement may occur spontaneously\(^4\).

Therapeutic options for relapsing cases or as an alternative to steroids include azathioprine, cyclophosphamide, mycophenolate mofetil, methotrexate, IV immunoglobulin and plasmapheresis, alone or in combination\(^8\). Hepato-toxicity led to the interruption of azathioprine in this case.

Alopecia is associated with polyglandular autoimmune. CNS involvement is rare in this context, HE being the most common example. It was suggested that the hypoparathyroidism, hypothyroidism and alopecia areata. Some aspects warrant particular attention: prolonged and fluctuant course (school difficulties were probably an episode in adolescence); hypothalamic problems; association with hypoparathyroidism and alopecia areata. Diagnostic criteria include: exclusion of other causes of encephalopathy, high levels of anti-TPO and a good response to glucocorticoids.

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