Thyrotoxic autoimmune encephalopathy: a repeat positron emission tomography study

S W Seo, B I Lee, J D Lee, S A Park, K S Kim, S H Kim, M J Yun

J Neurol Neurosurg Psychiatry 2003;74:504–506

Thyroid related autoantibodies have been related to the development of encephalopathy, known as Hashimoto’s encephalopathy. However, their relation with the encephalopathy occurring in patients with Graves’ disease has not been well established. The case is reported of a 51 year old woman presenting with subacute progressive dementia, multifocal myoclonus, and raised TRAb. Her encephalopathy was not improved by antithyroid drugs, but promptly responded to corticosteroid treatment, and stabilised with a gradual reduction of thyroid related autoantibodies. Brain positron emission tomography initially showed a diffuse and multifocal cerebral hypometabolism with subsequent normalisation on her clinical recovery, which was consistent with the acute and reversible cerebral inflammation probably mediated by autoimmune mechanisms.

Mild and thyrotoxicosis are known causes of treatable dementia. Additionally, thyroid related autoantibodies (TRAb) can precipitate an encephalopathy even in the euthyroid state, which was named Hashimoto’s encephalopathy (HE) by Brain et al in 1966.3

We report on a patient presenting with a subacutely progressive dementia, multifocal myoclonus, and raised TRAb. The patient was found to fit the diagnostic criteria of both Graves’ disease (GD) and HE.3 We also report the findings of the 18 F-fluorodeoxyglucose positron emission tomography (FDG-PET) conducted during the exacerbation and the recovery phases of the thyrotoxic autoimmune encephalopathy.

CASE REPORT

A 51 year old right handed woman was brought to the hospital because of progressive cognitive deterioration and behavioural changes, with associated involuntary movements that had occurred during the past two weeks. She was a high school graduate and ran a dress repair shop. She had been healthy until six months ago, when she reported frequent heat intolerance with a significant weight loss, from 60 kg to 45 kg over the previous six months. However, she had been reliable and efficient at her work until two weeks previously, when she began to ask how to operate the dryer that she had used for years. She seemed to be in a mildly depressed mood, and somewhat withdrawn, with decreased verbal fluency. One week before her admission she had difficulty in finding words, spent hours searching for familiar objects, and could not recall her working schedules. These symptoms further progressed and developed into mental confusion, impaired language and communication skills, and diffuse tremulousness.

On admission, her blood pressure was 130/80 mm Hg, with a pulse rate of 110 per minute and a body temperature of 36.8°C. Physical examination revealed a restless thin, middle aged woman in no acute distress. Exophthalmos was present bilaterally, but the thyroid gland was not enlarged. On neurological examination, she was alert, but disoriented to time and place. She could follow simple commands, but was apprehensive and restless with a pronounced decrease in attention span and memory. She failed to give a reliable medical history and her Korean-Mini Mental State Examination (K-MMSE) score was only 3 of 30 (table 1), with one point for her person orientation and two points for memory registration. She had ataxia, postural tremors, and multifocal myoclonus in all four extremities. Neuropsychological tests revealed severe impairment in all aspects of cognition, with particular impairment in concentration, anoma, amnesia, apraxia, visuospatial and frontal executive dysfunctions. Detailed results of neuropsychological assessment (table 2) can be found on the journal web site (www.jnnp.com).

The thyroid function tests at that time showed hyperthyroidism state. The levels of antimicrosomal antibodies, antithyroglobulin antibodies, and thyrotrophin binding inhibiting immunoglobulin were considerably increased (table 1). The cerebrospinal fluid analysis showed a mildly increased protein level (61 mg/dl), but with normal cell counts and glucose level. A thyroid scan disclosed a diffuse goitre and increased thyroid activity, consistent with GD. The EEG demonstrated a diffuse background slowing with excessive diffuse slow theta and delta waves. MRI of the brain revealed no abnormality. She was initially treated with antithyroid therapy for three days. Her heart rate normalised, but her cognitive dysfunction showed no improvement, with further deterioration in behaviour and involuntary movements. From the fourth day of hospitalisation, she was intravenously given 20 mg per day of dexamethasone for five days, with significant cognitive and behavioural improvements becoming noticeable on day 3 of corticosteroid treatment. She has shown a good clinical recovery and her K-MMSE score was significantly improved to 22 points after the five day course of high dose corticosteroid treatment. However, after the reduction in dexamethasone to 15 mg per day, she fell into a confused state again. Her thyroid function at that time was in an euthyroid state. The relapse of her mental deterioration was considered to be related to the rapid reduction of dexamethasone, and she was treated with high doses of intravenous corticosteroid (methylprednisolone 1 g/day for five days), which was followed by prednisolone (60 mg/day), and showed an excellent clinical recovery over the next three days. On the 18th day, she was discharged from the hospital completely recovered. Two weeks after the discharge she remained neurologically stable, which was confirmed by a K-MMSE score of 28 of 30. The thyroid function test showed an euthyroid state and the...
pet tests revealed that she had GD, associated with raised TRAb. The PET scan also revealed a diffuse multifocal cerebral glucose hypometabolism, which may have been responsible for her global cognitive impairment. GD may cause an encephalopathy by two independent mechanisms: as the direct effect of the increased thyroid hormone or from the TRAb related autoimmune mechanism. If the encephalopathy was precipitated by the direct toxic effects of increased thyroid hormones, it should be reversed by antithyroid treatment alone, but this was not the case in our patient. In fact, she deteriorated further during the phase of only antithyroid treatment despite the normalisation of thyroid hormone levels, but rapidly responded to the dexamethasone treatment. Additionally, her symptoms relapsed shortly after reducing the dose of dexamethasone, but responded again to a high dose intravenous corticosteroid treatment, with a complete recovery under the maintenance corticosteroid treatment. Her clinical course strongly indicated that autoimmune mechanisms have been responsible for her encephalopathy.

The encephalopathy associated with raised TRAb has been termed HE because these thyroid diseases are mostly Hashimoto’s thyroiditis. Moreover, most were presented in either an euthyroid or a hypothyroid state. However, she was diagnosed with GD and was in a state of hyperthyroidism at the time of admission. There have been only two cases of HE, associated with thyrotoxicosis, previously reported, with both cases showing a dramatic response to corticosteroid treatment. The diagnosed thyroid disease was: GD in one, but was uncertain in the other. Considering that GD, associated with raised TRAb, can also precipitate HE, the term proposed by Canton et al, encephalopathy associated to autoimmune thyroid disease, seems more appropriate than Hashimoto’s encephalopathy.

The central nervous system symptoms of thyrotoxicosis are mainly allusion or psychosis. However, some thyrotoxic patients have been observed with mental confusion, seizure, manic or depressive attack, and delusion, and they have often responded to plasmapheresis or corticosteroid treatment. Although it has been reported that the incidence of raised TRAb in those patients was low, TRAb have not been evaluated in most patients, which makes it difficult to exclude the possibility of autoimmune mechanisms as the universal pathogenesis of thyrotoxic encephalopathy.

Various neuroimaging features have been reported in HE. MRI may show either normal, diffuse cortical atrophy, or increased T2 signals in the subcortical or the mesiotemporal regions, representing as diffuse oedema or inflammation. Single photon emission computed tomography (SPECT) may show multiple areas of hypoperfusion, and Forchetti et al suggested autoimmune cerebral vasculitis as the aetiology of hypoperfusion on SPECT. However, most patients with HE have a normal erythrocyte sedimentation rate and angiographic features, with a necropsy study revealing very peculiar vasculitis involving only venules of the brain stem. Consequently, it is uncertain whether the perfusion defect on SPECT is attributable to vasculitis itself, or is a secondary

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Summary of patient’s laboratory finding and results of K-MMSE</th>
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</thead>
<tbody>
<tr>
<td>Date</td>
<td>HD 1</td>
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<tr>
<td>TD (80–120 ng/dl)</td>
<td>657.21</td>
</tr>
<tr>
<td>FT4 (0.73–1.95 ng/dl)</td>
<td>8.11</td>
</tr>
<tr>
<td>TSH (0.35–3.5 uIU/ml)</td>
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<tr>
<td>AAMA (50 IU/ml)</td>
<td>3000x</td>
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<tr>
<td>TGB (50 IU/ml)</td>
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</tr>
<tr>
<td>TBI (12%–26%)</td>
<td>59.59</td>
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<tr>
<td>K-MMSE</td>
<td>3/30</td>
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</tbody>
</table>

AMA, antinuclear antibodies; FT4, free T4; HD, hospital day; K-MMSE, Korean version of Mini-Mental State Examination; NL, normal; TBI, thyrotrophin binding inhibiting immunoglobulin; TGB, antithyroglobulin antibodies.

Figure 1: Brain PET using 18 F-fluorodeoxyglucose obtained 40 minutes after the injection. (Top) Selected transaxial PET images of the brain during the height of the patient’s deterioration showed diffusely decreased, non-uniform FDG uptake in the brain, most severely affecting the right parietal, the right temporal, and the left inferior frontal areas. The FDG uptake in the basal ganglia and the thalamus were comparatively well preserved. (Below) Transaxial PET images of the brain after the patient’s clinical improvement demonstrated symmetric distribution of FDG suggesting a significant improvement of the cerebral glucose metabolism compared with the previous study.
feature related to the autoantibody mediated cerebral inflammation and oedema. Our patient had a normal MRI, but her initial brain PET revealed a diffuse and multifocal cerebral hypometabolism, which was consistent with her globally affected severe cognitive impairment. The cerebral hypometabolism was reversible and normalised in her follow up brain PET as the improvement of central nervous system symptoms and the decreased titres of TRAb. The underlying pathogenesis of PET abnormalities is still unclear, but the autoimmune mediated inflammation in multifocal brain structures is certainly the most probable cause. The prompt clinical response to the corticosteroid treatment, and the acute relapse upon the reduction of the corticosteroid dose during her early stay in hospital, when the titres for the TRAb were still persistently increased, strongly supports that the encephalopathy was precipitated by the autoimmune mediated inflammatory reactions, rather than the direct effect of the TRAb against neuronal function. We suggest that any attempt to reduce the dose of corticosteroid should be delayed until a significant lowering of the TRAb titres has been achieved.

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Funding: the study was supported by a grant from the BK-21 project of Yonsei University College of Medicine.

References
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doi: 10.1136/jnnp.74.4.504

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