INTRODUCTION
Hashimoto’s encephalopathy (HE), known eponymously as steroid-responsive encephalopathy associated with autoimmune thyroiditis, is an uncommon, poorly understood, and often misdiagnosed neuropsychiatric condition. The term, first used by Shaw et al. in 1991, broadly subsumes patients who present with varied signs of encephalopathy coupled with elevated levels of thyroid antibodies and good, often dramatic, response to corticosteroid therapy. The first probable case of Hashimoto’s disease manifesting with tremors, change in consciousness, cognition and stroke-like episodes was described by Brain et al. in 1966 and since then many reports have emerged that highlight the protean neuropsychiatric manifestations of this intriguing condition.

The pathogenesis of the condition remains poorly understood. Specifically, it has been observed that while nearly all patients with HE demonstrate elevated levels of antithyroid antibodies, a causal or linear relationship between antibody titers and HE has not been established. Other factors thought to play a crucial role in pathogenesis of HE include impairments in cerebral perfusion and metabolism owing to diffuse vasculitis and/or disseminated encephalomyelitis. This, in turn, gives rise to broad spectrum of multifocal deficits that are difficult to capture through rigid diagnostic criteria. Fortunately, there are no such challenges on the treatment side as the condition traditionally responds well to steroid therapy. Early recognition of the syndrome remains an important unmet need in HE. Currently, there are no recognized or universally accepted criteria to aid clinicians in making a diagnosis of HE.

In such a scenario, physicians have to rely on clinical observations in the form of case reports/series/analytical...
synthesis of cases reported in literature to delineate common presentations of this condition. Psychiatric presentations constitute a significant proportion of HE. Although many cases of HE with initial psychiatric presentation have been reported in literature, they vary in their demographic, clinical, and treatment characteristics. We could not identify any systematic review that summarizes the evidence in this regard. To bridge this knowledge gap, we undertook the present review with the objective of examining the demographic, clinical, and treatment-related factors of HE cases reported in literature, focusing on those reports where psychiatric manifestations have heralded the eventual diagnosis of HE.

**Materials and Methods**

**Search strategy and study selection**

Electronic searches of PubMed, ScienceDirect, and Google Scholar databases were carried out with the aim of identifying published case reports describing preliminary psychiatric presentations of HE. The search was done using the following subject headings or free text terms: HE, Hashimoto’s thyroiditis, Hashimoto’s disease, steroid responsive encephalopathy, hypothyroidism, and autoimmune thyroiditis. The searches were carried out in July 2016 and were independently performed by the two authors who were both qualified psychiatrists (Vikas Menon and Jaiganesh Selvapandian Thamizh). The search filter of “case report” was not used as many case reports are increasingly being published as letters to the editor. The search results of the two authors were compared and after weeding out duplicate articles, a consolidated list of abstracts was drawn up. Next, a supplemental Google search using random combinations of the above terms was done to further screen the available literature. Cross-references of selected papers were also screened to identify relevant articles. The search was restricted to articles in the English language without any restriction on the date of publication. We included reports that described pure psychiatric or mixed presentations (e.g., psychiatric and neurologic) of HE as the latter presentations may often come first to a psychiatrist. Any disagreement was sorted out through mutual discussion and consensus. We did not include unpublished material or those not available in peer-reviewed journals (e.g., conference presentations) as they were not readily accessible. We did not contact authors for further information and relied solely on electronic material available. Comprehensive hand-searches of the physical library were not carried out as part of the present review.

**Data extraction**

The full texts of the relevant articles were used to extract information about relevant demographic variables such as age, gender, and country of residence. Clinical and treatment related information such as typology of psychiatric manifestation (affective illness/psychotic illness etc.), levels of antithyroid antibodies, duration of hypothyroidism (if diagnosed earlier), adequacy of replacement therapy, name and dosages of psychopharmacologic agents, any special treatments used such as electroconvulsive therapy, dose of corticosteroid employed, and time course of response was also gathered. Data extraction was done by two of the authors (Vikas Menon and Karthick Subramanian).

**Data analysis**

Descriptive analysis was used to depict the data collected. Demographic and clinical variables were expressed as simple frequencies and percentages. We focused on the summary numbers in each category. Inferential statistics were not required. As the review included only individual case reports, we could not calculate effect sizes. For the same reason, we also did not assess the quality of data collected.

**Results**

The flowchart depicting the results of the literature search is shown in Figure 1. The majority (n = 27, 67.5%) of the case reports/series were published after 2010, indicating an increased awareness of the protean manifestations of HE. After following the inclusion and exclusion criteria and removing duplicates, a total of forty articles describing 46 cases were identified. These reports varyingly described one, two, or a maximum of three cases. Of the 46 cases, 28 (60.9%) had not been reported in literature, they vary in their demographic, clinical, and treatment-related factors of HE cases reported in literature, focusing on those reports where psychiatric manifestations have heralded the eventual diagnosis of HE.

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required 3 years of steroid maintenance therapy to induce clinical response.\cite{14}

The electroencephalographic findings showed a normal record in nine patients (19.6%)\cite{12,14,16,18,20,24,26-28,32-34,36,39,41-45,49,50} while the most common abnormality noted was an intermittent or diffuse background slowing mostly in the frontal and temporal leads with or without bursts of sharp wave discharge (n = 25.54.3%).\cite{12‑14,16,18,20,24,26‑28,32‑34,36,39,41‑45,49,50}

Magnetic resonance imaging (MRI) returned normal study in 26 patients (56.5%).\cite{14,15,16,17,20,21,23‑28,31,32,36‑39,41‑44,46,48,50} Of the others whose imaging data were available, the single most common abnormality reported were nonspecific white matter hyperintense lesions (n = 9.19.6%).\cite{12,13,19,32,35,47,49} Functional neuroimaging imaging data (single photon emission computed tomography [SPECT]) were available for seven cases and while one of them was within normal limits,\cite{26} the others demonstrated global cerebral hypoperfusion as well as perfusion asymmetry.\cite{15,40,41,45,47,48} Cerebrospinal fluid analysis (CSF) results were available for 28 out of the 46 cases. The most common anomaly reported in CSF was elevated proteins indicating a disturbance in the blood brain barrier (n = 15, 32.6%).\cite{12,13,16,18,19,27,32,36,41,46,49,50} While five cases tested positive for antithyroid antibodies in CSF,\cite{14,20,23,31,37} one report identified no antithyroid antibodies when specifically tested for it.\cite{32} CSF analysis was normal in eight patients.\cite{22,26,28,38,43‑45,47,49} In four cases, where a detailed analysis of antibody profile, including antinuclear antibodies, anti-double-stranded DNA, anti-Sjogren syndrome-related antigen A and B and anticardiolipin antibodies was done, all the tested antibodies were found to be within normal limits.\cite{23,31,32,46} High serum levels of IgG were found in one patient\cite{31} while two patients tested positive for antimicrosomal antibodies, respectively.\cite{18,44}

### Discussion

The majority of the reported cases in the present systematic review involved females and aged above 50 years. This evidence converges with extant literature that shows a female preponderance in HE with a male to female ratio of around 1:5. This gender difference has been explained based on sex

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**Table 1: Demographic characteristics of included cases (n=46)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>5 (10.9)</td>
</tr>
<tr>
<td>21-30</td>
<td>3 (6.5)</td>
</tr>
<tr>
<td>31-40</td>
<td>3 (6.5)</td>
</tr>
<tr>
<td>41-50</td>
<td>10 (21.7)</td>
</tr>
<tr>
<td>51-60</td>
<td>9 (19.6)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>16 (34.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>9 (19.6)</td>
</tr>
<tr>
<td>Female</td>
<td>37 (80.4)</td>
</tr>
</tbody>
</table>

**Table 2: Diagnostic typology of index presentation (n=46)**

<table>
<thead>
<tr>
<th>Psychiatric diagnosis</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute psychosis</td>
<td>12 (26.1)</td>
</tr>
<tr>
<td>Depressive disorder</td>
<td>11 (23.9)</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>7 (15.2)</td>
</tr>
<tr>
<td>Dementia</td>
<td>5 (10.9)</td>
</tr>
<tr>
<td>Acute encephalopathy</td>
<td>5 (10.9)</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Others</td>
<td>5 (10.9)</td>
</tr>
</tbody>
</table>

**Table 3: Clinical and treatment variables (n=46)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD) or n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Already diagnosed with hypothyroidism(^1)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>17 (37.0)</td>
</tr>
<tr>
<td>No</td>
<td>28 (60.9)</td>
</tr>
<tr>
<td>Anti-TPO titer(^1)</td>
<td>2988.6±50.2</td>
</tr>
<tr>
<td>Anti-TG titer*</td>
<td>789.67±22.2</td>
</tr>
<tr>
<td>Steroid dose initiated (mg)</td>
<td></td>
</tr>
<tr>
<td>≥1000</td>
<td>18 (39.1)</td>
</tr>
<tr>
<td>500</td>
<td>6 (13.0)</td>
</tr>
<tr>
<td>≤200</td>
<td>8 (17.4)</td>
</tr>
<tr>
<td>Not mentioned</td>
<td>15 (32.6)</td>
</tr>
<tr>
<td>Steroid dose maintained(^1) (mg)</td>
<td></td>
</tr>
<tr>
<td>40-60</td>
<td>18 (39.1)</td>
</tr>
<tr>
<td>No maintenance given</td>
<td>21 (45.7)</td>
</tr>
<tr>
<td>Time taken to respond to steroids(^1)</td>
<td></td>
</tr>
<tr>
<td>Less than a week</td>
<td>5 (10.9)</td>
</tr>
<tr>
<td>Few weeks to months</td>
<td>32 (69.6)</td>
</tr>
<tr>
<td>Electroencephalography findings</td>
<td></td>
</tr>
<tr>
<td>Normal study</td>
<td>9 (19.6)</td>
</tr>
<tr>
<td>Diffuse cortical dysfunction</td>
<td>3 (6.5)</td>
</tr>
<tr>
<td>Intermittent/diffuse slowing</td>
<td>25 (54.3)</td>
</tr>
<tr>
<td>Missing/not done</td>
<td>7 (15.2)</td>
</tr>
<tr>
<td>Non-specific changes</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Increased fast wave activity</td>
<td>1 (2.2)</td>
</tr>
</tbody>
</table>

Data not available for \(^1\), \(^7\), \(^8\) and \(^10\) cases. TPO: Thyroperoxidase, TG: Thyroglobulin, SD: Standard deviation
Several mechanisms such as diffuse or rhythmic slowing as most frequently documented anomaly in the EEG.[46] Other abnormalities documented include frontal intermittent rhythmic delta activity,[46] periodic sharp waves or epileptiform discharges, photomyogenic response, and photoparoxysmal response.[67,68] The background slowing on EEG may often be a reflection of the severity of underlying encephalopathy. In a prior review of adult patients with steroid-responsive encephalopathy associated with autoimmune thyroiditis, all cases reviewed showed some degree of generalized slowing, and these changes often reversed with successful treatment.[48] Henchey et al. mention that nonspecific EEG abnormalities are seen in 90%–98% of HE patients but our review suggests a slightly lower percentage (80% with abnormal EEG).[49]

MRI either returned a normal study (56.5%) or most commonly showed nonspecific focal or diffuse white matter hyperintensities. This resonates with figures quoted earlier, and the overall consensus is that MRI findings may not have diagnostic specificity for HE and other causes need to be ruled out.[53,66] Apart from subcortical hyperintensities, other findings in literature include cerebral atrophy or rarely focal cortical abnormalities that often reverse with treatment.[56] Functional imaging data were available for only a few cases and mostly showed widespread hypometabolism. Nonspecific patterns of diffuse or patchy hypoperfusion have been consistently shown in HE and appear not to correlate with clinical presentation.[40,41,72] Brain hypoperfusion detected in SPECT supports the vasculitic model of pathogenesis in HE. CSF analysis was normal in 28.5% of patients with available data. Elevated proteins were noted in about a third of patients while a few patients also demonstrated the presence of antithyroid antibodies in CSF. Mild or nonspecific inflammation characterized by mononuclear pleocytosis or elevated proteins are common in HE and rarely oligoclonal bands have also been reported.[6,73]

A few limitations of the present review should be kept in mind. We included only published case reports in English language journals. Hence, it is possible that some reports may not have been included. Another shortcoming was that we relied only on data available in the published manuscripts and did not contact authors for more information. As the review focused only on case reports and case series, we did not attempt a quantitative synthesis of data.

**Conclusion**

Psychiatric presentations heralding HE can be quite heterogeneous but mostly comprise of acute psychotic episodes.
followed by depression. Schizophrenic presentations and frank dementia may occur less commonly. Antithyroid peroxidase may be a more useful and sensitive marker than anti-TG levels. EEG, MRI, and CSF findings are nonspecific and seem to be reversible with treatment. Clinicians should maintain a high index of suspicion when dealing with psychiatric presentations in individuals above 40 years of age. Subtle clinical clues such as atypical age of onset, poor response to isolated antipsychotic or antidepressant therapy coupled with raised antithyroid antibody titers should point the finger toward HE. Prevalent thyroid status does not seem to be a clinically useful metric. Evidence suggests that steroid dose needs to be initiated at 500–1000 mg/day for first 3–5 days and it may be prudent to continue oral prednisolone (1–2 mg/kg/day) for few weeks to months followed by gradual tapering. Keeping the above considerations in mind can facilitate an early diagnosis and hasten resolution of HE.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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