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Original Article

Evaluation of Diagnostic Criteria for Hashimoto Encephalopathy Among Children and Adolescents

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ABSTRACT

Background: The recently proposed adult diagnostic criteria for Hashimoto encephalopathy (HE) include a requirement of subclinical or mild thyroid disease. However, reports indicate that most children treated for HE do not have evidence of thyroid disease. We aim to evaluate the impact of applying the current adult diagnostic criteria to pediatric patients.

Methods: Pediatric patients with HE were evaluated at time of symptom onset and follow-up at least 1 year after initiation of immunomodulatory treatment for degree of impairment within the neuropsychiatric domains of cognition, language, psychiatric disturbance, seizure, movement disorder, sleep disruption, and overall functionality. We compared the response to treatment among patients stratified by the presence or absence of subclinical or mild thyroid disease using the Modified Rankin Scale, the Liverpool Outcome Score, and a novel multidomain scale designed for the population with pediatric autoimmune brain disorders.

Results: Of 17 pediatric patients treated for HE, 6 met full adult diagnostic criteria, whereas 11 patients did not meet criteria solely owing to the absence of thyroid disease. Using our novel scale, the 6 patients meeting full criteria had statistically significant improvement from time of onset of disease to follow-up in the domain of cognition. The 11 patients who did not meet full criteria based on their absence of thyroid disease exhibited statistically significant improvement from time of onset of disease to follow-up in the domains of cognition, language, psychiatric disturbance, movement, and sleep.

Conclusions: Rigidly applying the current diagnostic criteria to pediatric patients with suspected HE may result in the failure to treat potential responders. We propose a set of diagnostic criteria for HE in children, which does not require thyroid disease but include abrupt onset cognitive regression with deficits in one or more other neuropsychiatric domains in the setting of antithyroid antibodies.

Introduction

Hashimoto encephalopathy (HE) is a clinical entity, first described in 1991, characterized by neurological and psychiatric symptoms in association with increased levels of antithyroid antibodies. Cognitive decline, seizures, psychosis, and mood changes are most commonly seen in patients with HE, but the disease can present with a wide range of neuropsychiatric symptoms. The disease is often referred to as "steroid-responsive encephalopathy associated with autoimmune thyroiditis" given its strong therapeutic response to steroids. However, some patients with HE may not respond to steroids alone and have required other treatments used for autoimmune brain diseases, including intravenous immunoglobulin, plasmapheresis, and immunosuppressant medications.

HE has been conceptualized as an autoimmune process owing to its association with other autoimmune diseases, female predominance, and response to steroids. Identifying a common pathophysiology has been complicated by the variability in presenting features, ranging from stroke-like manifestations seen with

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TABLE 1
Diagnostic Criteria for Hashimoto Encephalopathy[4]

All six of the following:
1. Encephalopathy with seizures, myoclonus, hallucinations, or stroke-like episodes
2. Subclinical or mild overt thyroid disease (usually hypothyroidism)
3. Brain MRI normal or nonspecific abnormalities
4. Presence of serum thyroid (TPO, TGB) antibodies (no disease-specific cutoff)
5. Absence of well-characterized neuronal antibodies in the serum or CSF
6. Reasonable exclusion of alternative cause

Abbreviations:
CSF = Cerebrospinal fluid
MRI = Magnetic resonance imaging
TGB = Thyroid binding globulin
TPO = Thyroid peroxidase

vasculitis to symptoms commonly seen in encephalopathy, such as seizures or hallucinations. It is therefore not surprising to see variable imaging findings on magnetic resonance imaging (MRI) and cerebral angiography.[1] Antithyroglobulin and anti–thyroid peroxidase antibodies have been identified as being elevated in patients with HE.[2] Although there have been some cases identifying antithyroid antibodies in the cerebrospinal fluid (CSF) of patients with HE suggesting intrathecal synthesis, these antibodies neither appear to confer disease nor have clear antineuronal tissue binding.[3] Most experts theorize that these antibody elevations simply represent a propensity for autoimmunity or are an indirect marker of autoimmunity affecting the brain.[1,3]

The current diagnostic criteria for HE (Table 1), proposed by Graus and colleagues, require the presence of encephalopathy with hallucinations, seizures, stroke-like episodes, or myoclonus, elevated serum thyroid antibodies, and subclinical or mild overt thyroid disease.[4] The criteria also require a normal or nonspecifically abnormal MRI, the absence of antineuronal antibodies in the serum or CSF, and the reasonable exclusion of an alternative cause of the individual's symptoms.[4]

The largest meta-analysis of case reports of HE in adults found that only 80 of 251 (32%) patients had evidence of hypothyroidism or hyperthyroidism at the time of diagnosis with HE.[5]

Most adults with HE (categorized based on the presence of antithyroid antibodies and symptoms of encephalopathy) do not have thyroid disease at the time of diagnosis.[1,6]

Among providers who treat children with autoimmune brain diseases there is an ongoing debate about applying these criteria to the pediatric population. Experts in the field believe that the majority of pediatric patients with suspected HE fit the clinical picture of the disease and meet all criteria with the exception of the presence of clinical thyroid disease; the majority of case reports of children with suspected HE confirms this.[7-9] However, there are no empirical studies documenting the prevalence of clinical thyroid disease in pediatric patients treated for HE. In addition, the description of various neuropsychiatric presentations in case reports as well as our practice is widely variable beyond the limited inclusion of "hallucinations, seizures, stroke-like episodes, or myoclonus." There has been no empirical study on the specific neuropsychiatric symptoms exhibited by pediatric patients with HE; the only literature describing the disease in children exists in the form of case reports. Given the association between early treatment for autoimmune brain diseases and positive long-term outcomes, it is imperative that providers have an accurate understanding of the clinical and paraclinical presentation of HE among children and adolescents.[10]

We aim to provide the first quantitative description of neuropsychiatric symptoms and paraclinical findings exhibited by children with suspected HE. We also hope to evaluate the efficacy of the current diagnostic criteria when applied to children suspected to have HE, specifically along parameters of (1) the neuropsychiatric symptoms present at the onset of disease as well as (2) the presence or absence of clinical thyroid disease.

Experts in the field of autoimmune brain diseases have struggled to find comprehensive assessment scales and outcome measures that capture the multifaceted presentation of symptoms associated with this group of diseases. Several studies, including

TABLE 2
Multidomain Assessment Scale for Autoimmune Encephalitis

Degree of Impairment	Cognition	Language	Seizure	Psychiatric	Movement	Sleep
2 Severe impairment	Unable to function in academic environment, profound impact on memory and learning	Exhibits mutism or aphasia	Severely disabled by seizures (impairing cognition, functionality, including safety, unable to attend school/community activities)	Severe impairment in ADLs, unable to attend school or community, danger to self or others	Severe impairment in gross and/or fine motor movements resulting in inability to perform ADLs	Severe insomnia or hypersomnia causing inability to attend or perform age-appropriate activities
4 Moderate impairment	Impairments in memory or learning requiring substantial accommodation	Only able to communicate needs and wants, gestures, single words, or short phrases ("I want drink")	Moderately disabling seizures (able to attend some school/activities but with some accommodations)	Moderate disability, able to attend some school/community activities but may require accommodations and/or higher level of supervision	Motor impairments, can perform some ADLs but requiring assistance/accommodations	Significant disruption in sleep causing some impairment in ability to function in school or community
6 Mild impairment	Mild learning issues, below premorbid level of academic performance	Able to speak in full sentences with only mild word finding difficulty and/or immature speech	Free of most seizures (rare seizures that are not activity limiting) (i.e., can attend all school activities, with an occasional seizure that did not impact function)	Mild symptoms present but not impacting age-appropriate activities	Mild motor abnormalities present, but not impacting function of ADLs	Delayed sleep onset and/or frequent nighttime awakenings not impairing ability to function in school/community
8 Baseline	No cognitive deficits	No language deficits	No seizures	No psychiatric symptoms	No movement abnormalities (voluntary or involuntary)	No impairment

Abbreviation:
ADLs = Activities of daily living

the largest multi-institutional observational study to date, have used the modified Rankin Scale (mRS) to assign outcomes in *N*-methyl-D-aspartate autoimmune encephalitis as either "good outcome" or "complete recovery."[10,11] The Glasgow Outcome Scale has been used to assess outcomes in studies focusing on all causes of childhood encephalitis[12] as well as the correlation between antithyroid antibody titers and outcomes in adult patients with HE.[13] The Liverpool Outcome Score has been validated to evaluate outcomes in children with infectious encephalitis.[14] Although these scales may function well in other conditions, the multidomain manifestations of autoimmune encephalitis are difficult to fully capture with any one of these scales and complicate our ability to truly assess degrees of impairment or improvement across domains.[2] We aim to describe an example of a multidomain scale with the potential to assess impairment and response to therapy in children with autoimmune encephalitis.

Materials and Methods

Setting and participants

A total of 171 charts were reviewed from patients evaluated for autoimmune encephalopathies through the Duke University School of Medicine Autoimmune Brain Disease Program and/or the Duke Children's Hospital Pediatric Consultation Liaison Psychiatry team from 2014 to 2017. Patients were included in the study if they were aged 18 years or less at the time of onset of symptoms and were treated for HE based on the abrupt onset of neuropsychiatric symptoms in the presence of high titer of antithyroid antibodies after exclusion of alternative diagnoses.

Study design

Our study was a retrospective review using the Duke University Hospital electronic medical record. We collected demographic information for each patient, including gender and age in years at onset of illness. The time in months from onset of symptoms to diagnosis and initiation of definitive treatment was recorded for each patient. The presence or absence of various neuropsychiatric symptoms and paraclinical factors, including standard laboratory and imaging tests, was denoted for each patient.

To quantify the degree of impairment and response to treatment for this disease, we initially applied the mRS as well as the Liverpool Outcome Score[14] to each patient. We also created a multidomain scale to assess patients specifically along the six domains of cognition, language, seizure, psychiatric disturbance, movement disorder, and sleep disruption (Table 2). These domains represent the areas of impairment most commonly seen in our clinical practice with the pediatric autoimmune encephalitis population and are in alignment with those described in the existing literature on autoimmune encephalitis.[10] To quantify each patient's overall level of impairment we created the Global Functionality Score (Table 3), and to quantify each patient's response to immunomodulatory treatment we created the Global Improvement Score (Table 4). All three scales (mRS, Liverpool Outcome Score, and our multidomain scale) were applied to each patient at both the onset of symptoms as well as at their most recent follow-up evaluation at greater than or equal to one year after the initiation of immunotherapy with steroids, intravenous immunoglobulin, or other intravenous or oral immunomodulatory agents. The scales were applied to patients by a team of providers including a child neurologist, pediatric rheumatologist, and a child and adolescent psychiatrist.

TABLE 3
Global Functionality Score (To Be Applied at Any Point in Time)

8 Baseline	No Impairment
6 Mild impairment	Mild symptoms present but not impacting ability to participate in school/community activities or other age-appropriate activities
4 Moderate impairment	Able to attend some activities/school and participate with some assistance/supervision/accommodations
2 Severe impairment	Severe impairment, unable to attend school/community activities

Odd values (3, 5, and 7) can be given for improvement in functionality that does not meet the full criteria of the next anchored score.

Statistical methods

We recorded the data on symptoms at presentation and the application of the multidomain scales for our cohort of patients treated for HE. Patients were divided into groups based on whether they met the current diagnostic criteria[4] outlined in Table 1, with each patient ultimately falling into one of two categories: (1) HE, i.e., meeting full diagnostic criteria based on current guidelines as described in Table 1, including the presence of overt or subclinical thyroid disease, or (2) euthyroid HE, i.e., meeting all current criteria except the presence of overt or subclinical thyroid disease. Overt thyroid disease was defined as elevated or low T3, free T4, or the presence of a goiter; subclinical thyroid disease was defined as an elevated or low thyroid-stimulating hormone (TSH) level.

We report the demographics and baseline characteristics using descriptive statistics for the overall cohort and by subgroups defined as mentioned earlier in the article (HE versus euthyroid HE). Two-tailed Wilcoxon matched-paired signed ranked tests were used to compare the median scores on the Multi-Domain Assessment as well as the Global Functionality Score at onset versus time of follow-up within each subgroup. A Mann-Whitney test was used to compare the median scores on the Global Improvement Score for the six patients meeting full HE criteria (HE) against those for the 11 patients failing to meet full criteria based on the absence of overt or subclinical thyroid disease (euthyroid HE).

Results

Patient baseline characteristics are presented in Table 5. Six patients (two males, four females) met the full current criteria for HE (HE), whereas 11 (seven males, four females) failed to meet the full criteria solely due to the absence of thyroid disease (euthyroid HE). The average age of the onset of symptoms was 12.0 and 9.1, for those with HE versus euthyroid HE, respectively. One-third of the patients with HE had been diagnosed and/or treated for a neuropsychiatric disease before the onset of their symptoms associated with HE, whereas this number rose to just over half in the group of patients with euthyroid HE. On average, the patients with HE were

TABLE 4
Global Improvement Score (To Be Applied at Follow-up)

0 No Improvement	No Improvement
2 Mild improvement	Improvement in some functionality but still requiring substantial assistance, not able to return to most activities
4 Moderate improvement	Return to activities with some assistance
6 Substantial improvement	Not fully back to baseline but not requiring assistance
8 Baseline	Back to baseline

Odd values (1, 3, 5, and 7) can be given for improvement in functionality that does not meet the full criteria of the next anchored score.

TABLE 5
Patient Characteristics

Patient Characteristic	Patients Meeting Full Criteria for HE, Including Presence of Thyroid Disease, Designated as "HE" (n = 6)	Patients Failing to Meet Full Criteria for HE Due to Lack of Overt or Subclinical Thyroid Disease, Designated as "Euthyroid HE" (n = 11)
Male	2	7
Female	4	4
Mean (S.D.) age at onset (yr)	12.00 (2.83)	9.09 (3.83)
Number (%) with premorbid psychiatric disease	2/6 (33%)	6/11 (55%)
Mean (S.D.) time to diagnosis in months	11.67 (8.89)	21.00 (13.44)
Number (%) with moderate to severe impairment in cognition with deficits in ≥3 other domains	6/6 (100%)	11/11 (100%)
Number (%) with severe psychiatric impairment	4/6 (67%)	9/11 (82%)
Mean (S.D.) number of domains affected	4.83 (0.75)	5.36 (1.50)

Abbreviation:
HE = Hashimoto encephalopathy

diagnosed 11.7 months from onset of symptoms, whereas those with euthyroid HE took an average of 21.0 months to be diagnosed. Figure 1 describes the percentage of patients exhibiting specific neuropsychiatric symptoms at the time of onset of symptoms and before the initiation of treatment. Table 6 describes the prevalence rates of abnormalities on paraclinical laboratory test results and imaging parameters among patients with HE and euthyroid HE.

Table 7 provides the scores for the mRS, Liverpool Outcome Score, and our novel scale, at both onset of symptoms and most recent follow-up greater than or equal to one year after initiation of treatment. Previous studies have used the mRS to evaluate outcomes for patients with autoimmune encephalitis, with one study defining a "good outcome" as a score of 2 or above. The largest study using this definition with the mRS had only applied the scale at follow-up.[10] In our study we applied the mRS to patients at both time of onset of symptoms and at follow-up greater than or equal to one year after initiation of treatment. Thus, we applied the designation of "good outcome" only if patients had an mRS score of 3 or below at the time of onset, which then improved to 2 or above at follow-up. Using this method, five of six (83%) patients with HE had a good outcome following treatment, and nine of 11 (82%) patients with euthyroid HE had a good outcome. It should be noted that only six of the 17 total patients had an initial mRS score below 3. Three of six (50%) patients with HE had improvement in their Liverpool Outcome Score from onset of symptoms to most recent follow-up. Similarly, only six of the 11 (54%) patients with euthyroid HE had any improvement in their Liverpool Outcome Score from onset of symptoms to most recent follow-up; this may be attributed to the content validity of this scale, which is further addressed in the discussion.

Upon applying our novel scale we found statistically significant symptomatic improvement from the time of onset of symptoms to follow-up greater than or equal to one year across our patient cohort. Figure 2 demonstrates moderate to severe impairment at the onset of symptoms in the domains of cognition, language, psychiatric disturbance, and sleep for the six patients with HE; application of our scale also demonstrated statistically significant improvement following immunotherapy in their median score for cognition ($P = 0.03$). Figure 3 demonstrates that the group of 11 patients with euthyroid HE experienced moderate to severe impairment at onset of symptoms in the domains of cognition, language, and psychiatric disturbance. Application of our novel scale to the group of 11 patients with euthyroid HE also demonstrated statistically significant improvement following

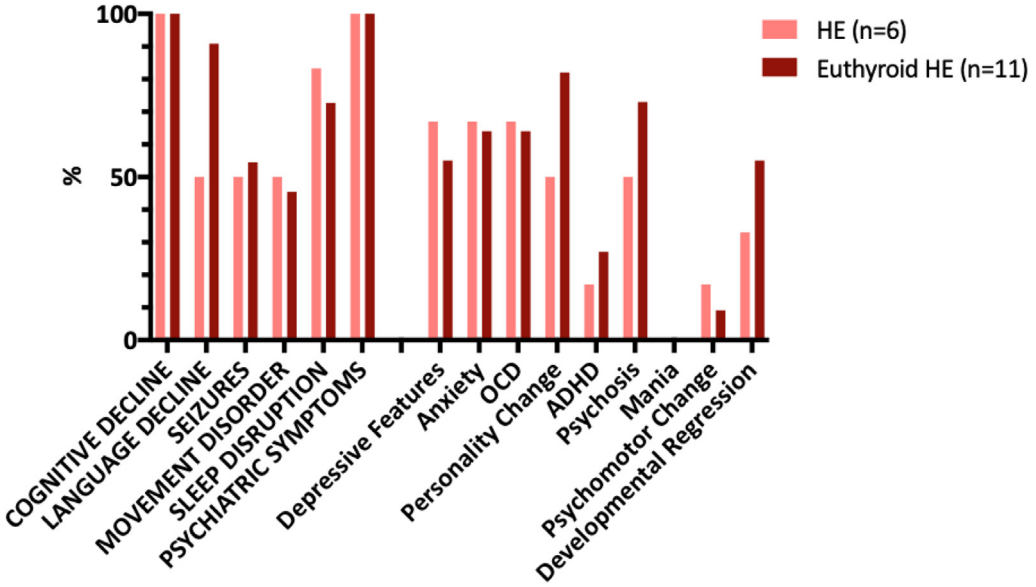

FIGURE 1. Percentage of patients presenting at onset of symptoms with neuropsychiatric symptoms, grouped by patients with HE (n = 6) and patients with euthyroid HE (n = 11). HE, Hashimoto encephalopathy. The color version of this figure is available in the online edition.

TABLE 6
Paraclinical Parameters Present, When Testing Was Performed, in Patients With HE (n = 6) and Euthyroid HE (n = 11)

Paraclinical Parameter	HE (n = 6)	Euthyroid HE (n = 11)
Anti-thyroid antibodies	6/6 (100%)	11/11 (100%)
Anti-TPO (microsomal) antibodies	5/6 (83%)	6/11 (55%)
Anti-thyroglobulin antibodies	4/6 (67%)	7/11 (64%)
Abnormal TSH or T3/T4	4/6 (67%)	0/11 (0%)
Enlarged thyroid	2/6 (33%)	0/11 (0%)
Anti-beta 2 glycoprotein antibodies	0 (0%)	2/10 (20%)
Low-titer ANA	3/6 (50%)	7/11 (64%)
High-titer ANA	1/4 (25%)	1/11 (9%)
Cardiolipin antibodies	0 (0%)	1/9 (11%)
Sm, RNP, Ro, La antibodies	0 (0%)	2/9 (22%)
Low C3/C4	1/4 (25%)	2/8 (25%)
Elevated IgG, IgM, IgA	0/3 (0%)	3/8 (38%)
vWF antigen	0/2 (0%)	2/8 (25%)
Mycoplasma IgM	1/2 (50%)	1/5 (20%)
Elevated ESR	2/6 (33%)	0/9 (0%)
Elevated CRP	0/5 (0%)	0/10 (0%)
CSF pleocytosis	2/6 (33%)	2/10 (20%)
CSF protein elevation	0/5 (0%)	2/10 (20%)
Oligoclonal bands	1/5 (20%)	1/7 (14%)
MRI abnormalities	2/6 (33%)	4/11 (36%)
EEG abnormalities (i.e., diffuse slowing, epileptic activity, etc.)	3/6 (50%)	5/10 (50%)
Vital sign abnormalities	0/6 (0%)	1/10 (10%)

Abbreviations:
ANA = Antinuclear antibody
CRP = C-reactive protein
CSF = Cerebrospinal fluid
EEG = Electroencephalography
ESR = Erythrocyte sedimentation rate
HE = Hashimoto encephalopathy
MRI = Magnetic resonance imaging
TPO = Thyroid peroxidase
TSH = Thyroid stimulating hormone
vWF = von Willebrand factor

immunotherapy for their median scores in the domains of cognition ($P = 0.004$), language ($P = 0.004$), psychiatric disturbance ($P = 0.006$), symptoms of movement disorder ($P = 0.02$), and sleep disruption ($P = 0.008$). Figure 4 demonstrates that both groups of patients, regardless of the presence or absence of thyroid disease, exhibited significant improvement on their Global Functionality Score from a median score of severe impairment to mild impairment following immunotherapy. The two groups did not differ significantly in their mean Global Improvement Score, with both groups exhibiting a median score between moderate and substantial improvement in functionality or quality of life (Figure 5).

Although we attempted to objectively quantify the response to treatment for this condition with the above-mentioned scales, we recognize that a narrative description of each patient's illness course may also augment providers' understanding of what to expect upon initiation of treatment. Appendix Table 1 provides a subjective description of each patient's course of treatment following diagnosis and initiation of immunomodulatory therapy.

Discussion

Based on the findings from previous analyses of case reports that the majority of pediatric patients with HE do not have evidence of thyroid disease, we sought to describe the thyroid status of our cohort of pediatric patients before receiving treatment for HE. The majority (11 of 17) of the children in our cohort did not demonstrate evidence of overt or mild thyroid disease (identified as euthyroid HE), but upon application of our multidomain assessment scale these patients were just as likely to respond to immunotherapy as patients presenting with thyroid disease (identified as HE). In addition, patients with HE can present with numerous neuropsychiatric symptoms beyond those included in the current diagnostic criteria (hallucinations, seizures, myoclonus, or stroke-like symptoms). Thus, rigidly applying the current diagnostic criteria to pediatric patients with suspected HE may result in the unintentional failure to treat potential responders. We propose a modified set of diagnostic criteria for HE in the pediatric population that includes (1) abrupt-onset cognitive regression with deficits in one or more other neuropsychiatric domain(s) and (2) the presence of high-titer antithyroid antibodies with or without clinical thyroid disease following exclusion of other alternative diagnoses.

We found that neither the mRS nor the Liverpool Outcome Scale captured the impairments and improvements that correlated with our subjective experience with this patient cohort,

TABLE 7
Scale Application Results

Patient	Global Functionality Score at Onset	Global Functionality Score at Follow-up	Liverpool at Onset	Liverpool at Follow-up	mRS at Onset	mRS at Follow-up
HE patient #						
1	2	4	2	2	4	3
2	4	5	2	2	3	2
3	2	8	3	4	4	0
4	2	7	2	5	4	1
5	4	7	3	5	3	1
6	2	6	2	2	3	1
Euthyroid HE patient #						
7	2	6	2	2	2	1
8	2	5	2	2	3	2
9	4	6	2	2	3	1
10	2	2	2	2	4	3
11	2	7	2	4	4	2
12	2	7	2	4	5	1
13	2	5	2	4	3	1
14	2	5	2	4	3	1
15	2	8	2	4	3	0
16	2	6	2	4	3	1
17	4	2	2	2	3	3

Abbreviations:
HE = Hashimoto encephalopathy
mRS = Modified Rankin Scale

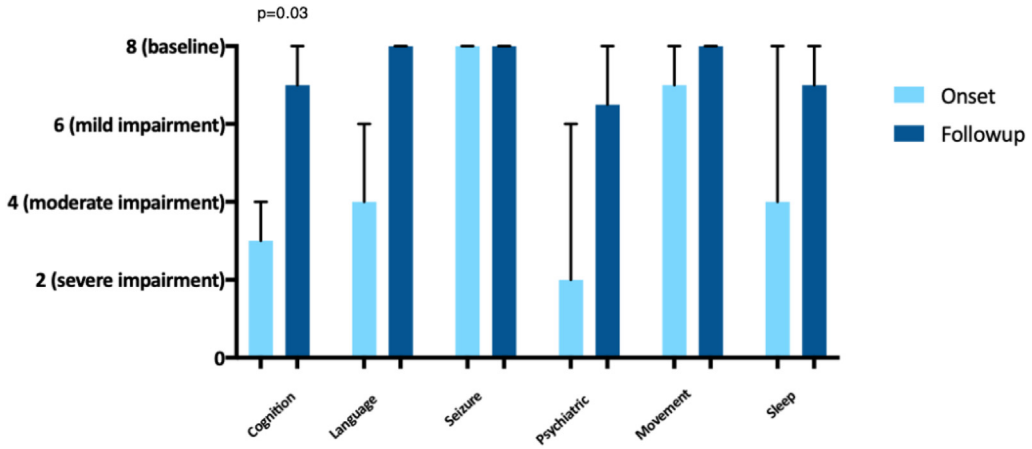

FIGURE 2. Median scale scores by neuropsychiatric domain at onset versus follow-up for patients with HE (n = 6). HE, Hashimoto encephalopathy. The color version of this figure is available in the online edition.

prompting us to question the content validity of these scales when applied to the population of children with suspected HE or the larger autoimmune encephalitis population in general. For example, many patients who were severely impaired by their psychiatric symptoms or seizures could not be given a score below 3 on the mRS because they retained their ability to walk. We feel the limited domains of the mRS may prohibit this scale from accurately measuring the impairment of patients with autoimmune encephalitis. Given the nuanced phenotypes evident across the spectrum of the autoimmune encephalitides, an outcome measure needs to include all the domains that can impact functionality. Similarly, the Liverpool Outcome Score, which requires each patient be given a final score based on the lowest score on any individual question did not capture the objective measurement of improvement. Half of the patients in our cohort were described as not having any improvement based on their scores on the Liverpool Outcome Score. These patients may not have had a change in their lowest score on any individual question between the onset of disease and their most recent follow-up, whereas many of them exhibited significant improvement in other domains as well as their overall functionality. In addition, the Liverpool Outcome Score includes several items assessing physical ability while only including one question assessing behavioral disruption. We feel this limits its ability to accurately assess functionality for children affected by a disease frequently characterized by prominent psychiatric manifestations. Our perception of low content validity when using the mRS or Liverpool Outcome Scale to assess HE in the pediatric population prompted us to develop our own multidomain assessment scale for use in this population.

In our clinical practice, we routinely assess patients across the key domains affected in autoimmune brain disorders and determine a functionality score at visits. Given the limitations of the current outcome measures, we constructed a multidomain assessment scale that allowed us to evaluate both the degree of impairment and response to treatment in our patient population presenting with possible HE. We believe this scale offers the ability to identify a degree of impairment in several different domains, in addition to overall functionality, at any point in time. Although it may be desirable to have a scale that is shorter in length for the sake of ease of application, we found that assessing each patient across all individual domains, in addition to overall functionality, allowed for a more nuanced and thus more accurate description of each patient's response to treatment. Our experience highlights the need for a formal process to develop and validate an outcome measure for patients with autoimmune encephalopathies, as this will be an invaluable addition to the field and future research.

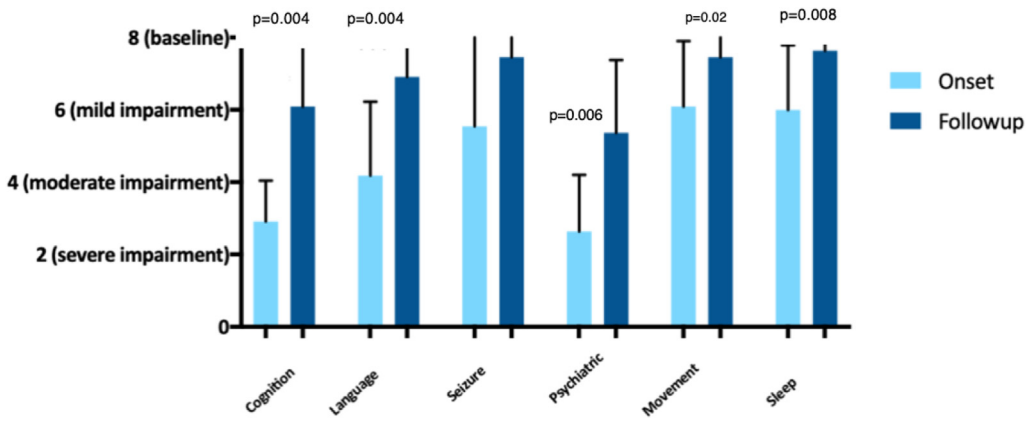

FIGURE 3. Median scale scores by neuropsychiatric domain at onset versus follow-up for patients with euthyroid HE (n = 11). HE, Hashimoto encephalopathy. The color version of this figure is available in the online edition.

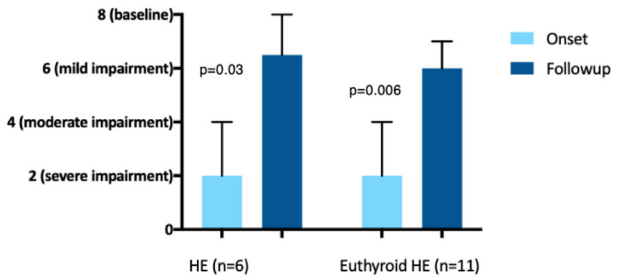

FIGURE 4. Median Global Functionality Score at onset versus follow-up. The color version of this figure is available in the online edition.

We acknowledge the presence of several limitations within our study, including the lack of quantified data on thyroid hormone levels or antibody titer levels. Given the retrospective nature of our study it was not possible to standardize the timing at which thyroid studies and antibody titers were obtained. In addition, given that patients may have had initial laboratory tests completed before arriving at our center, there was a lack of standardization across the units and reference ranges used for laboratory values, including thyroid studies and CSF analyses. In many cases it was impossible to know the exact antibody titer levels that were drawn at institutions in which patient's results were identified simply as "positive" or "negative." We therefore chose not to include data using exact laboratory values or multiple reference ranges, but to instead label patients as having either "normal" or "abnormal" values in relation to the standardized reference ranges provided by each institution's laboratory.

Only one patient in our study who was in the HE group had elevated T3 and T4 levels with a normal TSH. Although we recognize that there is potential for overlap between this patient's clinical presentation and sick euthyroid syndrome, in this study we determined that the abnormal TSH in the setting of elevated thyroid antibodies made true thyroid disease more likely and the placement in the HE group fitting.

Finally, we acknowledge the limitations of the retrospective nature of the application of all three scales based on electronic medical record review for our patients. In spite of this, we do believe that the application of this scale objectively captured the degree of impairment and evidence of improvement with therapy, which was comparable to our subjective experience with this cohort in our clinic. Likewise, we acknowledge the importance of validating our scale before applying it prospectively to eliminate the possibility of observer bias. Future efforts should be aimed at validating a scale for the pediatric autoimmune brain diseases population, as well as identifying positive and negative prognostic factors within this patient population.

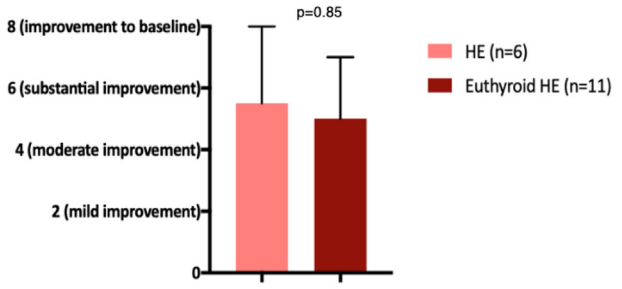

FIGURE 5. Median Global Improvement Score for patients with HE (n = 6) versus patients with euthyroid HE (n = 11). HE, Hashimoto encephalopathy. The color version of this figure is available in the online edition.

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Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pediatrneurol.2019.12.011.

References

1. Marshall GA, Doyle JJ. Long-term treatment of Hashimoto's encephalopathy. J Neuropsychiatry Clin Neurosci. 2006;18:14–20.
2. Mooneyham GC, Gallentine W, Van Mater H. Evaluation and management of autoimmune encephalitis: a clinical overview for the practicing child psychiatrist. Child Adolesc Psychiatr Clin N Am. 2018;27:37–52.
3. Zhou J, Xu B, Lopes J, et al. Hashimoto encephalopathy: literature review. Acta Neurol Scand. 2017;135:285–290.
4. Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol. 2016;15:391–404.
5. Laurent C, Capron J, Quillerou B, et al. Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT): characteristics, treatment and outcome in 251 cases from the literature. Autoimmun Rev. 2016;15:1129–1133.
6. Menon V, Subramanian K, Thamizh JS. Psychiatric presentations heralding Hashimoto's encephalopathy: a systematic review and analysis of cases reported in literature. J Neurosci Rural Pract. 2017;8:261–267.
7. Lee J, Yu HJ, Lee J. Hashimoto encephalopathy in pediatric patients: homogeneity in clinical presentation and heterogeneity in antibody titers. Brain Dev. 2018;40:42–48.
8. Yu HJ, Lee J, Seo DW, Lee M. Clinical manifestations and treatment response of steroid in pediatric Hashimoto encephalopathy. J Child Neurol. 2014;29:938–942.
9. Gulen GM, Horoz OO, Herguner MO, et al. Hashimoto's encephalopathy: four cases and review of literature. Int J Neurosci. 2014;124:302–306.
10. Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 2013;12:157–165.
11. Zekeridou A, Karantoni E, Viaccoz A, et al. Treatment and outcome of children and adolescents with N-methyl-d-aspartate receptor encephalitis. J Neurol. 2015;262:1859–1866.
12. Wong AM, Lin J, Toh C, et al. Childhood encephalitis: relationship between diffusion abnormalities and clinical outcome. Neuroradiology. 2015;57:55–62.
13. Litmeier S, Prüss H, Witsch E, Witsch J. Initial serum thyroid peroxidase antibodies and long-term outcomes in SREAT. Acta Neurol Scand. 2016;134:452–457.
14. Lewthwaite P, Begum A, Ooi MH, et al. Disability after encephalitis: development and validation of a new outcome score. Bull World Health Organ. 2010;88:584–592.