Published Ahead of Print on December 27, 2019 as 10.1212/WNL.0000000000008785

ARTICLE

Hashimoto encephalopathy in the 21st century

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Neurology® 2020;94:e1-e8. doi:10.1212/WNL.0000000000008785

Abstract

Objective

To report the presenting syndromes and to determine whether pretreatment criteria of Hashimoto encephalopathy (HE) predict response to steroids.

Methods

We assessed symptoms and steroid responsiveness in 24 patients with pretreatment criteria of HE, including (1) subacute onset of cognitive impairment, psychiatric symptoms, or seizures; (2) euthyroid status or mild hypothyroidism; (3) serum thyroid peroxidase antibodies (TPOAb) >200 IU/mL; (4) absent neuronal antibodies in serum/CSF; and (5) no other etiologies. Additional studies included determination of TPOAb (>200 IU/mL) in 74 patients with criteria of possible autoimmune encephalitis (AE) without neuronal antibodies and 205 patients with different neuroimmunologic diseases, psychosis, or new-onset refractory status epilepticus (NORSE). Serum antibodies to the amino (NH_2)-terminal of α-enolase (NH2-α-enolaseAb) were examined in the indicated 24 patients and 13 controls.

Results

The 24 patients (14 women) with suspected HE had a median age of 48 years (range 8–79 years). Four syndromes were identified: psychiatric (7, 29%), encephalopathy (7, 29%), NORSE-like (6, 25%), and limbic encephalitis (4, 17%). Only 6 of 19 (31.6%) patients completely responded to steroids. The frequency of TPOAb in the 74 patients with possible AE (6 of 74, 8.1%) was similar to that of the 205 controls (17 of 205, 8.2%; $p = 0.84$). NH2-α-enolaseAb were identified in 1 of 24 suspected HE cases and 1 of 13 controls.

Conclusion

Current pretreatment criteria of HE do not predict steroid responsiveness. The detection of TPOAb across all control groups reveals their poor disease-specificity. NH2-α-enolaseAb did not help in the diagnosis of HE. These findings imply a redefinition of HE that requires a systematic exclusion of antibody-mediated encephalitis.

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Glossary

AE = autoimmune encephalitis; **HE** = Hashimoto encephalopathy; **IVIG** = IV immunoglobulin; **LE** = limbic encephalitis; **NORSE** = new-onset refractory status epilepticus; **TPOAb** = thyroid peroxidase antibodies.

The diagnosis of Hashimoto encephalopathy (HE) is usually considered in patients with a wide range of neurologic symptoms accompanied by normal or nonspecific MRI and CSF findings, normal thyroid function or mild hypothyroidism, increased serum levels of thyroid peroxidase antibodies (TPOAb), and clinical response to steroids.[1] The beneficial effect of steroids was emphasized by renaming the disease steroid-responsive encephalopathy associated with autoimmune thyroiditis.[2] The most frequent presentation includes subacute cognitive deterioration, sometimes with stroke-like symptoms, myoclonus, change in behavior, or seizures.[3] Less frequently, the term HE is used to designate patients with isolated cerebellar ataxia, psychosis, or status epilepticus.[4–6] Prompt recognition of HE is important because, although the pathogenesis is unknown, the disorder is treatable. However, the diagnosis of HE has several important limitations. One is that there are no specific biomarkers of the disease. For example, 13% of healthy persons harbor TPOAb; therefore, the specificity of these antibodies is poor.[7] Moreover, the significance of antibodies against the amino (NH2)- terminal of α-enolase (considered a potential biomarker of HE) is unclear.[8,9] Another limitation is that the diagnostic confirmation depends on steroid responsiveness. Consequently, the frequency of TPOAb-associated syndromes that are identical to HE presentations but unresponsive to steroids is unknown. Finally, most patients previously reported with HE were not systematically investigated for neuronal surface antibodies.[10] This is a critical confounding factor because HE was described many years before the encephalitides associated with neuronal surface antibodies that, in contrast to TPOAb, are pathogenic, are more disease specific, and occur with steroid-responsive syndromes.[11,12] Here, we report the main neurologic syndromes and response to steroids in a series of 24 patients with pretreatment clinical criteria of HE.

Methods

Patients

We retrospectively selected 117 patients from our database whose serum and CSF samples were referred for neural antibody studies between January 1, 2011, and November 31, 2018. Forty-three patients were selected because the referring neurologists considered HE the most probable diagnosis and our preliminary studies did not identify antineuronal antibodies in serum or CSF. In addition, we randomly selected 74 patients whose serum and CSF were negative for neural antibodies but who had criteria of possible autoimmune encephalitis (AE) as previously described: (1) subacute onset, <3 months, of memory deficits or altered mental status; (2) at least 1 of the following features: new focal CNS findings, seizures, CSF pleocytosis, or MRI features suggesting encephalitis; and (3) exclusion of other etiologies.[12] TPOAb were measured in all 117 patients, leading to the identification of 24 with high serum levels of TPOAb (>200 IU/mL) who were further evaluated because they fulfilled the following criteria of possible HE before treatment with steroids (slightly modified from reference 2): (1) subacute onset of cognitive impairment, psychiatric symptoms, or seizures; (2) euthyroid status or mild clinical or subclinical hypothyroidism; (3) high serum TPOAb >200 IU/mL; (4) absent neuronal antibodies in serum and CSF; and (5) no evidence of infectious, toxic, metabolic, vascular, or tumoral causes that could explain the symptoms (figure 1). Referring neurologists of patients who fulfilled these criteria were contacted for additional clinical information.

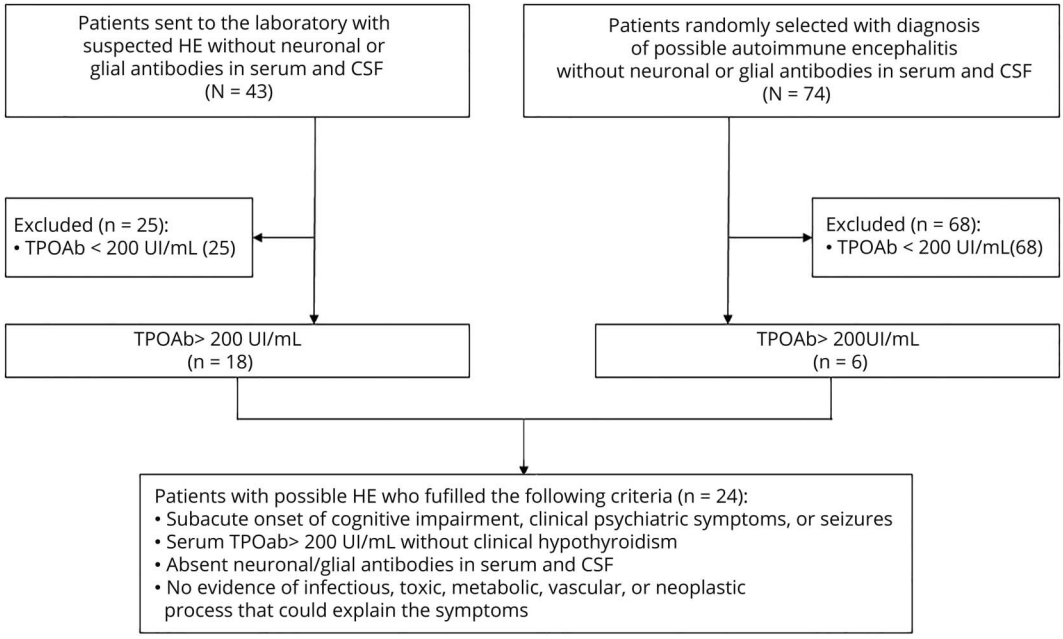
As controls, we included 205 patients with known diseases: 48 with AE associated with NMDAR, LGI1, CASPR2, or GABAaR antibodies and matched for age and sex with the 24 patients with suspected HE, 49 with neuromyelitis optica spectrum disorder and AQP4 antibodies, 50 with multiple sclerosis, 42 with a first psychotic episode, and 16 with cryptogenic new onset refractory status epilepticus (NORSE). Similar to the indicated 117 patients who fulfilled the criteria of possible AE or were suspected to have HE, these 205 control patients were tested for TPOAb as part of the current study.

Immunologic studies

Serum TPOAb were determined by chemiluminescent direct immunoassay with the ADVIA Centaur automated analyzer (Siemens Healthineers, Tarrytown, NY) according to the manufacturer's instructions (normal <28 IU/mL). All serum and CSF samples from the 24 patients with elevated TPOAb were examined for the presence of onconeural (Hu, Yo, Ri, CRMP5, amphiphysin, Ma2, Tr), GAD, AK5, and neuropil antibodies (NMDAR, AMPAR, $GABA_BR$, neurexin 3α, IgLON5, CASPR2, LGI1, DPPX, AQP4, mGluR1, and mGluR5) with immunohistochemistry on frozen sections of paraformaldehyde-perfused or postfixed rat brain as reported elsewhere.[13,14] Samples showing tissue immunoreactivity were further examined with immunoblot (Euroimmun, Lübeck, Germany) or cell-based assays using HEK293 cells transfected with the appropriate plasmids.[15] All samples were examined for GlyR, MOG, dopamine 2R, and GFAP antibodies by cell-based assays as reported previously.[16,17]

Rat hippocampal neuronal cultures were prepared as reported.[18] Fourteen-day-live neurons grown on coverslips were treated for 1 hour at 37°C with patients' or control serum (final dilution 1:200) or CSF (1:5). After removal of the media and extensive washing with PBS, neurons were fixed

Figure 1 Flowchart identifying the 24 patients with suspected HE



HE = Hashimoto encephalopathy; TPOAb = thyroid peroxidase antibodies.

with 4% PFA and incubated with anti-human immunoglobulin G (diluted 1:1000) Alexa Fluor secondary antibody (Molecular Probes, Eugene, OR). Results were photographed under a fluorescence microscope with Zeiss Axiovision software (Zeiss, Thornwood, NY).[19]

Antibodies against α-enolase were detected by immunoblot of HEK293 cells transfected with the antigen.[9] Briefly, the human full-length α-enolase-1 plasmid (RC205494; Origene, Rockville, MD) or the amino (NH2)-terminal region of α-enolase-1 (generated by Dr. Carolis, Centre for Genomic Regulation, Barcelona, Spain; Uniprot accession number P06733; amino acids 1–157) was transfected to HEK293 cells. A lysate of transfected HEK293 cells was run (10 μg/well) in a 4% to 12% BisTris electrophoresis gel (NP03222 NuPage; Thermo Fisher Scientific, Waltham, MA) and transferred into a nitrocellulose membrane (1704158; Bio-Rad, Hercules, CA). Strips were sequentially incubated with commercial anti–α-enolase rabbit antibody (1:1000; Abcam, Cambridge, UK) or sera of the patients (1:500) overnight, secondary peroxidase-conjugated antibodies against human (1:1000) (Jackson Inmunoresearch, West Grove, PA), or rabbit immunoglobulin G (1:1000) (NA934V; GE HealthCare, Buckinghamshire, UK) for 1 hour and read by chemiluminiscence with an ImageQuant LAS 4000 imager (GE Healthcare).

Standard protocol approvals, registrations, and patient consents

The Ethics Committees of the Hospital Clinic and University of Pennsylvania approved the study. All patients or proxies gave written informed consent for the storage and use of serum, CSF, and clinical information for research purposes. Serum and CSF samples were deposited in the collection of biological samples called Neuroinmunología registered in the biobank of Institut d' Investigació Biomèdica August Pi i Sunyer, Barcelona, Spain.

Statistics

We used the Fisher exact test or Pearson χ^2, as appropriate, to analyze the demographic and clinical features between the 24 patients with high serum anti-TPOAb titer and to compare the frequency of high TPOAb between patients with possible AE and controls. We used Stata version 14.2 (StataCorp, College Station, TX) for the statistical analysis.

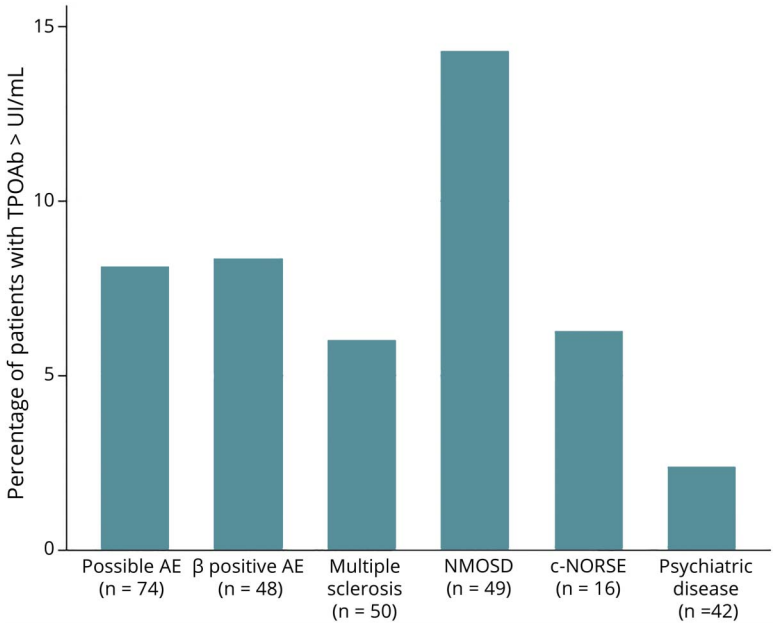
Data availability

Data from patients reported within the article are available and will be shared anonymously by request from any qualified investigator.

Results

Twenty-four patients were found to have TPOAb >200 IU/mL; these included 18 from the group of 43 patients previously suspected to have HE and 6 of 74 with possible AE (not previously suspected HE) (figure 1). The frequency of high TPOAb (6 of 74, 8.1%) in the latter group was similar to that of the control groups (17 of 205, 8.2%; $p = 0.84$) (figure 2). These findings did not change if, instead of high-titer TPOAb (>200 IU/mL), we used a clinical laboratory cutoff threshold for positivity (28 IU/mL) or >1,000 IU/mL (data not shown).

Figure 2 Frequency of high serum TPOAb levels (>200 IU/mL) was similar in patients with AE without neuronal antibodies and control groups

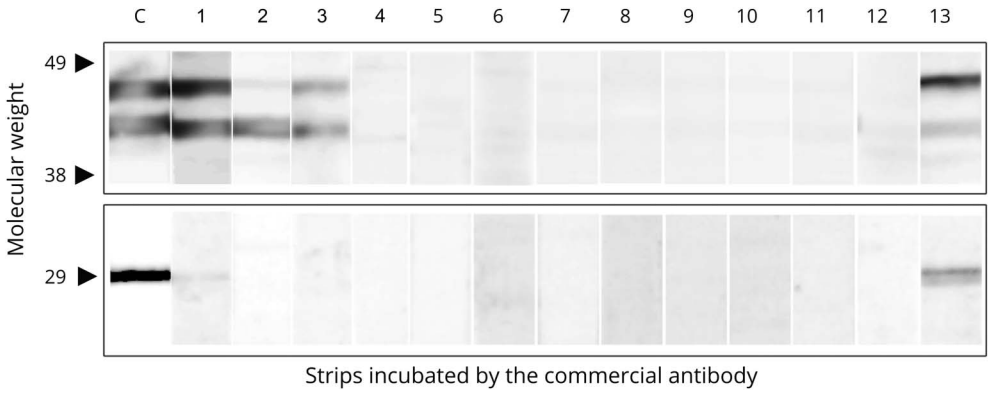


AE = autoimmune encephalitis; c-NORSE = cryptogenic new-onset refractory status epilepticus; NMOSD = neuromyelitis optic spectrum disorder; TPOAb = thyroid peroxidase antibodies.

Overall, the 24 patients (14 women) with high TPOAb had a median age of 48 years (range 8–79 years). All fulfilled the indicated criteria of HE (methods). Comorbid conditions were found in 4 of 24 patients, including vitiligo, skin and bladder cancer, and hypernephroma. Mild clinical or subclinical hypothyroidism was detected in 6 of 22 (27%) patients (no serum was available from 2 patients to repeat thyroid function tests). Immunologic studies confirmed the absence of neuronal or glial antibodies, and none had novel antibody reactivity with cultured live neurons. Antibodies against full-length α-enolase were identified in 3 of 24 patients with suspected HE, and one of those patients also reacted to the NH2-terminal domain. Antibodies against the NH2-terminal domain were also identified in 1 of 13 patients with other encephalitis and known antibodies against neuronal surface antigens used as the group control (figure 3).

In these 24 patients, the median duration of symptoms was 19 days (range 1–89 days). Four different clinical syndromes were identified (table). Seven patients, median age of 40

Figure 3 Detection of α-enolase antibodies



Detection of α-enolase antibodies by immunoblot of HEK293 cells transfected with the full-length α-enolase (top) or the amino (NH2)-terminal protein fragment (bottom). From left to right, strips incubated by the commercial antibody against α-enolase (C), sera from patients with Hashimoto encephalopathy (1–12), normal human serum (13), and serum from a patient with anti-LGI1 encephalitis (14). Sera 1 through 3 and 14 immunoreact with the full-length α-enolase; sera 1 (weak reactivity) and 14 also immunoreact with the NH2-terminal protein fragment. Molecular weight is indicated by arrows. Note that alternative splicing of full-length α-enolase gene produces 2 different proteins that are recognized by the commercial antibody and the positive samples.[31]

Table Demographic and clinical description of 24 patients with a diagnosis of HE

Clinical syndrome	Psychiatric (n = 7)	Possible AE (n = 7)	NORSE (n = 6)	LE (n = 4)
Median age (range), y, No. female	40 (8–71), 6 F	70 (35–79), 3 F	24 (11–53), 3 F	51 (28–61), 2 F
Main clinical features at presentation (n)	Acute episode of psychosis (6) with visual (3) or auditory hallucinations (2); 2 patients with chronic history of psychiatric disorder Acute episode of tics, obsessive-compulsive behaviour, and myoclonic jerks (1)	Subacute (in weeks) cognitive impairment (3) with rigidity and myoclonus Acute (days) decreased level of consciousness (3) with auditory hallucinations and seizures Cognitive deterioration in months with episodes of confusion and behavior changes lasting 4–6 h (1)	Status epilepticus with generalized tonic-clonic seizures	Memory deficit (4), decreased level of consciousness, seizures (3), psychosis (2), speech deficit (1)
Brain MRI	Normal or nonspecific	Normal or nonspecific (6); hyperintense lesion in left hippocampus (1)	Increased signal in medial temporal lobes (2)	Increased signal in medial temporal lobes
EEG	Generalized slowing (2), spike-wave complex (1)	Generalized or focal slowing	Continuous generalized epileptic activity	Generalized slowing
CSF pleocytosis, n	0	1	2	3
Treatment with steroids, n	5	4	6	4
Relapses, n	0	2	3	3
Complete recovery after treatment with steroids, n	3[a]	1	2	0

Abbreviations: AE = autoimmune encephalitis; HE = Hashimoto encephalopathy; LE = limbic encephalitis; NORSE = new onset refractory status epilepticus.
[a] One additional patient did not respond to steroids but completely recovered with antipsychotic medication.

years (range 8–71 years), 6 female, presented with a predominant psychiatric syndrome. Six of them were admitted to psychiatric wards for rapidly evolving psychotic features, including delusions, behavioral changes, and visual (3 patients) or auditory (2 patients) hallucinations. Two of these 6 patients had a history of chronic psychosis treated with antipsychotic medication. The remaining patient was admitted for an acute episode of tics, obsessive-compulsive behavior, and myoclonic jerks. None of these 7 patients had a decreased level of consciousness, aphasia, short-term memory loss, or focal neurologic deficits. Brain MRI and CSF studies were normal. Treatment and outcome information was available for 5 patients who were treated with corticosteroids alone or in association with IV immunoglobulins (IVIGs) (1 patient). Three of them responded well to these treatments and were asymptomatic at the last visit; 1 patient did not respond to the steroid therapy but completely recovered with the antipsychotic therapy.

Seven patients, median age of 70 years (range 35–79 years), 3 female, presented with symptoms of encephalopathy. Three patients had subacute (in weeks) cognitive impairment with rigidity and myoclonus; another 3 patients had an acute (days) decrease of the level of consciousness associated with orofacial dyskinesias, auditory hallucinations, or seizures. The remaining patient developed a rapidly evolving dementia (months) with repetitive episodes of confusion and abnormal behavior that lasted 4 to 6 hours. Brain MRI was normal in 6 patients and showed a unilateral hyperintense lesion in the left hippocampus in 1 patient. CSF analysis showed mild pleocytosis in only 1 patient, and EEG disclosed generalized or focal slow rhythmic activity in all patients. On the basis of clinical and ancillary tests results, only the patient with pleocytosis and abnormal MRI fulfilled the criteria of probable seronegative AE.[12] Two patients had a clinical relapse. Follow-up was available for 6 patients; 4 received steroids, and only 1 made a complete recovery. Of the remaining 2 patients, 1 patient was treated with antipsychotics and antiepileptics (without immunotherapy) with partial recovery, and 1 treated with IVIG had transient improvement followed by unresponsive catatonic-like features.

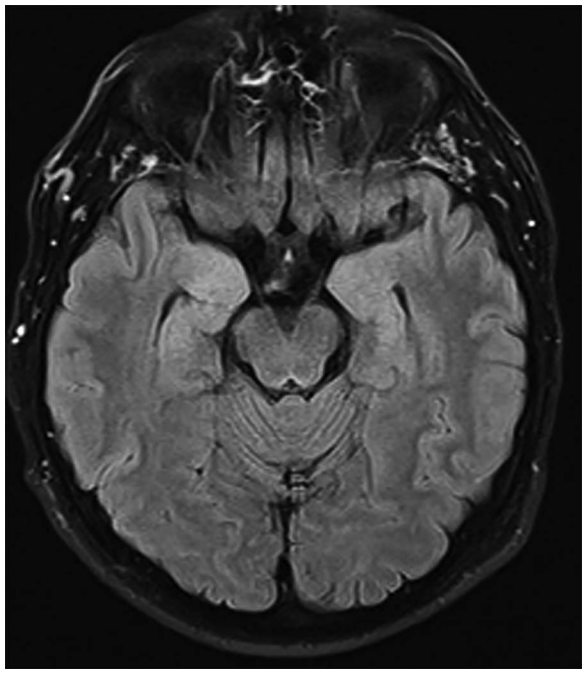
Six patients, median age of 24 years (range 11–53 years), 3 female, presented with NORSE. In 2 patients, the brain MRI obtained several days after being in status epilepticus showed increased T2 fluid-attenuated inversion recovery signal abnormalities in medial temporal lobes that were attributed to the seizures[20]; in the other 4 patients, the MRI was normal. CSF showed pleocytosis in 2 patients. All

patients received multiple antiepileptic drugs and were additionally treated with corticosteroids; 3 patients had relapses. At the last follow-up, only 2 of the 6 patients had complete recovery.

Four patients, median age 51 years (range 28–61 years), fulfilled the criteria of limbic encephalitis (LE).[12] They presented with subacute onset of memory deficits associated with decreased level of consciousness (3 patients), seizures (3), and behavioral changes (2). MRI studies of all 4 patients showed bilateral T2 fluid-attenuated inversion recovery hyperintense abnormalities in the amygdala and hippocampus (figure 4). Three patients had CSF pleocytosis. All patients were treated with steroids in addition to other therapies (antiepileptics, acyclovir, cyclophosphamide, IVIG, plasma exchange, or tacrolimus). All patients partially improved; 3 had relapses; but none had a complete recovery at the last visit (median follow-up 17 months, range 12–22 months).

Considering the entire series of 24 patients, information on response to therapy and outcome was missing in 3 patients (2 with isolated psychosis and 1 with encephalopathy). At the last follow-up, only 6 of 19 (31.6%) patients who received steroids had complete recovery. Eight additional patients improved but did not return to their premorbid status, and the remaining 5 did not improve. The steroid treatment delay from symptom onset was >1 month for 3 of the 5 patients who did not improve and <1 month for 13 of 14 patients who had partial or complete recovery ($p = 0.04$).

Figure 4 Fluid-attenuated inversion recovery MRI



Fluid-attenuated inversion recovery MRI showing high signal intensity in both hippocampi compatible with the diagnosis of limbic encephalitis.

Discussion

In this study, we show that only 31% of patients with suspected HE showed complete clinical response to steroids. These patients were otherwise similar to those who did not respond to steroids; therefore, it is impossible to distinguish them before treatment. In previous studies using similar criteria, only 20 of 36 (56%) and 4 of 11 (36%) patients with suspected HE responded to steroids.[2,21] Taken together, these data indicate that there are no good predictors of treatment response, and current criteria of HE are unable to discriminate between this disorder (which by definition responds to corticosteroids) and other conditions. For example, a previous study showed that among 12 patients who failed to respond to steroids, 4 had at autopsy findings of prion or neurodegenerative diseases.[2]

HE is usually suspected in adult patients, predominantly women, with subacute or fluctuating cognitive impairment, behavioral change, and decreased level of consciousness.[22,23] This clinical presentation occurred in 11 (46%) of our patients, and 4 of them fulfilled the criteria of LE. The association of high serum TPOAb with LE without neuronal antibodies was first described in 3 children and later in 14 adult patients.[24,25] Together with our 4 cases (n = 21), the frequency (52%) of female sex was lower than that in patients with HE without criteria of LE; relapses occurred in 48%; and despite treatment with steroids and other immunotherapies, only 33% achieved complete recovery, which is similar to the outcome reported in seronegative LE (negative for both neuronal antibodies and TPOAb).[26]

In the current series, we identified 7 (29%) patients who presented with isolated psychiatric syndromes and 6 (25%) with a clinical picture resembling NORSE (table). Whether these 2 clinical presentations should be considered within the clinical spectrum of HE is a matter of debate. In a review of 251 patients with HE who responded to steroids, 10% presented with isolated psychiatric symptoms. However, most of these 251 patients (≈80%) were not tested for neuronal surface antibodies, and therefore, the diagnosis of HE is questionable.[10,27] Our patients with isolated psychiatric presentation were remarkable because none developed neurologic symptoms, and in 4, the EEG was normal. We acknowledge that without cognitive decline or decreased level of consciousness, which are required by some criteria of HE,[2,22] detection of TPOAb is not sufficient for the diagnosis of this disorder or the initiation of steroids. The findings, however, point to important caveats and pitfalls in the diagnosis of HE. Moreover, the assessment of steroid treatment in these patients is complicated by the concomitant use of antipsychotic therapy, which can also contribute to clinical improvement.

Similar considerations are applicable to patients who present with status epilepticus and clinical features of NORSE. Status

epilepticus has been reported in 12% of patients with HE but almost always in association with other neurologic deficits.[22] Predictive models of response to immunotherapy in epilepsy suggest that patients with isolated epilepsy without clinical, MRI, and CSF features of encephalitis who are negative for neuronal surface antibodies are unlikely to respond to treatment.[28] In this scenario, the detection of serum TPOAb, as the only abnormal finding, is associated with a similar low probability of response to steroids.

We found that all control groups used in the study (neuronal antibody–positive AE, multiple sclerosis, neuromyelitis optic spectrum disorder, among others) had a similar proportion of patients with high serum levels TPOAb. This occurred despite the use of a threshold of TPOAb positivity that was 10 times higher than that used in clinical laboratories, raising concern for considering TPOAb as reliable biomarkers of HE, particularly in patients with encephalopathy of unknown etiology and negative neuronal antibodies. Indeed, the encephalopathy currently considered HE might very well represent not 1 single entity but a heterogeneous group of disorders with several yet unknown pathogenic mechanisms. For example, it is potentially plausible that the high serum levels of TPOAb reflect a subclinical autoimmune thyroiditis and that the associated neurologic syndrome is due to a completely unrelated etiology.

Antibodies against the amino (NH2)-terminal domain of α-enolase have been proposed as more reliable markers of HE. However, these antibodies have been described in only a few reports, showing that 17 of 25 (68%) patients with HE were positive compared with 2 of 17 (12%) patients with thyroiditis and 0 of 25 (0%) controls.[8,9] Moreover, these antibodies were identified in a patient with Creutzfeldt-Jakob disease and in patients with LE and neuronal antibodies, casting doubt on the HE specificity.[25,29] Our experience in the current study indicates that NH2-α-enolase antibodies are not reliable biomarkers of HE.

After the application of the most frequently used criteria of HE and exclusion of alternative etiologies (e.g., neuronal surface antibodies), the findings of our study challenge the concept of HE. All pretreatment features usually considered in this disorder (encephalopathy, elevated levels of TPOAb, nonspecific MRI, EEG, or CSF findings) are not specific and do not help to predict whether patients will respond to steroids. The indicated clinical features of those who respond to steroids are similar to those of individuals who do not. For example, in patients with LE and TPOAb, the chance of steroid responsiveness is similar to that of patients without TPOAb. Considering the poor disease specificity of TPOAb, it is inaccurate to consider that patients with isolated epilepsy or cerebellar symptoms in association with these antibodies have HE; for these syndromes, other predictive models are better for assessing the potential response to immunotherapy.[28,30]

Future studies in patients with neuronal antibody-negative encephalopathies but with TPOAb should focus on determining more useful clinical and laboratory predictors of steroid responsiveness. This is a difficult task because, without a specific biomarker, a distinctive syndrome, or characteristic neuropathologic findings, the definition of a disease is barely sustainable, as shown here for HE.

Acknowledgment

The authors thank Drs. Eric Lancaster (University of Pennsylvania), Daniela Pohl (Children's Hospital of Eastern Ontario, Ottawa, Canada), Alejandra Guerrero (Universidad CES, Medellín, Colombia), and Renan Perez (Centro Médico Nacional Siglo XX1, México DF, México) for providing useful clinical information and Dr. Carlo Carolis and the Biomolecular Screening and Protein Technologies Unit at CRG (Centre for Genomic Regulation, Barcelona, Spain) for providing the plasmid of the NH2 amino-terminal of α-enolase.

Study funding

This study was supported in part by Fondo de Investigaciones Sanitarias, FEDER, Spain (FIS 15/00377, F.G.; FIS 14/00203, J.D.; FIS 18/00067 L.S.), NIH RO1NS077851 (J.D.), Fundació Cellex (J.D.), and a research grant provided by Pratima Naithani for the study of HE.

Disclosure

S. Mattozzi, I. Sabater, D. Escudero, H. Ariño, T. Armangue, M. Simabukuro, T. Iizuka, M. Hara, A. Saiz, and S. Sotgiu report no disclosures relevant to the manuscript. J. Dalmau receives royalties from Athena Diagnostics for the use of Ma2 as an autoantibody test and from Euroimmun for the use of NMDA, GABAB receptor, GABAA receptor, DPPX, and IgLON5 as autoantibody tests. F. Graus received a licensing fee from Euroimmun for the use of IgLON5 as an autoantibody test and honoraria from MedLink Neurology. Go to Neurology.org/N for full disclosures.

Publication history

Received by *Neurology* April 29, 2019. Accepted in final form August 2, 2019.

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Lidia Sabater, PhD	Institut d'Investigació Biomèdica August Pi i Sunyer, Barcelona, Spain	Author	Established the assay for enolase antibodies; analysis and interpretation of the data; revised the manuscript for intellectual content

Continued

Appendix *(continued)*

Name	Location	Role	Contribution
Domingo Escudero, MD, PhD	Hospital Clínic, Barcelona, Spain	Author	Acquisition of clinical data; analysis and interpretation of the data; revised the manuscript for intellectual content
Helena Ariño, MD, PhD	Hospital Clínic, Barcelona, Spain	Author	Determination of neuronal antibodies; analysis and interpretation of the data; revised the manuscript for intellectual content
Thais Armangue, MD, PhD	Institut d'Investigació Biomèdica August Pi i Sunyer, Barcelona, Spain	Author	Determination of neuronal antibodies; analysis and interpretation of the data; revised the manuscript for intellectual content
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Stefano Sotgiu, MD	University of Sassari, Italy	Author	Review of clinical data; analysis and interpretation of the data; revised the manuscript for intellectual content
Josep Dalmau, MD, PhD	Hospital Clínic, ICREA, Barcelona, Spain; University of Pennsylvania, Philadelphia	Author	Design and conceptualized study; review of clinical data; analysis and interpretation of the data; revised the manuscript for intellectual content
Francesc Graus, MD, PhD	Institut d'Investigació Biomèdica August Pi i Sunyer, Barcelona, Spain	Author	Design and conceptualized study; review of clinical data; analysis and interpretation of the data; revised the manuscript for intellectual content; wrote the final version

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