Review Article

Autoantibody-Mediated Encephalitis

Differential Diagnosis in Patients With Impaired Consciousness of Unclear Origin

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Summary

Background: Acute and subacute disturbances of wakefulness and cognitive function are common neurological manifestations in the hospital and in outpatient care. An important element of the differential diagnosis was described only a few years ago: autoimmune encephalitis, a condition whose diagnosis and treatment pose an interdisciplinary challenge.

Methods: This review is based on pertinent publications from the years 2005–2017 that were retrieved by a selective search in PubMed, and on the authors' personal experience and case reports.

Results: The incidence of autoimmune encephalitis in Germany is estimated at 8–15 cases per million persons per year. In some patients with psychotic manifestations or impaired consciousness of acute or subacute onset, an autoimmune pathogenesis can be demonstrated by the laboratory detection of autoantibodies against neuronal target antigens (e.g., glutamate receptors). Testing of this type should be performed in patients with inflammatory changes in the cerebrospinal fluid or on magnetic resonance imaging (MRI), or those who have had an otherwise unexplained first epileptic seizure or status epilepticus. The cumulative sensitivity of testing for all potentially causative antineuronal antibodies in patients with clinically defined autoimmune encephalitis is estimated at 60–80%. Figures on cumulative specificity are currently unavailable.

Conclusion: The detection of antineuronal antibodies in patients with the corresponding appropriate symptoms implies the diagnosis of autoimmune encephalitis. Observational studies have shown that rapidly initiated immunosuppressive treatment improves these patients' outcomes. Further studies are needed to determine the positive predictive value of antineuronal antibody detection and to develop further treatment options under randomized and controlled conditions.

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Acute or subacute disorders of wakefulness (quantitative impairment of consciousness, ICD-10 R40.-) and qualitative impairment of consciousness (confusion, impaired orientation, amnesia syndromes; ICD-10 R41.-) are frequently occurring causes of hospitalization. In a large neurological emergency department, quantitative disorders of consciousness were the cardinal symptom in every fifth patient seen (reduced vigilance 9%, epileptic seizures 11%) (1). Around 20 to 30% of all hospital inpatients, 50% of elderly patients, and up to 70% of intensive care patients suffer from delirium, i.e., acute deterioration of alertness, organized cognition, memory, attentiveness, and perception (2, e1–e3). Particularly with delirium syndromes the causes are unclear and the treatment principally comprises supportive measures, e.g., management of systemic infections or electrolyte shifts (3).

Recently an additional differential diagnosis has been described, namely a group of previously unknown immune-mediated forms of encephalitis with

autoantibodies against neuronal antigens (4). These diseases are rare, but can be clearly delineated from noninflammatory causes with the aid of a rigorous diagnostic work-up for antibodies. Their detection and diagnosis is of great importance, as immune therapy is a causal, frequently successful form of treatment (5). Owing to the wide heterogeneity of immune-mediated forms of encephalitis, these diseases demand close interdisciplinary cooperation on the part of neurologists, intensive care specialists, oncologists, pediatricians, gynecologists, and psychiatrists (*eBoxes 2 and 3*).

The aim of this review is to impart basic familiarity with autoimmune encephalitis and the diagnostic options for this group of diseases. The following questions are answered:

- What symptoms and findings may point to the presence of underlying autoimmune encephalitis?
- In which patients is an antibody diagnostic work-up for autoimmune encephalitis appropriate and how should it be carried out?

- What factors and sources of error must be considered in interpreting the results?

Methods

The PubMed database (www.pubmed.gov) was surveyed for relevant scientific research. The search strategy is described in *eBox 1*.

Results

Clinical symptoms

Many forms of autoimmune encephalitis manifest as “limbic encephalitis,” i.e., psychiatric symptoms or qualitative impairment of consciousness in combination with epileptic seizures and memory disorders (4). Because the seizures are often not generalized (6), but occur focally as psychomotor episodes with isolated impaired consciousness and disorientation (dyscognitive seizures) (7), these patients often receive an incorrect diagnosis of delirium, encephalopathy, or neurodegenerative dementia (5).

The year 2016 saw the publication of the first consensus criteria for the diagnosis of possible autoimmune encephalitis prior to knowledge of the antibody results (8). The principal warning signs are rapidly progressive (<3 months) qualitative or quantitative impairment of consciousness, lethargy, personality changes, and deterioration of short-term memory. Further diagnostic “red flags” are newly occurring epileptic seizures, psychiatric symptoms, changes in magnetic resonance tomography (MRI) findings in the temporal lobes (bilateral alterations of the mesial portions of the lobes on T2-weighted MRI), inflammatory changes of the cerebrospinal fluid (CSF), and alterations on electroencephalography (EEG) (epilepsy-typical potentials or regional decelerations) (8). In particular, an unprovoked first occurrence of status epilepticus should prompt suspicion of autoimmune encephalitis until another cause is demonstrated (9). In many patients, however, especially the elderly, the memory deterioration takes place over a period exceeding 3 to 6 months and the initially mostly focal epileptic seizures may be misconstrued by the patients and their relatives (10, 11, e4, e5).

Antineuronal antibodies

It has been known since the 1960s that limbic forms of encephalitis may occur as paraneoplastic neurological syndromes (e6). In these cases the patients are often found to have antibodies to neuronal intracellular antigens (onconeural antibodies) (e7), are mostly elderly, almost always have a malignant tumor, and respond only poorly to immunotherapy (*Table*).

In 2005, previously unknown antineuronal antibodies were detected in patients with severe encephalitis and benign ovarian teratomas who responded well to immunotherapy. These antibodies were directed at structures located on the surface of axons and dendrites (e8). In time, the N-methyl-D-aspartate (NMDA) receptor was identified as the underlying

target antigen (12). Thirteen further “neuronal surface antigens” were identified in the following few years, mostly receptors or synaptic scaffolding proteins (*Table*) (13).

Incidence of autoimmune encephalitis

From what is known so far, autoimmune encephalitis is a rare disease. Its precise incidence in Germany has not yet been investigated. The German Network for Research on Autoimmune Encephalitis (GENERATE e.V.) estimates the incidence at 8 to 15 patients/1 000 000 inhabitants/year. Data from southern England suggest a similar figure (14). However, studies on the frequency of autoimmune encephalitis specifically in inpatients or outpatients with acutely or subacutely impaired consciousness are lacking as yet in Germany. Probably some members of this group of patients suffer from unrecognized autoimmune encephalitis. For example, an autoimmune or paraneoplastic etiology was found in 13 to 37% of patients with newly occurring, unprovoked, refractory status epilepticus (9, 15, 16). It can therefore be assumed that a meaningful number of undetected cases exist and that the incidence of autoimmune encephalitis is actually higher than previously thought.

Pathophysiology

In some patients the primary trigger factor for autoimmune encephalitis is a (usually previously undetected) tumor that is expressing the target antigen, e.g., ovarian teratoma in the case of anti-NMDA receptor encephalitis (17, 18). The cause of cases of autoimmune encephalitis in which no tumor is demonstrated is unclear, although viral infection (e.g., after herpes [HSV-I] encephalitis) and genetic predisposition have been postulated (19–21) (*Figure 1*).

In a second step, probably unrelated events (e.g., systemic infections) (22) lead to migration of auto-antibody-producing activated B lymphocytes across the blood–brain barrier into the brain (18). The antibodies that are then produced there exert a direct effect by binding to their target antigens (17, 23, 24). This effect is dose dependent and reversible, comparable with pharmacological inhibition (25, 26) (*Figure 1*). Therefore, the symptoms of most forms of autoimmune encephalitis with synaptic antibodies can be reversed by early treatment (13).

Diagnosis

Cerebral imaging and the general CSF findings—leukocyte count, cytology, and analysis of autochthonous immunoglobulin synthesis—are important for the demonstration of autoimmune encephalitis (24). Both investigations serve above all to narrow down the differential diagnoses (*Box*). The finding of bilateral temporomesial hyperintensities on T2/FLAIR MRI sequences may point to limbic encephalitis, but in most cases conventional imaging reveals only unspecific changes or a lack of abnormalities (27).

TABLE

Neuronal and glial autoantibodies in autoimmune encephalitis with acute or subacute impairment of consciousness

Antigen	Syndrome	Tumor association
Antibodies to neuronal intracellular antigens		
Hu, CV2/CRMP5, amphiphysin	Limbic encephalitis	> 95 %; small-cell BC
Ma2	Limbic encephalitis ^{*1}	> 95 %; testicular tumors
GAD65	Limbic encephalitis, temporal lobe epilepsy	Max. 25 % thymomas, small-cell BC
Antibodies to neuronal surface antigens		
NMDA receptor (GluN1)	Anti-NMDA receptor encephalitis	25–50 % ovarian teratomas in women aged 14 to 45 years
LG11	Limbic encephalitis, usually no inflammatory CSF, faciobrachial dystonic seizures	5–10 % thymomas
CASPR2	Limbic encephalitis, Morvan syndrome ^{*2} , neuropathic pain syndromes	20–50 % thymomas (usually in Morvan syndrome)
GABA(B1) receptor	Limbic encephalitis	50 % small-cell BC
AMPA receptor (GluR1/2)	Limbic encephalitis, refractory seizures	65 % thymomas, small-cell BC
mGluR5	Limbic encephalitis	70 % Hodgkin lymphomas
GABA(A) receptor (α1/β3)	Limbic encephalitis, status epilepticus	< 5 % thymomas
DPPX	Limbic encephalitis, diarrhea, hyperekplexia, stiff-person spectrum	< 10 % lymphomas
Glycine receptor (αGlyR)	Stiff-person spectrum, progressive encephalomyelitis with rigidity and myoclonus (PERM)	< 5 % thymomas, lymphomas
Neurexin-3α	Encephalitis (similar to anti-NMDA receptor encephalitis)	None yet known
IgLON5	Encephalitis with sleep disorders, stridor, chronic course	None yet known
Antibodies to glial antigens		
MOG	ADEM ^{*3} , encephalopathy and focal seizures ^{*4} , neuromyelitis optica spectrum diseases ^{*5}	None yet known

In the column "Antigen", in the case of multimeric receptors the principal antigenic subunits are given. ^{*1} Often with distinct mesencephalic and hypothalamic involvement. ^{*2} Morvan syndrome: combination of limbic encephalitis and neuromyotonia. ^{*3} Acute, disseminated encephalomyelitis particularly in children. ^{*4} Individual cases of focal cortical encephalitis with MOG antibodies have been described (e10, e11). ^{*5} Generally without impairment of consciousness
 AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; BC, bronchial carcinoma; CASPR2, contactin-associated protein 2; CRMP5, collapsin response-mediator protein 5; CSF, cerebrospinal fluid; DPPX, dipeptidyl-peptidase-like protein 6; GABA(A) receptor, γ-aminobutyric acid receptor A; GABA(B) receptor, γ-aminobutyric acid receptor B; GAD65, glutamate decarboxylase 65 kD; GFAP, glial fibrillary acidic protein; IgLON5, IgLON family member 5; LG11, leucine-rich glioma inactivated protein 1; mGluR5, metabotropic glutamate receptor 5; MOG, myelin oligodendrocyte glycoprotein; NMDA receptor, N-methyl-D-aspartate receptor

If the CSF shows signs of inflammation with pleocytosis or detection of isolated oligoclonal bands and infection has been excluded, the encephalitis may be of autoimmune origin (*Box*). In autoimmune encephalitis the leukocyte count may be as high as 100/μl, or occasionally even 500/μl, and isolated oligoclonal bands are often present in the CSF (8, 28). In general, however, these inflammatory CSF changes are observed more frequently in acute cases (e.g., anti-NMDA receptor encephalitis) (28) and much less often in subacute/chronic autoimmune encephalitis (11). Therefore, while a constellation of CSF findings pointing to inflammation in a patient with impaired consciousness should always prompt consideration of underlying autoimmune encephalitis, the absence of such signs does not rule out encephalitis. Indeed, for some subforms, e.g., LG11 encephalitis (LG11: leucine-rich glioma inactivated protein 1), absence of these signs is typical (5, 11).

The international consensus, however, is that early diagnostic work-up for autoimmune encephalitis by means of antibody determination is required in all cases of acute or subacute qualitative or quantitative impairment of consciousness in which there is no convincing alternative etiology (*Figure 2*) (8). This is particularly true in the presence of the following:

- An inflammatory CSF syndrome
- Prominent epileptic seizures
- MRI findings suggestive of unilateral or bilateral involvement of the limbic system (mesial temporal lobes) (8).

Antibody detection

As specific biomarkers, antineuronal antibodies in serum and CSF are of key importance (8). Proof of their presence enables both delineation from other differential diagnoses and also identification of the subform of

Figure 1: Pathomechanism of synaptic encephalitis: the example of anti-NMDA receptor encephalitis

Trigger factors: The misdirected autoimmune reaction may be triggered by the expression of N-methyl-D-aspartate (NMDA) receptors in ovarian teratomas or by the secretion of these receptors in the inflamed brain, e.g., following herpes simplex-I (HSV-I) encephalitis. In many cases, however, the trigger factor is unknown.

Establishment of immune reaction: While the systemic immune reaction does not lead to sufficient antibody levels in the brain in the presence of an intact blood–brain barrier, the passage of antibody-producing plasma cells (e.g., triggered by infection) brings about high concentrations of antibodies in the cerebrospinal fluid.

Antagonistic effect of antibodies on synapses: The presence of the autoantibodies causes internalization of the receptors and impairment of glutamate transfer. Immunotherapy and/or plasmapheresis lead to reduction of the antibody concentration in the synapse. This enables newly formed receptors to reach the surface of the neuron in sufficient numbers. (Reproduction by kind permission of Katja Duwe-Schrinner, Duwe.Design)

autoimmune encephalitis involved. This differentiation is important for the prognosis and the recognition of a possible tumor association (*Table*).

In some forms of autoimmune encephalitis, autoantibody testing possesses high diagnostic sensitivity and specificity (e.g., CSF sampling in anti-NMDA receptor encephalitis: specificity 100%, sensitivity 100% [98.5 to 100.0%]) (23). Predictive values cannot currently be ascertained owing to lack of data on prevalence of the antibodies in patients with impaired consciousness from other causes.

However, autoantibodies cannot always be demonstrated in cases where clinical findings indicate that autoimmune encephalitis is probable (8). For this reason the cumulative sensitivity of comprehensive antibody testing for all potential neuronal antibodies is lower (estimated at 60 to 80%) in clinically defined autoimmune encephalitis. No data are yet available on cumulative specificity.

The following aspects have to be taken into account when testing for autoantibodies:

- Standardized commercial test systems are now available for specific detection of the most frequently occurring antibodies (*Table*). The examinations can thus be performed in any laboratory where the staff are familiar with autoimmune diagnostic methods (immunofluorescence, ELISA, immunoblotting). Because symptoms overlap among the various disease presenta-

tions, and owing to the multiplicity of newly identified autoantibodies, generation of an autoantibody profile (*Figure 2*) with inclusion of neuronal tissue is superior to the testing of individual antibodies. In a retrospective study of 2716 requests for analysis (2608 results negative, 108 positive), around 30% of the positive tests identified antibodies other than those suspected (29).

- In certain subforms serum testing without accompanying CSF analysis is considerably less sensitive and specific (e.g., anti-NMDA receptor encephalitis: 16% false-negative results for serum testing alone) (23). For this reason it is recommended to test for antibodies in both CSF and serum in parallel.

- Our own observations, in agreement with published data (30), show that isolated analysis of serum for antibodies to neuronal surface antigens using transfected cells can result in false-positive rates of 1 to 2%. Therefore any low-titer detection of these antibodies in serum (<1:40) that is not backed up by corresponding findings in the CSF should be viewed skeptically and the findings should be double-checked by means of other techniques at a laboratory with special expertise in autoimmune encephalitis (*Figure 2*) (17, 23).

- The autoantibodies associated with encephalitis belong, without exception, to immunoglobulin (Ig) class G (24). The diagnostic value of antineuronal antibodies of classes IgA and IgM is unclear. For example,

BOX

Differential diagnoses of autoimmune encephalitis

- **Intoxication**
 - Ethanol, opiates, benzodiazepines, tricyclic antidepressants, neuroleptics, carbon monoxide, etc.
- **Epileptic seizures**
 - Other symptomatic forms of epilepsy, nonconvulsive status epilepticus
- **Infection**
 - Herpes (HSV-I) encephalitis
 - Other viral encephalitides (varicella zoster virus [VZV], human herpes viruses [HHV6/7] especially in immunocompromised patients, tick-borne encephalitis [TBE], enteroviruses, West Nile virus, Japanese B-encephalitis)
 - Syphilis
 - Progressive multifocal leukoencephalopathy (PML)
- **Other autoimmune diseases**
 - Collagenoses (systemic lupus erythematosus, Sjögren syndrome)
 - Bickerstaff encephalitis/Miller–Fisher syndrome
- **Malignancies**
 - Non-Hodgkin lymphoma, neoplastic meningitis
- **Cerebrovascular events**
 - Vasculitis, septic focal encephalitis
- **Metabolic derangements**
 - Wernicke encephalopathy, renal or hepatic encephalopathy

IgA or IgM antibodies to NMDA receptors in serum are found in up to 10% of patients with various neuropsychiatric illnesses—and in the same proportion of healthy persons (30).

- In patients with anti-NMDA receptor encephalitis there is a correlation between disease activity and antibody titer in CSF but not in serum (23). However, the titer depends on the test system used, so this correlation may not be found in routine diagnostic practice. Moreover, persistence of the given antibodies has been described in the remission phase for patients with LGII encephalitis and anti-NMDA receptor encephalitis (11, 31).

- The most frequently occurring antineuronal antibodies can be detected with the currently available test kits, but there are no validated systems for many less common target antigens. Furthermore, increasing numbers of new antigens are being identified (32–34, e9). In patients with clinical suspicion of autoimmune encephalitis, this diagnostic gap can be bridged to some extent by means of special immunohistochemical methods, but these can usually only be carried out in specialized laboratories. These investigations, using specific tissue slices prepared in such a way as to preserve the integrity of membrane proteins, represent an expanded search system for new antibodies and simultaneously serve to verify and confirm known

antibodies (*Figure 2, eFigure*) (13, 17). Therefore, clinically suspected autoimmune encephalitis can only be considered seronegative if this tissue-based screening test also yields no evidence of antineuronal antibody activity (8).

- Not infrequently, other systemic (e.g., antinuclear antibodies, ANA) or organ-specific (e.g., anti-thyroperoxidase, TPO) autoantibodies are detected in patients with autoimmune encephalitis. Findings of this kind, which point to a general autoimmune diathesis, may give rise to incorrect diagnoses (such as neuropsychiatric lupus erythematosus or Hashimoto encephalitis) in the absence of knowledge of the specific antineuronal antibodies and disease pattern. These diseases should thus only be considered after comprehensive testing for antineuronal antibodies, including extended serological tests (8).

In summary, the following are required for rational antibody diagnosis in patients with qualitative or quantitative impairment of consciousness:

- General familiarity with the clinical warning signs of underlying autoimmune encephalitis on the part of the treating physician
- Consensus among hospital staff or provision by the laboratory of an antibody panel for standardized, syndrome-oriented antibody testing
- Cooperation with a laboratory experienced in the diagnosis of autoimmune encephalitis
- Close communication between treating physician and laboratory in the event of atypical clinical signs with a positive antibody constellation, or high clinical suspicion without antibody detection.

Treatment and prognosis

No randomized controlled trials on the topic of treatment for autoimmune encephalitis have been published. Encephalitis with antibodies to neuronal surface antigens generally have a good prognosis provided it is detected promptly and treated at an early stage (28). However, the prognosis in individual cases varies depending on the target antigen of the autoantibody, the presence or absence of associated tumors, the patient's age, and the severity of the disease (10, 11, 28). For instance, 77 to 98% of patients with anti-NMDA receptor encephalitis are able to live independently by 2 years after diagnosis (multicenter observational study with 577 patients, evidence level III) (28). However, multimodal imaging and neuropsychological testing demonstrated long-term impairment of memory function (35, 36). In LGII encephalitis, structural damage to the hippocampus often leads to permanent cognitive deficits (37). These persisting deficits can, however, be prevented by early immunotherapy after the first epileptic seizures (retrospective cohort study, n = 80, 56% cognitive deficits without immunotherapy, 1.3% with immunotherapy, evidence level III) (6). In general, early and adequate immunotherapy seems to be one of the most important prognostic factors (11, 28).

While the swiftest possible initiation of treatment—usually intravenous steroid pulse therapy and

FIGURE 2

Proposed diagnostic algorithm for investigation of autoimmune encephalitis (AE) (based on [8])

*1 A particularly strong sign of encephalitis on magnetic resonance imaging (MRI) is bilateral edema of the mesial temporal lobe. Unspecific changes are most common, however, and MRI serves especially to exclude differential diagnoses. *2 Standardized, commercially available test kits (immunofluorescence tests with tissue and fixed, transfected cells, ELISA, immunoblotting). *3 Serum testing is sufficient for these antibodies. *4 Immunofluorescence results with commercial cell-based assays with low titers (<1:40) but without corresponding CSF findings may be false positive. *5 For rarely occurring antibodies, individual decisions are necessary in the event of isolated serum positivity without corresponding CSF findings. AB, Antibodies; CSF, cerebrospinal fluid; GENERATE, German Network for Research on Autoimmune Encephalitis; for further abbreviations see foot of Table

plasma exchange—and resection of any underlying tumor are of primary importance, patients who do not respond positively should be given rituximab or cyclophosphamide as early as possible (8, 28). Those who remain refractory to this treatment have benefited from IL6 blockade (tocilizumab) or plasma cell-specific therapy (proteasome inhibitors) (38, 39). Nevertheless, it is not uncommon for a patient to need several months of convalescence with intensive rehabilitation (11, 28). Most cases of monophasic autoimmune encephalitis do not require immune therapy stretching over a period of years (evidence level V), but such measures can be considered in the event of repeated recurrence (evidence level V) (40). All the treatments described above are off label.

Despite all the laboratory tests that have recently become available, autoimmune encephalitis is still not infrequently seronegative (8). However, many of these patients benefit from immunotherapy. Therefore, all patients with high clinical suspicion of autoimmune encephalitis, even those who are seronegative, should be given immunotherapy (8). Clinical criteria for probable seronegative autoimmune encephalitis have recently been published, but the diagnosis should be made only after exclusion of rarely occurring auto-antibodies (Figure 2) (8).

Crucial for the collection of data on the whole spectrum of autoimmune encephalitis are national and international networks and registers for this group of diseases (e.g., the German Network for Research on Autoimmune Encephalitis, GENERATE e. V.; www.generate-net.de [in German]).

Conflict of interest statement

Prof. Wandinger worked for Euroimmun up to December 2012. He has received payment for a lecture from the laboratory Dr. Fenner und Kollegen.

Dr. Leypoldt has received payments for lectures from Grifols, Teva, Roche, Biogen, Merck, and Fresenius.

All three authors—Prof. Wandinger, Dr. Leypoldt, and Prof. Junker—are employed at a university institute where the work includes investigation of antineuronal antibodies.

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Key messages

- Autoimmune encephalitis is an important differential diagnosis in patients with acute and subacute impairment of consciousness; the warning signs are memory deficits, epileptic seizures (especially status epilepticus), inflammatory signs in the cerebrospinal fluid (CSF), and temporomesial abnormalities on magnetic resonance imaging.
- In analogy to the observations in anti-NMDA receptor encephalitis, it can be assumed that also in other forms of antibody-mediated encephalitis the patient's prognosis or disease pattern depends largely on early diagnosis and initiation of treatment (28).
- The determination of antineuronal antibodies in serum and CSF defines subgroups of autoimmune encephalitis with different treatment needs and prognoses.
- The antibody diagnostic work-up should include testing of samples from serum and CSF with a combination of various test systems in order to attain the best possible specificity and sensitivity.
- Investigation should include a comprehensive profile of the frequently relevant antibodies. In the event of atypical antibody constellations (low titer only in serum, IgA/IgM isotypes) or an atypical clinical presentation, the findings should be verified in a specialized laboratory if at all possible. The same is true for seronegative findings in cases of high clinical suspicion of autoimmune encephalitis.

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► Supplementary material

For eReferences please refer to:
www.aerzteblatt-international.de/ref4018

eBoxes, eFigure:
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CLINICAL SNAPSHOT

A Slowly Receding Hairline

A 75-year-old woman presented with a 10-year history of slowly progressing hair loss confined to the hairline and eyebrows. Clinical examination revealed a band of alopecia with marked recession of the frontotemporal hairline, which was clearly demarcated from the actinically damaged skin of the brow. Previous treatment with methotrexate and acitretin had been unsuccessful. On the basis of the typical clinical findings we diagnosed frontal fibrosing alopecia (FFA). This is a rarely occurring form of cicatricial alopecia that predominantly affects postmenopausal women. The etiopathology of FFA has not been established, but a connection with lichen planus has been suggested. Only in unclear cases and for distinction from other forms of alopecia it is ever

necessary to obtain a biopsy sample for laboratory examination. There is no causal treatment for FFA. We prevented further hair loss by treatment with hydroxychloroquine and topical corticosteroids.

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Supplementary material to:

Autoantibody-Mediated Encephalitis

Differential Diagnosis in Patients With Impaired Consciousness of Unclear Origin

by Klaus-Peter Wandinger, Frank Leypoldt, and Ralf Junker

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eFigure: Experimental analyses

In the case of persistent clinical suspicion in the face of a negative result, or to check an implausible positive result, more detailed analysis of antineuronal antibodies can be carried out using experimental methods in specialized laboratories.

a) A tissue-based test using specially prepared sagittal slices of rat brain serves for both screening and confirmation. This panel shows the hippocampal and cerebellar staining after incubation of serum (1 : 200) from a patient suspected of having autoimmune encephalitis. The results point to the presence of a synaptic autoantibody with an unknown target antigen. Antihuman secondary antibody and DAB immunohistochemistry. Scale bar: 200 μ m.

b) In contrast to commercial cell-based test kits, unfixed cell cultures could be used for antigen-specific testing in the specialized laboratory (live cell staining without potential fixation artifacts). This panel shows HEK293T cells (HEK, human embryonal kidney), which express AMPA receptors on their surface after transfection with specific cDNA and were stained with serum (green, 1 : 40) from a patient with anti-AMPA receptor encephalitis or a control patient. Incubation with a monoclonal antibody to AMPA receptors (red) is shown for comparison. The fusion images show that colocalization of both colors (yellow) occurs, which confirms the presence of AMPA receptor specific IgG antibodies in this patient's serum. Scale bar: 20 μ m.

c) Neuronal primary cell cultures are used to confirm a new neuronal surface antibody (e.g., from panel a). The example of an anti-IgLON5 antibody (in green) illustrates the binding of the autoantibody to the surface of the neurons and their dendrites. The nuclei of the neurons and the adjacent glial cells are stained blue (neuronal, embryonal, murine hippocampal primary culture DIV21; incubation with serum 1 : 200 in culture with unfixed, unpermeabilized neurons and staining with green-marked secondary antihuman IgG antibodies). Scale bar: 20 μ m.

AMPA, α -Amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; DAB, 3,3'-diaminobenzidine; IgG, immunoglobulin G;

DIV21, 21 days in vitro

IgLON5, Iglon family member 5

eBOX 1

Supplementary information on method

The MEDLINE database (www.pubmed.gov) was searched for relevant publications using the terms “autoimmune encephalitis,” “autoimmune encephalopathy,” “NMDA receptor encephalitis,” and “LG11 encephalitis” for the period from 2005 to 1 September 2017. Records were filtered for “clinical trials,” “reviews,” and “human species” as well as for “NOT multiple sclerosis,” “NOT neuropathy,” “NOT lupus erythematosus,” and “NOT vasculitis”.

Articles without an abstract, articles in languages other than German or English, single case reports, case series with fewer than five patients, and reviews and original articles with a purely pathophysiological thrust were manually filtered out. The remaining 72 publications were screened and evaluated by the authors.

eBOX 2

Case 1

A 70-year-old woman was admitted to the internal medicine department because she was suspected to have dementia. There was a 4-month history of progressive short-term memory loss with personality changes and repeated erroneous actions. Clinical examination on admission found that the patient was disoriented in place and time, showed attention disorder, sometimes displayed diminished affect, and was intermittently indifferent. She had no focal neurological deficits. Clinical chemistry demonstrated hyponatremia of 125 mmol/L; the cerebrospinal fluid findings were normal. Neurocranial magnetic resonance tomography showed increased signal and bilateral thickening of the hippocampus. An autoimmune panel investigation for paraneoplastic antibodies, prompted by the patient's weight loss, detected antibodies to LG11 with a serum titer of 1:100. Each day during the patient's stay in hospital there were several episodes, each lasting a few seconds, in which she grimaced and waved her arms around bizarrely. A neurologist later classified these events as facio-brachial dystonic seizures (FBDS). On the basis of the clinical and laboratory findings, LG11-antibody-positive limbic encephalitis was diagnosed. The patient was treated with intravenous steroids (1 g methylprednisolone/day) for 3 days, followed by oral prednisolone for 5 months. Immune therapy rapidly resulted in remission of the FBDS and the patient's orientation increasingly improved. With time, the symptoms resolved completely; however, there was retrograde amnesia for the time spent in the hospital.

eBOX 3

Case 2

A 21-year-old woman was admitted to the hospital because of progressive personality change with repeated phases of transient mental distraction. The initial clinical examination found fluctuating disorientation but no focal neurological deficit. The patient subsequently developed a hallucinatory psychosis and both complex focal seizures and generalized seizures occurred. Neurocranial magnetic resonance imaging (MRI) showed no abnormalities. Notably, the patient had been admitted to the pediatric department at the age of 16 years and treated for several weeks due to subacute personality change with loss of motivation and weepy behavior. Clinical chemistry at that time had shown an inflammatory cerebrospinal fluid (CSF) syndrome with 47 leukocytes/ μ L and demonstrated a serum titer of 140 IU/mL for antibodies to thyroperoxidase (TPO). Cranial MRI, analysis of the antineuronal antibodies known in 2006, and a comprehensive survey for pathogens had revealed no abnormalities. Hashimoto encephalitis had been suspected, and treatment with glucocorticoids and neuroleptics had led to complete remission. A few weeks before this new admission, the patient had begun studying at the university. On admission, clinical chemistry again showed an inflammatory CSF syndrome, this time with 108 leukocytes/ μ L. Analysis for antineuronal antibodies, carried out in the form of an encephalitis profile, demonstrated the presence of antibodies to NMDA receptors in CSF and serum. Recurrence of anti-NMDA receptor encephalitis was diagnosed. Despite treatment with intravenous steroids, immunoadsorption, and intravenous immunoglobulins, the patient's clinical condition deteriorated progressively and she experienced recurring complex focal seizures with some generalized seizures. A complex focal episode that necessitated midazolam anesthesia signaled the beginning of an 8-week period of intensive care. The immunosuppressive therapy was escalated by the addition of rituximab and cyclophosphamide, and a combination of levetiracetam, phenytoin, phenobarbital and lacosamide was introduced as anticonvulsive treatment. An extensive search, including explorative laparoscopy, revealed no teratoma. After 3 months the patient's condition had become stable and she was transferred for rehabilitation. At a follow-up visit 9 months after admission there were minor residual deficits in verbal and nonverbal short-term memory and working memory. A year after falling ill, the patient was able to resume her studies.