Intrathecal Thyroid Autoantibody Synthesis in a Subgroup of Patients With Schizophreniform Syndromes

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Schizophreniform syndromes in combination with autoimmune thyroiditis and increased serum thyroid antibodies lead healthcare practitioners to consider a diagnosis of Hashimoto's encephalopathy. To detect specific biomarkers, the authors analyzed whether intrathecal antithyroid antibody synthesis occurred in a subgroup of schizophreniform patients. In doing so, the authors analyzed thyroid antibodies in paired cerebrospinal fluid and serum samples from 100 schizophreniform patients. Increased antibody indices (AIs) for antithyroid peroxidase or antithyroglobulin autoantibodies in 13 schizophreniform patients were found. AIs were increased in 68% of the seropositive patients. These findings support the hypothesis that autoimmune processes may contribute to the pathophysiology in these patients.

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Schizophreniform syndromes are common phenomenologies in psychiatry. There are clinical phenotypes with different combinations of delusional, hallucinatory, catatonic, dysexecutive, amotivational, dysorganizational, or affective symptoms. From a pathophysiological perspective, primary forms without and secondary forms with a recognizable cause can be distinguished. Patients with primary forms often display familial liability probably as a result of a polygenetic vulnerability. Secondary forms may be acquired through substance abuse or a variety of brain disorders.[1] Such secondary brain disorders might be due to mild inflammatory (e.g., immunological encephalopathies), neurodegenerative (e.g., Huntington's chorea), epileptic (e.g., paraepileptic psychosis, temporal lobe epilepsy), metabolic (e.g., porphyria), vascular (e.g., vasculitis, strategic infarcts), or traumatic causes (traumatic brain injury).[2] In the field of secondary schizophreniform syndromes, immunological encephalopathies have received increased interest over the recent years due to the discovery that autoantibody-associated limbic and nonlimbic autoimmune encephalitis can mask schizophrenia.[3–9] In this context, antineuronal antibodies against intracellular synaptic antigens (GAD, amphiphysin), intracellular onconeural antigens (e.g., Yo, Hu, CV2/ CRMP5, Ri, Ma1/2, SOX1), neuronal cell surface antigens (e.g., *N*-methyl-D-aspartate-R, AMPA-1/2-R, GABA-B-R, voltage gated potassium channel-complex complex), and antithyroid autoantibodies (thyroid peroxidase [TPO], thyroglobulin [TG], thyroid-stimulating hormone receptor antibodies) can be distinguished.[3] Neuropsychiatric syndromes in combination with autoimmune thyroiditis should lead to the consideration of a putative diagnosis of Hashimoto's encephalitis (HE).[3,10–13] Several case reports supported the idea that HE can mimic schizophreniform syndromes.[14–19] In patients with this condition, treatment with steroids can be very successful.[3] In this case, HE is also called steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT).[3,10–13]

HOW TO DEAL WITH INCREASED ANTITHYROID AUTOANTIBODIES IN SCHIZOPHRENIFORM DISORDERS

Increased serum thyroid autoantibodies were found in 13% of healthy individuals (more often in females and older patients).[10,20] This observation complicates the question of how we should deal with schizophreniform patients with increased anti-TPO and/or anti-TG serum antibodies? Which additional findings should lead to corticosteroid treatment? Should all such patients be diagnosed with HE and therefore be treated with corticosteroids? The diagnostic criteria for HE do not fully answer these questions; they are inconsistent and unspecific, and HE is still diagnosed by exclusion. Following the German S1 guidelines (www.dgn.org), SREAT can be diagnosed if a patient presents encephalopathic symptoms (i.e., subacute onset in addition to neuropsychiatric symptoms

or other neurological symptoms) and increased thyroid autoantibody levels plus positive response to corticosteroids (after exclusion of alternative causes with laboratory and cerebral magnetic resonance imaging [cMRI] measurements).[13] However, following a recent position paper by Graus et al.,[10] a positive response to corticosteroids is no longer required. Instead, the authors use the term HE leaving the SREAT concept. They suggest considering corticosteroids for all patients with thyroid disease, elevated antithyroid antibodies, and nonspecific encephalopathy that cannot be explained by another condition.[10] However, in clinical practice it is difficult to decide whether to treat thyroid autoantibody positive schizophreniform patients with antipsychotics, in accordance with the guidelines for schizophrenia (e.g., Nice guidelines [http://www.nice.org.uk]; German S3-Praxisleitlinie [www.dgppn.de]), or with off-label corticosteroids even after taking EEG and cMRI alterations into account. High-dose corticosteroid pulse treatment may result in complete recovery, but it is not free of side effects. Obviously, there is a need for more neurobiological markers to guide the decision when to try immunomodulatory treatment.

Given this problem, in the present study we analyzed intrathecal thyroid autoantibody synthesis in order to identify a possibly more specific biomarker for HE.

Rationale of Our Study

In the Department of Psychiatry and Psychotherapy at the University Medical Center Freiburg, we have traditionally analyzed cerebrospinal fluid (CSF) in patients with schizophreniform syndrome if they showed any signs of neuroinflammation (e.g., sudden onset, atypical clinical presentation, neurological symptoms, altered EEG and cMRI findings). Based on our experience with psychiatric patients suffering from autoimmune encephalitis, we have offered CSF analysis as part of routine diagnostics since June 2009 for all patients with schizophreniform syndrome. Therefore, all patients who consented were investigated since 2009. Moreover, we performed broad serum analyses (including thyroid hormone status), EEGs, and cMRI measurements in our routine work-up for these patients.[4,21] Based on these experiences, we retrospectively performed paired antithyroid antibody testing of CSF and serum samples and calculated specific autoantibody indices (AIs) for the anti-TPO and anti-TG antibodies.[22,23] We hypothesized that we would find increased AIs in a subgroup of antithyroid antibody seropositive patients. For these patients, we planned to describe our clinical, laboratory, and instrument-based findings in detail. We also wanted to compare these findings between patients with and without increased AIs.

METHODS

The study received approval from the local ethics committee of the University of Freiburg (EK-Fr 609/14). Lumbar punctures were offered as part of patients' routine diagnostics. Only patients who gave their written consent were investigated.

Study Sample

We included 100 patients at our tertiary care hospital with schizophreniform syndrome. Patients diagnosed with schizophreniform syndrome included those with schizophrenia (N=56), schizoaffective disorder (N=29), acute polymorphic psychotic disorder (N=14), and substance-induced psychosis (N=1). Only CSF/serum samples from patients with complete thyroid hormone status (thyroid-stimulating hormone [TSH], triiodothyronine [t3], and thyroxine [t4]) were included. For pragmatic reasons, we selected the first 100 patients since 2006. The study included 13 patients who underwent lumbar puncture between 2006 and 2009 (i.e., CSF analysis was performed if there were signs of possible neuroinflammatory features). The other 87 patients underwent lumbar puncture since June 2009, when CSF analysis was offered as a routine procedure. The subgroups for the schizophreniform patient cohort as well as number of instrument-based diagnostics are presented in Table 1. The diagnostic classification was performed by a board-certified psychiatrist following the ICD-10 criteria.

ELISA

Paired CSF and serum samples were analyzed using an ELISA to identify anti-TPO and anti-TG antibodies. We used commercially available Medizym anti-TPO and Medizym anti-TG ELISA kits (Medipan GmbH, 15827 Dahlewitz/Berlin, Germany). We performed the ELISA according to the order of manufacturer's instructions; however, since this assay is not validated for analyzing CSF samples, and we expected the titers of the thyroid antibodies to be very low, we used undiluted CSF samples. The results of the measurements in the CSF were adjusted to match the serum dilution. Those serum samples exceeding the value limits were controlled in a second assay to confirm the first positive finding. The AIs were only calculated if the second test was also positive.

Specific Antibody Index

Measuring AIs allows the detection of intrathecal antibody synthesis by distinguishing brain-derived fraction thyroid antibodies from antibodies passively diffused out of the serum into the CSF.[22,23] The calculation of specific AIs depends on parallel antibody testing of CSF and serum samples and the reference to the relevant quotient of total CSF/serum IgG in relation to blood-brain barrier (BBB) function (the albumin quotient is used as a reference standard).[22] AIs were calculated in the case of increased antithyroid autoantibodies in the serum. The calculation of AIs was described in earlier papers.[22–25] The normal range for AIs is 0.7–1.3.[22] AI values >1.4 were assessed as indicating intrathecal-specific antithyroid autoantibody synthesis in our study.[23]

Data Handling and Statistical Analysis

In earlier projects,[4,26] we established a CSF database including all CSF findings since 2006, socio-demographic information, diagnoses, laboratory results, and cMRI and EEG ratings. The procedures we used to obtain CSF-based diagnostics and cMRI and EEG ratings were described earlier.[4,26] In our CSF-database, antithyroid-autoantibody findings from serum and CSF were added. Statistical analyses were performed using Statistical Package for the Social Sciences, version 22 (SPSS 22 [www-01.ibm.com/software/analytics/spss]). The AIs of both groups were described in detail. Group comparisons for continuous variables (age, protein concentration, etc.) were performed using two-sided independent sample t tests. Group comparisons for categorical variables (gender, general cMRI alterations, AIs, etc.) were carried out using Pearson's chi-squared test. Correlation analyses were performed using the Pearson correlation coefficient. For all statistical analyses, a p value <0.05 served as the criterion of significance. For the correlation analyses, we did not perform a Bonferroni correction for multiple tests because our analyses were exploratory.

RESULTS

Demographic Data

The patients' mean age was 33.32 years (±12.35 years) (ranging from 18 to 66 years), and more were female than male (females, N=59; males, N=41).

Thyroid Hormones and Antithyroid Antibody Findings

The patients' thyroid hormone statuses are presented in detail in Table 2, and the autoantibody findings are presented in Table 3. In our cohort of schizophreniform patients, we found increased anti-TPO antibodies in the sera of 18 of the 100 patients (18%). Twelve of these 18 seropositive patients (67%) showed increased AIs for anti-TPO antibodies (ranging from 1.54 to 8.16). Anti-TG antibodies were found in the sera of two of 100 patients (2%). One of these two patients showed an increased AI for anti-TG-antibodies (50%; AI: 1.84). Overall, we found increased thyroid autoantibodies in 19 of 100 (19%) of the patients. One patient showed both increased anti-TPO and anti-TG antibodies in the serum and increased AI only for anti-TPO antibodies (patient 3) (Table 4). Thirteen patients showed increased AIs. Increased AIs were found in 68% of the seropositive patients.

Clinical Characteristics of Schizophreniform Patients With Increased AIs

The age range of the sample with increased AIs varied from 19 to 61 years, and mostly women were affected (11/13 patients [84.6%]). Increased AIs were found in one of 13 (7.7%) patients in the nonscreened cohort (before June 2009) and in 12 of the 87 (13.8%) that underwent routine lumbar puncture (χ^2=0.263, p=0.608). Most patients with increased AIs suffered from paranoid-hallucinatory schizophrenia (6/13 [46%]) or schizoaffective disorder (6/13 [46%]). One patient with an increased AI presented with an acute polymorphic psychotic disorder (1/13 patients [8%]). Six of the 56 patients with schizophrenia showed increased AIs (10.7%), while the other 51 patients had normal thyroid antibodies or normal AIs (91.1%). In the schizoaffective group, increased AIs were found in six out of 29 patients (20.7%), while 22 patients (75.9%) had normal thyroid antibodies or normal AIs. Of the 14 patients with acute polymorphic psychotic disorder, only one showed increased AIs (7.1%), while 13 had normal thyroid antibodies or normal AIs (92.9%). The single patient with drug-induced psychosis was antibody-negative. The chi-square test showed no significant differences in increased AIs between the diagnostic categories (χ^2=2.349, p=0.503). Thyroid hormone status was normal in 10 of the 13 AI-positive cases (76.9%). Further CSF analyzes showed BBB dysfunction in three samples (23%) and displayed unspecific (identical pattern in CSF and serum) oligoclonal bands in two of 13 cases (15%). The cMRI showed alterations in nine of 13 cases (69%). The alterations were most likely unspecific white matter lesions (in 38%) (Table 5). EEGs were abnormal with intermittent slowing in five of 13 cases (38%). One patient with slowing had additional spike waves in the EEG (8%) (Table 5).

TABLE 1. Schizophreniform Subgroups and Instrument-Based Diagnostics

Schizophreniform Patient Cohort (N=100)	Number of Patients
Schizophrenia	56
Schizoaffective disorder	29
Acute polymorphic psychotic disorder	14
Substance-induced psychosis	1
Diagnostic Measurements	**Number of Samples**
Antithyroid peroxidase and antithyroglobulin antibodies	100[a]
CSF basis diagnostics (white blood cell count, protein concentration, albumin quotient, and intrathecal immunoglobulin synthesis)	100
Electroencephalography data sets	100
Magnetic resonance imaging data sets	93

[a] Retrospectively analyzed in this study.

Characteristics of Patients With Normal and Increased AIs

Females were significantly more likely to have increased antithyroid AIs (p=0.044). Patients with and without increased antithyroid AIs cannot be distinguished by the thyroid hormone status, CSF, and EEG findings separately. The cMRI alterations tended to be more frequent in the group with increased AIs (p=0.060) (Table 5).

DISCUSSION

We found increased AIs for anti-TPO and anti-TG autoantibodies in 13 schizophreniform patients. AIs were increased in 68% of the seropositive patients. Therefore, we were able

TABLE 2. Thyroid Hormones and Autoantibody Findings[a]

Hormones and Autoantibodies	Mean±SD (N=100)	Number of Alterations	Frequency of Alterations	Reference Values
Thyroid-stimulating hormone	2.39±2.24	↔: 88 ↑: 9 ↓: 3	12%	0.27–4.20 μU/ml
Triiodothyronine	4.73±0.90	↔: 92 ↑: 2 ↓: 6	8%	3.4–6.8 pmol/l
Thyroxine	16.60±3.23	↔: 94 ↑: 4 ↓: 2	6%	10.6–22.7 pmol/l
Antithyroid peroxidase antibodies in serum	50.15±104.96	↔: 82 ↑: 18	18%	<50 IU/ml
Antithyroglobulin antibodies in serum	14.87±23.79	↔: 98 ↑: 2	2%	<100 IU/ml

[a] Abbreviations: ↑, increased; ↔, normal; ↓, decreased; SD, standard deviation.

to confirm our working hypothesis that specific intrathecal antibody synthesis occurs in a subgroup of schizophreniform patients but also in a subgroup of patients with serum antibodies. Thus, the AI might be a more specific signal for suspected HE than the presence or absence of serum antibodies alone. Significantly more female patients showed increased AIs, similar to previous HE cohorts.[10]

Our Findings in the Context of Earlier Findings

Today, serum thyroid antibodies are the main indicator for considering the diagnosis of HE. However, elevated serum antithyroid antibodies are not disease-specific and are also present in healthy subjects, as well as in patients with other autoimmune diseases.[10,28] In a large sample of U.S. citizens (17,353 people), serum thyroid antibodies were increased in 13% of healthy individuals (more often in females and older patients).[10,20] Therefore, they are unreliable as the sole criterion for detecting HE. CSF antibody synthesis (represented by AI) might be a better diagnostic marker. In a previous study including six patients with HE and neurological manifestations (e.g., confusion, paresis, ataxia, falls, myoclonic jerks), the authors detected antithyroid autoantibodies in the CSF of six patients with HE (independent of BBB function), but not in a control group of 21 patients with different neurological conditions.[29] High levels of CSF antithyroid autoantibodies were also detected in the HE group of another study with 10 neurological HE patients and 33 controls.[30] From these observations, one might conclude that it is possible for autoantibodies to reach the CSF compartment in patients with normal BBB function. However, it remains unclear whether intrathecal antibody synthesis or only passive transfer of blood-derived antibodies to CSF is the origin of elevated antithyroid antibodies in CSF. Therefore, it might be necessary to calculate patients' AIs to investigate an intrathecal synthesis indicating presence of antithyroid specific autochthonous B-cell clones within the central nervous system (CNS). In a second study conducted by the Ferracci et al. group, they found increased specific antithyroid autoantibodies indices in nine antibody-seropositive patients with neurological manifestations (e.g., confusion, impaired consciousness, ataxia, paresis, paresthesias) of HE.[31] However, the authors did not systematically compare their findings to the albumin quotient. In patients with increased polyspecific intrathecal total IgG synthesis, these procedures would lead to overestimation of the disruption of BBB function and underestimation of AIs,[23] although the authors still found unexpectedly high AI levels (varying from 5.8 to 314.5).[31] It remains unclear whether these results can be applied to purely psychiatric (e.g., schizophreniform) cohorts. In our cohort of schizophreniform patients, we found increased AIs (varying from 1.54 to 8.16) in a relevant subgroup of 68% of antithyroid antibody seropositive patients. The increased AIs we found were lower than those reported by Ferracci et al.[31] Patients with increased AIs were mostly female and showed more frequent cMRI alterations. EEGs did not help to distinguish patients with and without increased AIs. Although this finding is remarkable given the frequent EEG alterations reported in earlier publications,[11,32]we recently published a case report of a female patient with a normal EEG that suffered from a purely psychiatric (i.e., affective) syndrome that turned out to be caused by SREAT. We speculated that the normal EEG might be the consequence of a less severe variant of SREAT without neurological deficits. The rate of increased CSF protein concentration in only 23.1% of patients is also lower, compared with a large literature review on SREAT characteristics, in which increased protein levels were found in 82%.[33] However, if increased AIs are a marker for corticosteroid responsiveness in schizophreniform HE patients, they would be more specific than serum autoantibody levels. Our patients were

TABLE 3. Thyroid Autoantibody Findings in the Entire Schizophreniform Syndrome Cohort[a]

Antibody Type	Serum Autoantibodies (N=100)	Specific Antibody Index	Frequency of Increased Specific Antibody Indices
Antithyroid peroxidase antibodies	↑: 18 ↔: 82	↑: 12 ↔: 88[b]	In the entire cohort: 12% In seropositive patients: 66.7%
Antithyroglobulin antibodies	↑: 2 ↔: 98	↑: 1 ↔: 99[b]	In the entire cohort: 1% In seropositive patients: 50%

[a] Abbreviations: ↑, increased; ↔, not increased.
[b] Antibody indices were only calculated in the case of increased antithyroid antibodies in the serum.

TABLE 4. Clinical Characteristics of the Schizophreniform Patients With Increased Specific Antibody Indices (AIs)[a]

Item	Age (Years), Gender, Syndrome	Serum Anti-TPO	AI Anti-TPO	Serum Anti-TG	AI Anti-TG	Thyroid Status	CSF	cMRI	EEG	Overall Alterations
1	19 years, female, schizoaffective disorder	213.24 (↑)	2.11 (↑)	↔	↔	TSH: ↔ T3: ↔ T4: ↔	Normal	Asymmetry of ventricles; one isolated WM lesion	Interm. gen. slow activity	AI TPO ↑ cMRI EEG
2	25 years; female, paranoid-hallucinatory schizophrenia	66.60 (↑)	4.39 (↑)	↔	↔	TSH: ↔ T3: ↔ T4: ↔	Normal	Enlarged Virchow-Robin's space	Normal	AI TPO ↑ cMRI
3	37 years; female, paranoid-hallucinatory schizophrenia	216.87 (↑)	6.17 (↑)	126.23 (↑)	↔	TSH: ↔ T3: ↔ T4: ↔	Slight BBB-dysfunction (protein concentration: 532 mg/L; albumin quotient: 6.6[b])	Asymmetry of ventricles with enlarged right lateral ventricle	Interm. bitemporal theta/delta slowing	AI TPO ↑ CSF cMRI EEG
4	49 years, female, acute polymorph psychotic disorder with schizophreniform symptoms	153.29 (↑)	1.84 (↑)	↔	↔	TSH: 0,03 (↓) T3: ↔ T4: ↔	Normal	Isolated unspecific white matter lesions	Normal	AI TPO ↑ TH cMRI
5	31 years, female, paranoid-hallucinatory schizophrenia	62.96 (↑)	5.17 (↑)	↔	↔	TSH: ↔ T3: ↔ T4: ↔	Normal	Isolated unspecific frontal white matter lesions; asymmetry of ventricles with enlarged left lateral ventricle	Normal	AI TPO ↑ cMRI
6	25 years, male, schizoaffective disorder	88.25 (↑)	2.32 (↑)	↔	↔	TSH: ↔ T3: ↔ T4: ↔	Normal	Normal	Interm. frontal slowing	AI TPO ↑ EEG
7	30 years, female, schizoaffective disorder	697.28 (↑)	8.16 (↑)	↔	↔	TSH: ↔ T3: ↔ T4: ↔	Normal	Posttraumatic changes with a right frontal contusion lesion: right side accentuated gliosis of WM	Normal	AI TPO ↑ cMRI
8	24 years, male, paranoid-hallucinatory schizophrenia	183.83 (↑)	2.38 (↑)	↔	↔	TSH: ↔ T3: ↔ T4: ↔	Distinct BBB-dysfunction (protein concentration: 1510 mg/L; albumin quotient: 20.8)	Normal	Interm. general. theta/delta slowing; rare epileptic activity	AI TPO ↑ CSF EEG
9	49 years, female, schizoaffective disorder	54.24 (↑)	3.76 (↑)	↔	↔	TSH: 0.25 (↓) T3: ↔ T4: 23.40 (↑)	One isolated band in CSF and serum	Isolated unspecific white matter lesions	Intermitt. general. theta slowing	AI TPO ↑ TH CSF cMRI EEG
10	52 years, female, schizoaffective disorder	319.53 (↑)	7.65 (↑)	↔	↔	TSH: 6.83 (↑) T3: ↔ T4: ↔	Identical oligoclonal bands in CSF and serum	Normal	Normal	AI TPO ↑ TH CSF

continued

TABLE 4, *continued*

Item	Age (Years), Gender, Syndrome	Serum Anti-TPO	AI Anti-TPO	Serum Anti-TG	AI Anti-TG	Thyroid Status	CSF	cMRI	EEG	Overall Alterations
11	21 years, female, paranoid-hallucinatory schizophrenia	166.91 (↑)	1.54 (↑)	↔	↔	TSH: ↔ T3: ↔ T4: ↔	Normal	Slightly enlarged perivascular spaces in the basal ganglia on both sides	Normal	AI TPO ↑ cMRI
12	21 years, female, paranoid-hallucinatory schizophrenia	96.02 (↑)	1.67 (↑)	↔	↔	TSH: ↔ T3: ↔ T4: ↔	Normal	Normal	Normal	AI TPO ↑
13	61 years, female, schizoaffective disorder	↔	↔	112.67 (↑)	1.84 (↑)	TSH: ↔ T3: ↔ T4: ↔	Slight increased protein concentration (556 mg/L)	Unspecific white matter lesions	Normal	AI TG ↑ cMRI CSF

[a] Abbreviations: ↑, increased; ↔, normal; ↓, decreased; AI, antibody index; CSF, cerebrospinal fluid; cMRI, cerebral magnetic resonance imaging; EEG, electroencephalography; TSH, thyroid-stimulating hormone; t3, triiodothyronine; t4, thyroxine; TG, thyroglobulin; TH, thyroid hormones; TPO, thyroid peroxidase; WM, white matter.

[b] Age-dependent reference value was $6{,}5\times10^{-3}$ in this case (see reference [27]).

not treated with corticosteroids; therefore, this question cannot be answered at present.

Pathophysiological Meaning of Increased AIs

Increased AIs can be found in inflammatory neurological conditions (e.g., herpes zoster, Lyme neuroborreliosis).[22,27] For antibodies against intracellular synaptic antigens (e.g., anti-GAD antibodies) and intracellular onconeural antigens (e.g., anti-Yo antibodies), AIs have also been shown to be effective in the detection of intrathecal antibody synthesis.[24,25] Increased AIs allow semi-quantitative evaluation of the intrathecal antigen-specific humoral immune reaction. Intrathecal antibody synthesis occurs as a consequence of activated plasma cell clones within the CNS. Therefore, our results support the idea of central autoimmunity in the pathophysiology of schizophreniform patients with thyroid autoantibodies. However, it is still unclear whether the thyroid anti-TPO and anti-TG antibodies play an etiopathogenic role (i.e., cytopathic or functional effects) or whether they are only an epiphenomenon of underlying autoimmune processes, comparable with the "MRZ reaction" in patients with multiple sclerosis.[34,35] The hypothesis of a direct etiopathogenic role of antithyroid autoantibodies could be supported by cross-reactivity between the thyroid gland and CNS epitopes.[35] Findings in line with this were provided by Blanchin et al.,[30] who demonstrated that anti-TPO antibodies in patients with HE can bind to cerebellar astrocytes. In contrast, serum antibodies from patients with only Hashimoto's thyroiditis did not bind to cerebellar tissue.[30] In turn, astrocytes are important for immunomodulation via cytokines and for glutamatergic signaling, which might be associated with neuronal dysfunction and schizophreniform symptoms in a subgroup of patients with HE.[35,36] To our knowledge, similar results have not been found for anti-TG antibodies. Clearly, further research is necessary. In particular, it would be interesting to clarify whether passive transfer of anti-TPO antibodies (from HE patients) produces the same symptoms in animal studies, which would contradict the hypothesis that such antibodies are a pure epiphenomenon. Moreover, researchers should analyze the binding sites of antithyroid autoantibodies on brain slices and whether immunization with putative antigens allows the development of an animal model for HE.[30]

The Role of Antithyroid AI Measurement in Diagnostic Procedures

Thyroid antibodies should be measured independently of thyroid hormone status, as we found normal thyroid hormone levels in 10 of 13 patients with thyroid autoantibodies. Based on the results of this study and earlier studies by our group,[4,21] we suggest a broad routine work-up for schizophreniform patients with increased thyroid antibodies. The routine work-up should include a cMRI (to detect white matter lesions or other nonspecific alterations), an EEG (to detect frequent slowing or epileptic activity), neuropsychological

TABLE 5. Laboratory and Instrument-Based Findings in Patients With and Without Increased Antithyroid Antibody Indices (AIs)[a]

	Patients With Increased AIs (N=13)			Patients With Normal AIs (N=87)			p
Measurement	Mean±SD	Number of Cases	Frequency of Alterations	Mean±SD	Number of Cases	Frequency of Alterations	Statistics
Serum[b]							
TSH	2.29±1.90	↔: 10 ↑: 1 ↓: 2 (range: 0.03–6.83)	23.1%	2.40±2.29	↔: 78 ↑: 8 ↓: 1 (range: 0.06–19.32)	10.3%	p=0.865
T3	4.66±0.81	↔: 13 ↑↓: 0 (range: 3.84–6.52)	0%	4.74±0.92	↔: 79 ↑: 2 ↓: 6 (range: 2.43–7.20)	9.2%	p=0.784
T4	17.29±2.67	↔: 12 ↑: 1 (range: 12.50–23.40)	7.7%	16.50±3.31	↔: 82 ↑: 3 ↓: 2 (range: 9.20–26.30)	5.7%	p=0.410
CSF[b]							
White blood cell count	1.46±0.66/μl	1–4 cells: 13 ≥5 cells: 0 (range: 1–3 cells/μl)	0%	2.29±6.32/μl	1–4 cells: 84 ≥5 cells: 2 (range: 1–59 cells/μl)	2.3%	p=0.639
Protein concentration	432.62±341.72 mg/l	↔: 10 ↑: 3 (range: 206–1510 mg/l)	23.1%	450.39±303.39 mg/l	↔: 51 ↑: 36 (range: 165–2890 mg/l)	41.4%	p=0.847
Albumin quotient	5.58±4.78	↔: 11 ↑: 2 (range: 2.50–20.8)	15.4%	5.80±4.17	↔: 70 ↑: 17 (range: 2.00–38.70)	19.54%	p=0.867
Immunoglobulin-G-index	0.48±0.05 mg/l	↔: 13 ↑: 0 (range: 0.41–0.61 mg/l)	0%	0.50±0.08 mg/l	↔: 85 ↑: 2 (range: 0.42–0.95 mg/l)	2.3%	p=0.558
Oligoclonal bands		No: 11 Yes: 2 (restricted to CSF: 1; OCBs mirror pattern: 1)	15.4% restricted to CSF: 7.7% mirror pattern: 7.7%		No: 80 Yes: 7 (restricted to CSF: 2; OCBs mirror pattern: 5)	8% restricted to CSF: 2.3% mirror pattern: 5.7%	

	Number of Cases	Frequency	Number of Cases	Frequency	Statistics
cMRI[c]					
White matter lesions/ cerebral microangiopathy	5/13	38.5%	19/80	23.8%	
Generalized cortical atrophy	0/13	0%	3/80	3.8%	
Localized cortical atrophy	0/13	0%	1/80	1.3%	
Other alterations	1/13	7.7%	5/80	6.3%	

continued

TABLE 5, *continued*

	Number of Cases	Frequency	Number of Cases	Frequency	Statistics
Anatomic variations	3/13	23.1%	5/80	6.3%	
Overall alterations	Yes: 9 No: 4		Yes: 33 No: 47		p=0.060
EEG[c]					
Continuous generalized slow activity	0/13	0%	2/87	2.3%	
Continuous regional slow activity	0/13	0%	0/87	0%	
Intermittent generalized slow activity	3/13	23.1%	20/87	23.0%	
Intermittent regional slow activity	1/13	7.7%	3/87	3.4%	
Epileptic activity	1/13	7.7%	1/87	1.1%	
Overall alterations	Yes: 5 No: 8		Yes: 26 No: 61		p=0.533

[a] Abbreviations: ↑, increased; ↔, normal; ↓, decreased; cMRI, cerebral magnetic resonance imaging; CSF, cerebrospinal fluid; EEG, electroencephalography; t3, triiodothyronine; t4, thyroxine; TSH, thyroid-stimulating hormone.
[b] Serum and CSF values ware compared using two-sided independent sample t tests.
[c] Only the predominant EEG/cMRI alteration was depicted, EEG and cMRI alterations were compared using Pearson's chi-squared tests.

testing (to identify frequent cognitive impairments and as a follow-up parameter during corticosteroid treatment), CSF diagnostics (to detect BBB dysfunction, increased white blood cell count, or oligoclonal bands), and autoantibody measurements (onconeural/synaptic and cell surface antigens). In cases where SREAT is suspected, an analysis of anti-TPO and anti-TG antibodies in CSF with additional calculation of respective AIs could produce additional information in the diagnostic process. Earlier studies showed that a specific AI seems to be a marker for HE.[29,31] We also found increased AIs in a subgroup of schizophreniform patients. However, further research is needed to determine whether an elevated AI is a prognostic marker for steroid responsiveness and/or long-term prognosis of the disease course in such patients.

Limitations

The main limitation of our study is that it was uncontrolled, as we did not analyze a healthy control group for comparison. However, it would not be ethically justifiable to perform lumbar punctures on healthy controls due to potential complications. Since we included patients since 2006 (before we introduced CSF analyses as a standard procedure), the cohort is not representative of all schizophreniform patients. There was a potential selection bias, as we included only patients at a tertiary care hospital for whom CSF and serum material, as well as full thyroid hormone status, were available. Another limitation is that we focused on thyroid antibodies; however, patients with autoimmune disorders may harbor a panoply of antibodies that might also play a pathophysiological role. Future studies should combine measurements of different, potentially relevant antibodies. One patient with negative antibodies suffered from drug-induced psychosis, and substance abuse could sufficiently explain this patient's symptoms. Future studies should analyze more homogenous cohorts without obvious explanations for their psychiatric symptoms. In addition, it could be interesting to investigate whether drug consumption might lead to BBB dysfunction, allowing thyroid antibodies to transfer into the CNS. With regard to methodology, one criticism may be that the assays were not established for CSF. However, since there are no established measurements for thyroid antibody in CSF, no validated assays were available. Future projects should close this gap. The patients were treated primarily with antipsychotics, and sometimes with anticonvulsants, following the guidelines for schizophrenia. Only recently have we started to do treatment attempts with intravenous steroids in such constellations. Therefore, none of the patients in our sample had received such a steroid treatment, and thus we were unable to analyze difference in response to steroids between patients with and without abnormal AIs. Our results might be influenced by the effects of antipsychotic/anticonvulsant medications, for which no correction was performed. Additionally, the statistical analysis of possible group effects between patients with and without elevated AIs might have produced false

negative results because of the small size of the AI positive group (N=13).

CONCLUSIONS

In summary, we were able to detect increased antithyroid specific AIs in a relevant subgroup of our cohort of schizophreniform patients and also in the subgroup of those schizophrenia patients with positive serum thyroid antibodies. Therefore, the signal of intrathecal thyroid antibody detection might be more specific than the analysis of serum antibodies alone. The fact that we found increased AIs supports the hypotheses that intrathecal synthesis of antithyroid autoantibodies occurs in schizophreniform patients and that autoimmune processes might play a pathophysiological role in these patients. Further research is needed to determine whether increased AIs are a prognostic marker for corticosteroid response and disease course.

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