Anti-Neural Autoantibodies Associated with Major Depressive and Bipolar Disorders: Characterization of Psychopathology and Literature Review

Niels Hansen[1,*], Bianca Teegen[2], Dirk Fitzner[3], Jens Wiltfang[1, 4, 5] and Berend Malchow[1]

[1]*Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Göttingen, Germany*

[2]*Clinical Immunological Laboratory Prof. Stöcker; Groß Grönau, Germany*

[3]*Department of Neurology, University Medical Center Göttingen, Göttingen, Germany*

[4]*German Center for Neurodegenerative Diseases (DZNE), Göttingen, Germany*

[5]*Neurosciences and Signaling Group, Institute of Biomedicine (iBiMED), Department of Medical Sciences, University of Aveiro, Aveiro, Portugal*

Abstract: *Background;* Neural autoantibodies in depression are rarely reported, and their prevalence in depression is unknown. Our study was therefore dedicated to analyzing the frequency of neural autoantibodies in a cohort of patients presenting mood disorders. In addition, the study served to describe the clinical psychopathology of the patients with depressive disorders and neural autoantibodies.

Methods; We retrospectively examined a cohort of 41 patients with major depressive disorder and bipolar affective disorder. Patient files were evaluated for clinical data, psychopathological assessment, as well as magnetic resonance imaging (MRI), electroencephalography (EEG), cerebrospinal fluid analysis findings and serum and/or cerebrospinal fluid (CSF) neural autoantibodies.

Results; Our study revealed neural autoantibodies in of 6 of 41 (14%) of patients with mood disorders suspicious for an underlying organic cause. CSF autoantibodies were verified in 3 of 41 (7%) patients with mood disorders. No differences between antibody-positive and -negative mood disorder patients were identified regarding psychiatric syndromes or CSF, EEG, MRI and psychopathological parameters. However, mood-disorder patients with autoantibodies revealed less loss of drive than those mood disorder patients without autoantibodies.

Conclusions; Our findings indicate that a minority of mood disorders might be associated with neural autoantibodies. The proof of CSF autoantibodies in three of six autoantibody-positive patients suggests highly likely paraneoplastic or autoantibody-mediated autoimmunity. Our study's novelty is the in-depth phenotyping of autoantibody-positive depressed patients via two different psychometric scoring systems. More research is required to confirm these preliminary results in larger cohorts with more homogeneous patient groups.

Keywords: Neural autoantibody, Depression, Autoimmunity, Mood dysfunction, Psychopathology.

1. INTRODUCTION

Affective disorders are frequent in humans. Accurate diagnosis is therefore important to enable early therapy and treatment of such patients. There is recent evidence that mood disorders are associated with neuronal autoantibodies [1-7], which may form an organic basis of affective disorders. Both unipolar depressive disorders [2, 5] and bipolar affective disorders [8, 9, 10] have been reported to be associated with neural autoantibodies. Mostly neural autoantibodies against membrane-surface autoantibodies such as antibodies against the N-methyl-D-aspartate receptor (NMDAR) [2], or (very seldom) antibodies against the intracellular target glutamic decarboxylase 65 (GAD65) [1] have been detected. However, investigations targeting autoantibodies in mood disorders are rare. The significance of these associated neural autoantibodies is not known in particular if no autoimmune encephalitis according to Graus criteria [11] is diagnosed. Less frequently than NMDAR autoantibodies, antibodies against contactin-associated protein-like 2 (CASPR2) and antibodies against α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) were detected in a minority of 925 psychiatric patients [9]. In contrast, antibodies against leucine-rich glioma-inactivated protein-1 (LGI1), γ-aminobutyric acid B (GABAB) receptor, and AMPAR are detected much less often than the aforementioned autoantibodies in psychiatric patients [9]. The aim of our study was to determine the occurrence of these and other neural autoantibodies in a cohort of psychiatric patients with diverse mood disorders ranging from bipolar affective disorder to major depressive disorder. As an additional goal, we posed the question as to whether the clinical

*Address correspondence to this author at the Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Von-Siebold-Str. 5, 37075 Göttingen, Germany; E-mail: niels.hansen@med.uni-goettingen.de

and psychopathological phenotypes of mood disorders with and without autoantibodies differ. We are keen to investigate the phenotype of patients with mood disorders and autoantibodies because we recently discovered in an exploratory analysis that psychiatric patients without autoantibodies more frequently present affective symptoms such as affective rigidity, blunted affect, and higher suicidality [12]. Our study was thus dedicated to investigating whether the psychopathology and clinical phenotype differ between autoantibody-positive versus -negative patients in a cohort of affective patients. We also aimed to describe the deep clinical phenotype of affective symptoms taking two different psychometric approaches in autoantibody-positive vs. negative patients.

2. METHODS

Between 2017 and 2020, we examined for differential diagnostic reasons the blood and cerebrospinal fluid (CSF) for neural autoantibodies in 41 patients with depression. We relied on the 10th version of the international classification system of diseases (ICD10) to classify mood disorders. We had our patients undergo extensive differential diagnostics to seek organic reasons for their mood disorder, including of the examination of serum and/ or CSF autoantibodies. We included patients with a depressive disorder in whom we screened for neural autoantibodies in their serum and/or cerebrospinal fluid (CSF) in our Department of Psychiatry and Psychotherapy during differential diagnosis to exclude an organically caused depressive disorder. Our sole exclusion criterion was any other psychiatric disorder apart from depression as the main diagnosis.

Psychopathology was retrospectively analyzed in patient files using two different rating systems. The AMDP (Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie) system [13] was used to assess psychopathology, whereas the HiTOP (Hierarchical Taxonomy of Psychopathology) system [14] was applied to reveal psychopathological abnormalities (in line with other viewpoints about psychopathology that supplements the AMDP system). The AMDP system considers the different domains of psychopathological findings and psychopathological syndromes. Applying the HiTOP classification, we highlighted the presence of certain spectra and factors in our patients. We retrospectively assessed additional clinical data from these patients such as CSF parameters, magnetic resonance imaging (MRI) and electroencephalography (EEG). MRI was done via 1.5T MRI in the Department of Neuroradiology, University Medical Center Göttingen or outside in a center for radiologic diagnostics. The EEGs (Natus GmbH, Planegg, Germany) were mainly performed in the Department of Psychiatry and Psychotherapy and Department of Neurology, University Medical Center Göttingen. CSF analysis was conducted in the Neurochemical Laboratory of the Neurological Clinic at the University Medical Center Göttingen. Neuronal cell destruction markers were assessed considering these cut-off values [non-pathological if a) tau protein <450 pg/ml, b) ptau181 <61 pg/ml, c) β-amyloid 42 (Aβ42) >450 pg/ml, and d) ratio Aβ1-42/Aβ1-40 ×10 >0.5]. Commercial ELISA from Fujirebio (Tokyo, Japan) [INNOTEST hTAU-Ag; INNOTEST PHOSPHO TAU (181P)] were used as assays to measure neuronal cell destruction markers in CSF. In contrast, to investigate amyloid-beta pathology in CSF, we relied on commercially available INNOTEST® β-AMYLOID (1-42) ELISA kit (Fujirebio) to determine Aβ1-42, and commercially available ELISA from IBL [AMYLOID BETA (1-40)] to assess Aβ1-40. Follow up investigations of patients are not performed and are not part of the cohort study. This study was approved by the Ethics Committee of the University Medical Center Göttingen (Protocol code: 1/6/20, date of approval: 15 June 2020) and concurs with the current Declaration of Helsinki. The study followed the STROBE guidelines for observational studies.

2.1. Assessment of Neural Autoantibodies

The autoantibody testing procedures were done at the Clinical Immunological Laboratory Prof. Stöcker.

2.1.1. Indirect Immunofluorescence Testing

We used standard indirect IgG immunofluorescence (IFT) assays to detect neural IgG autoantibodies against the following membrane and/or intracellular localized antigens in CSF and serum: anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors 1/2 (AMPAR1/2), -amphiphysin, -aquaporin 4, -CASPR2, -dipeptidyl peptidase-like 6 protein (DPPX), -gamma-aminobutyric acid B1/2 receptor (GABAB1/2R), -GAD65, -Hu, -IgLON5, - LGI1, -Ma2/Ta, -myelin oligodendrocytic glycoprotein (MOG), -NMDAR, -Ri, -titin, -Tr/DNER, -Yo, and -Zic4. The cut-off positivity was 1:10 to detect the above-mentioned serum autoantibodies. We also ran standard IFT tests to screen for ANNA3 (anti-neuronal nuclear antibody type 3) (cut-off threshold 1:10) and anti-myelin autoantibodies (cut-off threshold 1:100). For the IFT test procedure, specific antibodies from the patient's

serum or CSF sample are bound when present in rodent brain tissue. A fluorescein-labeled antibody is then bound to the specific antibodies from the serum and CSF sample and visualized using a fluorescence microscope.

2.1.2. Cell-Based Assay

Separate cell-based assays were used to detect these autoantibodies against Hu, Ri, Yo, Tr/DNER, Ma/Ta, GAD65, amphiphysin, MOG, NMDAR, AMPAR, GABAA/BR, LGI1, CASPR2, IgLON5, Zic4, DPPX, glycine and recoverin.

2.1.3. Immunblots

Specific antibodies from a serum or a CSF sample are bound to the respective antigens by means of an immunoblot. A labeled antibody is then added, with an alkaline phosphatase label. This labeled antibody binds again to the specific antibodies. The additionally added nitro blue tetrazolium chloride/5-bromo-4-chloro-3-indolyl phosphate is catalyzed by the alkaline phosphatase and a dark line label appears at the respective antigen position. We used a EUROLINE immunoblot to study the following antigens: amphiphysin, CV2, Ma2/Ta, Ri, Yo, Hu, recoverin, SOX1, titin, Zic4, GAD65, and Tr/DNER. The EUROLINE immunoblot (DL 1111-X-G) consists of a BIOCHIP technology where multiparameter line blots allow combined antibody profiles to be visualized on one test strip via automatic evaluation. The EUROLine Scan performs a fully automated evaluation of the membrane-based test systems. The software identifies and measures the bands. For the determination of paraneoplastic antibodies, a combination of IIF on cerebellum rodent brain tissue (see 2.1.1) and line blot was performed.

2.2. Statistical Approach

We used Sigma Stat (Sigma Stat, Version 11) to calculate statistics and Sigma Plot (Sigma Plot, Version 11) to make the graphs. CSF data and age of patient groups were analyzed via Students *t*-tests. Relative frequencies of gender, psychiatric syndromes, autoimmune indicators, MRI pathology and EEG abnormalities between autoantibody-negative and -positive patients were addressed via Fisher´s exact test. The frequency of psychopathology items measured via HiTOP or AMDP system were also calculated by Fisher´s exact tests. The p-level of $p<0.05$ was considered significant.

3. RESULTS

3.1. Prevalence of Anti-Neural Autoantibodies in Patients with a Mood Disorder

Our group consisted of 41 patients presenting different types of mood disorders ranging from minor and major depressive disorder to bipolar disorder. All 41 patients were tested for neural autoantibodies in serum, and n=39 were also tested for neural autoantibodies in CSF. In our cohort, 6/41 (14%) of patients with mood disorders (clinical characterization in Tables **1**, **2**) revealed neural autoantibodies. Neural CSF autoantibodies were found in association with mood disorders in 3/41 (7%) patients. In addition, the antibody-positive patients had autoantibodies in serum (5/6 patients) or in CSF (3/6 patients) or in both serum and CSF (2/6 patients). No tumor was detected in the autoantibody-positive patients. While the autoantibody-negative group consisted of these mood-disorder diagnoses: F31.2 n=3, F31.3 n=1, F31.4 n=2, F32.1 n=2, F32.2 n=7, F32.3 n=6, F33.2 n=7, F33.3 n=6, F33.4 n=1, the autoantibody-positive group comprised the following diagnoses: F31.2 n=1, F32.1 n=1, F32.2 n=1, F33.1 n=1, F33.2 n=2. In summary, n=1 of the antibody-positive patients and n=5 of the antibody-negative patients had a bipolar affective disorder, whereas n=5 of the antibody-positive patients and n=29 of the antibody-negative patients had a unipolar affective disorder. Overall, 3/6 (50%) had suffered a chronic mood disorder and 3/6 (50%) a novel manifestation of a mood disorder as antibody-positive patients, whereas 25/35 (71%) of antibody-negative patients exhibited a chronic disease course, and 15/35 (42%) a subacute disease manifestation. Considering the unipolar-depressive disorder patients as a group, we detected neural autoantibodies in 5 of 29 (17%) of them, confirming a similar percentage as in the whole cohort of mood-disorder patients. 2/29 (7%) of patients with unipolar depression presented CSF autoantibodies. The clinical psychopathological features according to the AMDP- and HiTOP-systems of autoantibody-positive patients are shown in Table **3**. Our patient groups revealed no significant differences in age, gender, frequency of psychiatric syndromes, epileptic potentials or slowing in EEG, generalized, focal or hippocampal atrophy in MRI (Table **1**). Even relevant autoimmune indicators failed to differ between groups. Autoimmune indicators are "red flags," or clinical signs and symptoms often occurring simultaneously in patients with autoimmune encephalitis and psychiatric symptomatology [15]. Such "red flags" are signs such as

Table 1: Clinical and Laboratory Characteristics of Patients

	AB+ N=6	AB- N=35	STATISTICS, P-VALUE
AGE YEARS	52 ± 14	52 ± 17	
GENDER (FEMALE)	3/6 (50%)	16/35 (46%)	1
ADDITIONAL PSYCHIATRIC SYNDROMES			
Apathic	0/6 (0%)	3/35 (9%)	1
Hostility	1/6 (17%)	1/35 (3%)	1
Maniforme	1/6 (17%)	1/35 (3%)	1
Neurological	0/6 (0%)	5/35 (14%)	1
Obessive-compulsive	0/6 (0%)	2/35 (6%)	1
Parahallucinatory	1/6 (17%)	9/35 (26%)	1
Psychorganic	4/6 (67%)	20/35 (57%)	1
Vegetative	1/6 (17%)	2/35 (6%)	0.386
AUTOIMMUNE INDICATOR			
Actual or recent diagnosis of a tumor	0/6 (0%)	4/35 (11%)	1
Movement disorder	2/6 (33%)	6/35 (17%)	0.57
Adverse response to antidepressants	2/6 (33%)	12/35 (34%)	1
Severe cognitive dysfunction	5/6 (83%)	19/35 (54%)	0.37
Altered consciousness	0/6 (0%)	0/35 (0%)	1
Seizures	1/6 (17%)	1/35 (3%)	1
Aphasia, dysathria or mutism	1/6 (17%)	2/35 (6%)	0.386
Optic hallucinations	0/6 (0%)	2/35 (6%)	1
Infectious prodrome with fever	0/6 (0%)	0/35 (0%)	1
CSF			
Cell count (<5µg/l)	0.6±0.8	0.9±1.3	0.44
Total protein count (mg/l)	452±208	441±210	0.84
Intrathecal IgG synthesis	0/6 (0%)	3/35 (9%)	1
Blood brain barrier disturbance	2/6 (33%)	8/35 (23%)	0.6
T tau Protein (<450pg/ml)	292±183	226±199	0.58
P tau 181 (<61pg/ml)	47±26	49±33	0.94
Aβ42 (>450pg/ml)	1174±711	1177±576	0.99
Aβ40	11059±5856	9948±6801	0.73
Ratio Aβ42/Aβ40 (x10: >0.5)	1.27±0.68	1.1±0.5	0.26
MRI			
Generalized atrophy	1/3 (33%)	11/33 (33%)	0.645
Focal atrophy	0/3 (0%)	4/33 (12%)	1
Hippocampal atrophy	0/3 (0%)	2/33 (6%)	1
EEG			
Temporal focal slowing	2/3 (67%)	9/22 (41%)	0.56
Temporal epileptic potentials	0/3 (0%)	0/22 (0%)	1
Non-temporal focal slowing	2/3 (67%)	9/22 (41%)	0.56
Non-temporal epileptic potentials	0/3 (0%)	0/22 (0%)	1

Abbreviation: Aβ42 = β-amyloid 42, Aβ40 = β-amyloid 40, CSF = cerebrospinal fluid, EEG = electroencephalography, mg/L = milligram per liter, MRI = magnetic resonance imaging, P Tau Protein 181 = phosphorylated tau protein 181, pAb+ = psychiatric patients with neural autoantibodies, pAb- = psychiatric patients without neural autoantibodies, pg/ml = picogram/ milliliter, ratio Aβ42/40 = ratio β-amyloid 42/ β-amyloid 40, µg/L = microgram per liter, Statistics: *p<0.05 Fisher´s exact test. The mean ± standard deviation is given for the parameters cell count, protein count, markers of tau pathology and amyloid-β pathology.

Table 2: Characterization Patients with Anti-Neural Autoantibodies and Mood Disorder

Patient	Autoantibody	Material	Method	Current psychopathological features
1	Ma2 PB, Ma2 CSF	PB, CSF	Immunoblot (Euroline)	Manic episode with psychotic symptoms
2	Yo PB	PB, CSF	Immunoblot (Euroline)	Severe depressive episode without psychotic symptoms
3	Yo CSF	PB, CSF	Immunoblot (Euroline)	Moderate depressive episode without psychotic symptoms
4	REC PB	PB	Immunoblot (Euroline)	Cognitive dysfunction, moderate depressive episode
5	NMDAR PB, NMDAR CSF	PB, CSF	Anti-neural IgG IFT	Severe depressive episode without psychotic symptoms
6	Yo PB	PB, CSF	Immunoblot (Euroline)	Severe depressive episode without psychotic symptoms

Abbreviation: CSF = cerebrospinal fluid, ICD10 = international classification of disease, tenth version, IgG IFT = immunoglobulin immunofluorescence test, NMDAR = N-methyl-D-aspartate-receptor, PB = peripheral blood, REC = recoverin.

Table 3: Detailed Psychometric Data and Autoimmune Indicators of Autoantibody-Positive Patients

Patient	Domains, AMDP	Spectra and Subfactors, HiTOP	Syndrome, AMDP	Autoimmune Indicators ("Red flags")
1	• Disorientation • Formal thought disorder • Delusions • Ego disturbances • Affective disturbances • Psychomotor disturbances • Lack of insight into illness • Refusing treatment	• Internalizing mania • Thought disorder	• Parahallucinatory • Psychoorganic • Hostility • Manic	• Severe cognitive dysfunction
2	• Cognitive dysfunction • Formal thought disorder • Affective disturbances • Psychomotor disturbances	• Internalizing distress	• Depressive	• Severe cognitive dysfunction • Adverse response to antipsychotics or antidepressive drugs
3	• Cognitive dysfunction, • Formal thought disorder • Phobia • Affective disturbances • Psychotomor disturbances	• Somatoform • Sexual problems • Internalizing distress • Internalizing fear •	• Depressive • Psychoorganic	• Aphasia, mutism or dysarthria • Movement disorder • Severe cognitive dysfunction
4	• Cognitive dysfunction • Formal thought disorder • Ego disturbances • Affective disturbances • Compulsive thoughts	• Internalizing fear • Internalizing distress	• Psychoorganic • Depressive	• Severe cognitive dysfunction
5	• Affective disturbances • Psychomotor disturbances • Circadian rhyhm disturbances • Social withdrawal	• Intenalizing distress	• Depressive • Vegetative	• Autonomic dysfunction
6	• Cognitive dysfunction • Formal thought disorder • Affective disturbances • Self harm • Psychomotor disturbances	• Internalizing distress, • Disinhibited externalizing substance abuse • Disinibited externalizing antisocial behavior • Antagonistic externalizing antisocial behavior	• Depressive • Psychoorganic	• Epileptic seizure • Autonomic dysfunction • Movement disorder • Aphasia, mutism or dysarthria

Abbreviations: AMDP = Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie, HiTOP= Hierarchical Taxonomy of Psychopathology.

an actual or recent tumor, seizures, movement disorders, adverse response to antidepressant drugs, altered consciousness, severe cognitive dysfunction, aphasia, dysarthria and mutism, optic hallucinations

and/or infectious prodrome with fever. Neuronal cell destruction markers did not differ between groups either (p-tau181, total tau protein, Aβ42, Aβ40 and ratio Aβ42/Aβ40) (see Table **1**). We investigated neuronal cell damage markers because cohort studies have yielded evidence [16, 17] of neuronal cell damage in autoantibody-associated neuropsychiatric disorders. No additional immunotherapy was given to the patients, as there was no clinical evidence of an autoimmune or immunogenic cause despite the presence of neural autoantibodies.

3.2. Psychopathology Comparison between Mood-Disorder Patients with Versus without Anti-Neural Autoantibodies

We compared mood disorders associated with autoantibodies versus those without autoantibodies regarding their psychopathology domains and in particular, affective and psychomotor abnormalities and drive disorders, as also be referring to the AMDP system (Figure **1**).

Mood-disorder patients with autoantibodies showed less loss of drive compared to those patients with a mood dysfunction without autoantibodies ($p<0.05$, Figure **1**). Furthermore, the HiTOP classification showed no relevant differences between patient groups regarding HiTOP spectra, subfactors, fear, distress and the item emotional dysfunction (Figure **2**).

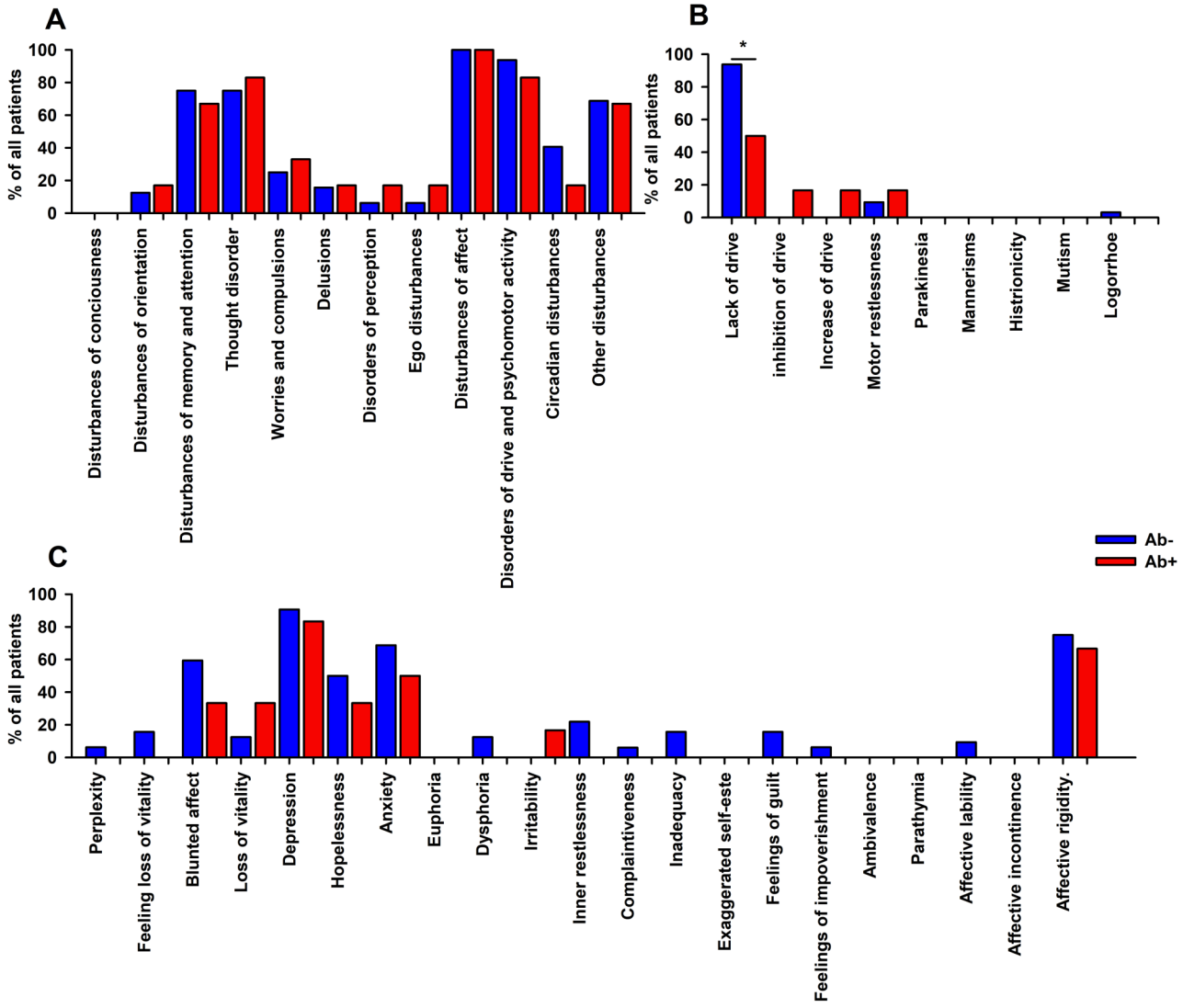

Figure 1: Psychopathology of antibody-positive versus -negative mood-disorder patients assessed by AMDP.

The lack of drive is more obvious in autoantibody-negative (Ab-) than in antibody-positive (Ab+) mood disorder patients. $p<0.05$, Fisher´s exact test. AMDP domains are shown in A, while other AMDP disorders are in B; the spectrum of affective disorders is in C.

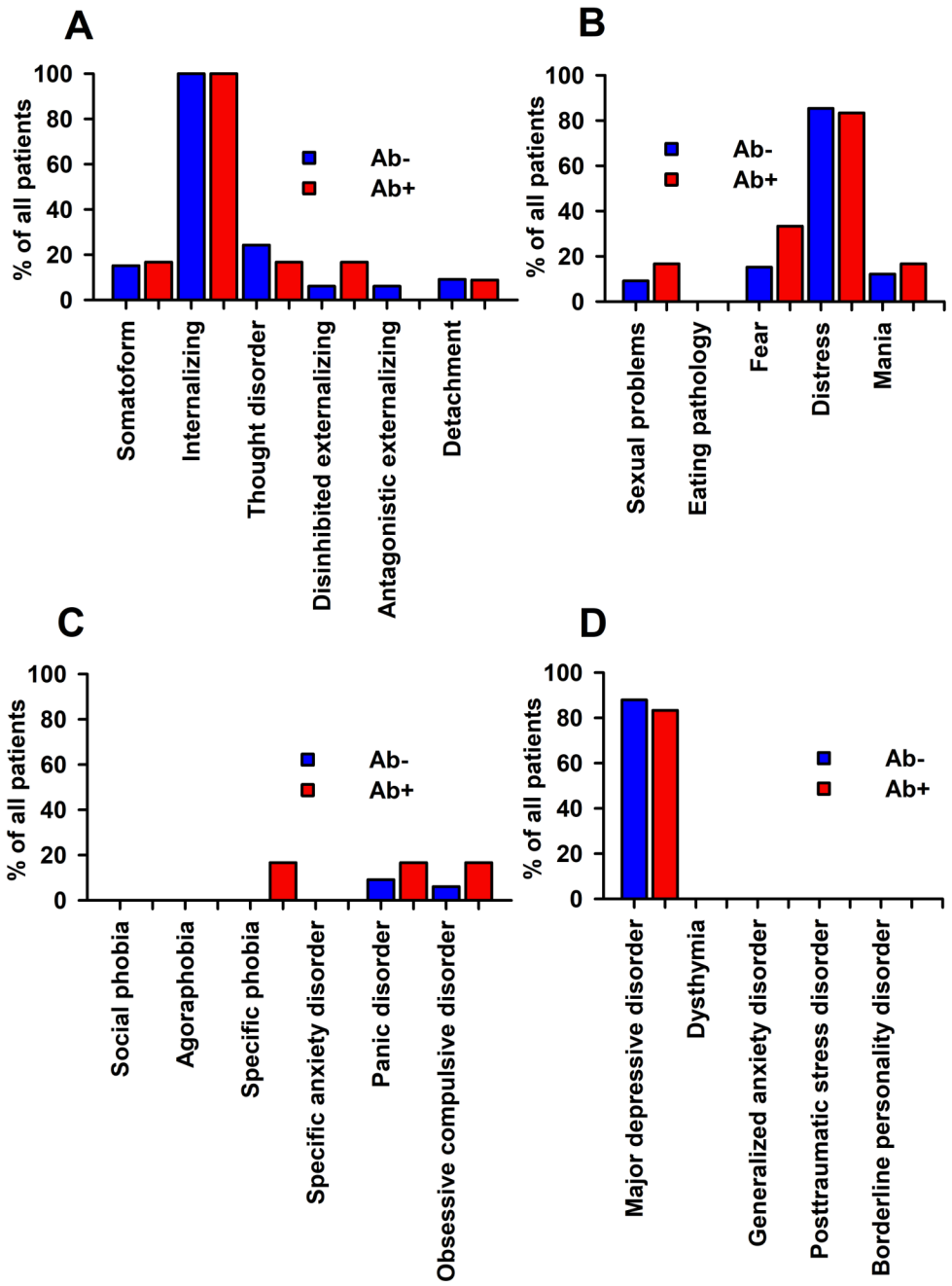

Figure 2: Psychopathology of antibody-positive versus -negative mood-disorder patients assessed by HiTOP.

No differences in their psychopathology were observed in autoantibody-positive (Ab+) versus -negative (Ab-) mood-disorder patients regarding HiTOP spectra, subfactors and subfactors of the spectra internalizing as well as subfactor fear and distress syndromes/disorders. In A the spectra of HiTOP classification are shown and in B the internalizing spectrum of HiTOP for the patient groups is delineated. The internalizing subfactors Anxiety of the patient groups in C and distress of the patient groups in D are shown.

4. DISCUSSION

Our main findings indicate that neural autoantibodies occur in a minority of psychiatric patients suffering a mood dysfunction and mainly major depressive disorder. The novelty in our research is that we have illuminated the psychopathology of these autoantibody-positive affective disorders in detail and compared their psychopathology to a group without neural autoantibodies. This is an entirely new approach. More neuroimmunological studies with blood and CSF samples are planned, ie, a study involving recent depression, the protocol of which has been published [1]. This therefore is a new approach; psychopathology has been studied in detail in psychiatric [12] and especially psychotic patients

[18-21], but not in predominantly depressed patients. The spectrum of neural autoantibodies in mood disorders is mainly characterized by cell surface, but less often by intracellular autoantibodies [1]. We detected mainly paraneoplastic autoantibodies in our mood-disorder patients. Paraneoplastic autoantibodies are believed to involve a T-cell mediated immunopathology [22] that differs from the probable antibody-mediated immunopathogenesis in most membrane-surface autoantibodies. The relevance of especially paraneoplastic autoantibodies in depression is thus unclear. Nevertheless, we should suspect a T-cell mediated immunopathology in patients presenting CSF paraneoplastic autoantibodies. Our findings indicate that a minority of autoantibodies are relevant also in depressive disorders, and they might also even indicate an underlying tumor prior to tumor manifestation. Therefore, a differential diagnostic procedure would be necessary especially when the clinical symptomatology such as hyperhidrosis or weight loss without intention indicates a potential neoplastic process. Our cohort possesses a relatively high proportion of patients with mood disorders associated with intracellular and membrane-surface autoantibodies compared to large previous studies [23]. Endres *et al*. [23] detected membrane-surface and intracellular autoantibodies in 4/ 535 (0.74%) patients with affective syndromes. The different prevalence of autoantibodies in affective disorders is probably based on the differences in the study cohorts. However, their rationale for assessing autoantibodies is less clear, as in our study we determined autoantibodies as part of an extensive differential diagnostic approach to exclude CNS inflammation. Another large analysis of NMDAR autoantibody-positive patients showed that a depressive symptomatology often coexists with a psychotic syndrome [2]. However autoimmunity in mood disorders has been far less often reported in conjunction with neural autoantibodies - more frequently with thyroid-based autoimmunity accompanied by anti-thyroid antibodies [24]. Recent reports postulated a relationship between aquaporin 4 antibodies and depressive disorders [25] – a finding we could not verify in our cohort, as Gur *et al*. did in their recent investigation [26]. Another interesting finding is that the lack of drive in our cohort's autoantibody-negative patients is much less obvious compared to autoantibody-positive patients with mood disorders. These preliminary data will have to be confirmed in larger studies, but this evidence might indicate that some psychopathological differences might have diagnostic relevance if confirmed in large-scale studies. We look forward to pursuing this line of research in future studies. Another interesting aspect is that the presence of autoantibodies in depressive disorders is higher in blood than in CSF. However, this only confirms cohort study evidence on autoantibody-associated psychiatric disorders [23, 1]. The presence of autoantibodies in the blood per se, without other indications of brain damage or brain inflammation, is of limited importance. Serum detection is very important to identify paraneoplastic antibodies, and justifies a subsequent tumor search, as the tumor is often located outside the brain. A recent study highlighted that the presence of autoantibodies per se does not define a causal relationship with symptomatology, as autoantibodies are found in 400 of 2748 (14.56%) healthy subjects as well, according to a recent study with control subjects and schizophrenic and depressive patients [27]. The differences in the presence of autoantibodies in blood and CSF probably cannot be explained by differences in technology, as the same technology was used in the CSF and blood probes to determine autoantibodies. On the other hand, a recently published study showed that stroke patients with predominantly IgA and IgM NMDAR autoantibodies presented worse depressive symptoms [28]. This suggests that there may be a relationship between autoantibody-associated immunopathology and the severity of affective symptoms, but we must add that there is no causal, only a subsidiary role that autoantibodies play in relation to depressive symptoms. However, the link between autoantibodies and depressive symptoms has also been confirmed in other autoimmune and inflammatory diseases, in which a subtype can be identified in which autoantibodies and depression often occur in combination [29].

4.1. Limitations

The limitations of this study concern a small cohort already suspected of having organic causes of depressive disorders. Due to the exploratory nature and the small number of patients in this retrospective study, we explicitly refrained from correcting for multiple testing. Keeping this limitation in mind, the occurence of autoantibodies in mood disorders must be considered carefully. This must also be especially considered because we cannot rule out a selection bias in all patients. This addresses the potentially organic cause of the affective disorder, which is more likely to be diagnosed in our patients than in a non-selected

patient group with depressive disorders, as we carried out autoantibody diagnostics in all of our affective patients for differential diagnostic reasons. Furthermore, our cohort is not homogeneous, as it comprises various mood disorders ranging from bipolar affective disorder to unipolar depression in a chronic or subacute *de novo* presentation. In addition, as the autoantibody spectrum is heterogeneous, the effect of specific autoantibodies on the psychiatric phenotype cannot be investigated in large sample sizes. In addition, the low number of seropositive patients limits our means of studying the relationship between autoimmunity and neuronal destruction in more detail here. It is well known that autoimmune processes can lead to neuronal dysfunction and even neurodegenerative processes, as recently shown in a study applying CSF proteomics [30]. It is also worth mentioning that the number of antibody-positive patients is low, but so is the number of patients in whom we detected serum and/or CSF autoantibodies, so that our conclusions can only be evaluated in consideration of the low patient numbers. We also add that there was no clear clinical evidence of an autoimmune-mediated cause despite the presence of neural autoantibodies. In principle, it is conceivable that immunotherapy could be administered to such patients as an individualized attempt to treat a probable immune-mediated cause of an affective disorder. However, this should be carefully considered, as such immunotherapy, especially corticosteroids, always carry the risk of inducing significant mood swings. The pathophysiological role of autoantibodies in the context of affective disorders is not yet understood, so no assumptions have been made in this regard. It is also important to mention that we cannot completely rule out the possibility that false positive measurements were taken. However, each measurement was carefully checked and additional cell-based assays were carried out, so that the probability of false positive test results is low. As we conducted combined testing using indirect immunofluorescence tests and lineblot, the probability that paraneoplastic antibodies are true positives is high.

4.2. Conclusions

Our cohort has a substantial minority of patients with mood disorders associated with CSF NMDAR and paraneoplastic autoantibodies. Although our finding is not novel, as paraneoplastic autoantibodies are known to be associated with mood dysfunction [31], its frequent occurrence in mood disorders is surprising as no study so far has proven the frequent occurrence of paraneoplastic antibodies in mood disorders. As every 10th patient might have neural autoantibodies in patients with mood disorders suspicious for organic origin, a routine check for autoantibodies is recommendable in every first diagnosis procedure in patients with mood disorders. Our study highlights the urgency for more studies with large, homogeneous cohorts comprising mood-disorder patients as autoantibodies are one potential cause for mood dysfunction.

AUTHOR CONTRIBUTIONS

NH wrote the manuscript. BT did part of the laboratory testing. All other authors revised the manuscript for important intellectual content.

CONFLICT OF INTEREST

The authors do not report any conflict of interest.

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