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Short Communication

Association of rheumatological markers with neuronal antibodies, cerebrospinal fluid, electroencephalography, and magnetic resonance imaging findings in 224 patients with psychotic syndromes

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ABSTRACT

Introduction: Psychotic syndromes can have autoimmune-mediated causes in some patients. Thus, this retrospective work aims to investigate the role of rheumatological markers in the development of psychosis.
Patients and Methods: In total, 224 patients with psychotic syndromes receiving a "rheumatological laboratory screening" (including C-reactive protein [CRP], immunofixation, complement factors, rheumatoid factor [RF], antiphospholipid antibodies [APAs], antineutrophil cytoplasmic antibodies [ANCAs], and antinuclear antibodies [ANAs]) were analyzed. A further diagnostic work-up included investigations of neuronal antibodies and cerebrospinal fluid (CSF), as well as electroencephalography (EEG) and magnetic resonance imaging (MRI) of the brain. ANA testing was routinely performed in all patients using serum on human epithelioma-2 (Hep2) cells, and a subset of patients (N = 73) also underwent tissue-based assays from serum and CSF. The number of cases with autoimmune psychotic syndromes was descriptively collected, and ANA-positive and −negative patients were compared in detail.
Results: CRP was elevated in 9 % of patients, immunofixation identified alterations in 8 %, complement factor C3 was decreased in 14 %, RF was elevated in 1 %, APAs were elevated in 7 %, ANCAs were not clearly positive, and ANAs were positive in 19 % (extractable nuclear antigen [ENA] differentiation resulted in positive findings in 14 patients). From the 73 patient samples additionally investigated using tissue-based assays, there were 26 positive results for some kind of ANA (36 %), and overall using both methods, 54 patients (24 %) were considered positive for ANAs. A neuropsychiatric evaluation revealed a possible autoimmune psychotic syndrome in seven patients (3 %) and a probable autoimmune psychotic syndrome in two patients (1 %). ANA-positive patients were more frequently treated with antidepressants ($p = 0.040$) and had a higher number of somatic comorbidities ($p < 0.001$). In addition, (chronic) inflammatory MRI lesions ($p = 0.008$) and focal atrophies ($p = 0.012$) were found more frequently in ANA-positive than ANA-negative patients.
Discussion: Rheumatological screening led to suspicion of a possible or probable autoimmune psychotic syndrome in 4%. ANAs were associated with MRI pathologies. Therefore, rheumatological processes may contribute to the development of psychotic syndromes in rare cases.

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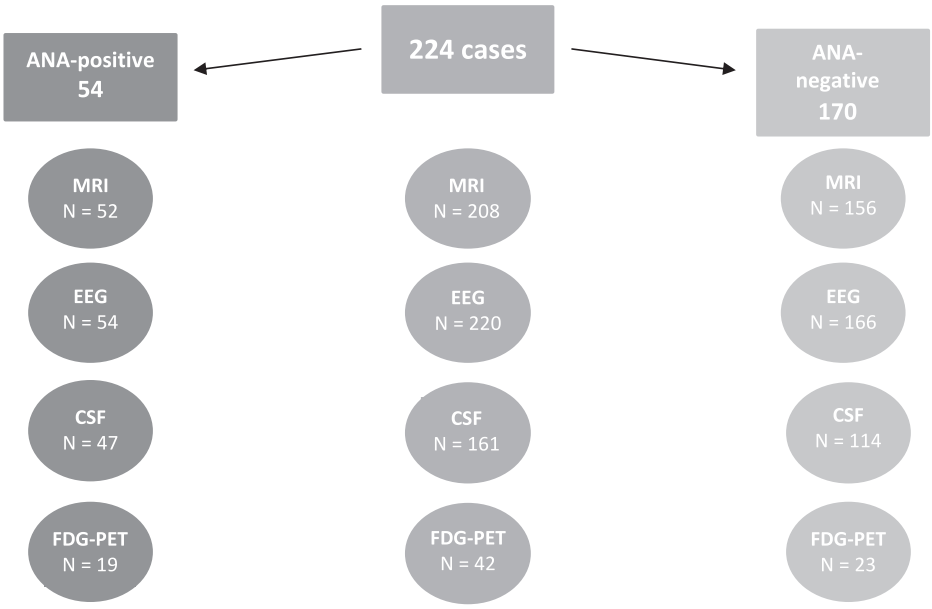

Fig. 1. Available datasets from all 224 patients with psychotic syndromes. Abbreviations: ANA, antinuclear antibodies; CSF, cerebrospinal fluid; EEG, electroencephalography; FDG-PET, [^{18}F]fluorodeoxyglucose positron emission tomography; MRI, magnetic resonance imaging.

1. Introduction

Psychotic syndromes can be caused by organic processes in some patients (Endres et al., 2020a; Keshavan and Kaneko, 2013; Pollak et al., 2020). In the current diagnostic classification systems, including the International Classification of Diseases, 11th Revision (ICD-11), and the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), cases having an organic origin are classified as secondary psychosis. However, an optimal diagnostic approach that excludes secondary psychosis must still be developed. With the initial description of anti-N-methyl-D-aspartate receptor (NMDA-R) encephalitis in 2007, which can manifest with psychotic symptoms, the focus turned to autoimmune-mediated secondary psychosis (Dalmau et al., 2018). In the last few years, numerous further neuronal antibodies have been discovered to be associated with psychosis (Pollak et al., 2020; Prüss, 2021), and international consensus criteria for the diagnosis and treatment of "autoimmune psychosis" have been published (Pollak et al., 2020).

However, long-known autoimmune rheumatological systemic disorders, such as connective tissue disorders (e.g., systemic lupus erythematosus [SLE] or Sjögren's syndrome), in which antinuclear antibodies (ANAs) can usually be detected; anti-neutrophil cytoplasmatic antibody (ANCA)-positive vasculitis (e.g., granulomatosis with polyangiitis or microscopic polyangiitis); or antiphospholipid syndrome with antiphospholipid antibodies (APAs), should also be considered in this context (Najjar et al., 2018; Oldham, 2017; Tebartz van Elst et al., 2022). In the case of inflammatory brain involvement in such rheumatological systemic disorders, psychotic symptoms may occur (e.g., Lüngen et al., 2019; Najjar et al., 2018; Oldham, 2017). Psychosis is explicitly mentioned as a diagnostic criterion in the current classification criteria for SLE (Aringer et al., 2019). As such, in clinical practice, a diagnostic approach to detect rheumatological diseases in patients with psychotic syndromes might be promising.

1.1. Rationale of the study

The results of a broad rheumatological screening of patients with psychotic syndromes are analyzed retrspectively. ANAs can be interpreted as immunological "screening markers," so patients with and without ANAs were compared based on their clinical and diagnostic findings, including neuronal antibodies, cerebrospinal fluid (CSF), electroencephalography (EEG), and magnetic resonance imaging (MRI) findings.

2. Patients and methods

This project is part of a larger retrospective project that was approved from the local ethics committee of the University of Freiburg (approved amendment to the original vote no.: 396/18).

2.1. Patient group

Experienced senior psychiatrists diagnosed patients according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) criteria. All adult patients (≥18 years) treated in our specialized ward for psychosis and secondary mental disorders for over 2.5 years were screened, and those with primary or secondary psychotic syndromes were included in the current analysis (schizophreniform syndromes: F20.X–F29.X, F06.0–2, F10.5–F19.5; depression with psychotic symptoms: F32.3, F33.3; mania with psychotic symptoms: F30.2; bipolar affective disorder, currently manic or major depressive episode with psychotic symptoms: F31.2, F31.5). Thus, patients with secondary psychoses or rheumatological diseases were not excluded. Only those with an available rheumatological laboratory screening involving at least the investigation of ANAs were included. Overall, 224 patients from the ward for psychosis and secondary mental disorders fulfilled these inclusion criteria. Fig. 1 provides an overview of the available findings. Patients were characterized according to the Clinical Global Impression (CGI; Rush et al., 2000) and the Global Assessment of Functioning (GAF; American Psychiatric Association, 2009), as well as according to rates of previous suicide attempts and inpatient stays.

2.2. Methods

Rheumatological screening involved assessing a variety of blood biomarkers (summarized in Table 1). This screening was incorporated into the extended diagnostic routine work-up, aligning with the best clinical interests for the patients (Endres et al., 2020b, 2020c). In the case of abnormal ANAs analyzed by indirect immunofluorescence (IIF)

Table 1
Rheumatological screening approach (for methods see Venhoff et al., 2019).

Biomarker	Methods
Acute phase protein	
C-reactive protein	Turbidimetric determination (Cobas 8000 – c701 module from Roche, Basel, Switzerland).
Immunoglobulins	
IgG, IgA, IgM, Immunofixation	IgG, IgA, IgM were analyzed by nephelometry on a Atellica NEPH 630 System (Siemens Healthcare, Erlangen, Germany). Immunfixation was performed on a Sebia Hydrasys 2.0 System (Sebia, Fulda, Germany).
Complement factors	
CH50, C3, C4, C3d	CH50 was measured by ELISA (Wieslab/SVAR, Malmö, Sweden). C3 and C4 were analyzed by nephelometry on a Atellica NEPH 630 System (Siemens Healthcare, Erlangen, Germany). C3d was determined using rocket electrophoresis with antibody reagents (Dako/Agilent, Hamburg, Germany).
Autoantibodies and rheumatoid factor	
Rheumatoid factor	Rheumatoid factor was analyzed by nephelometry on a Atellica NEPH 630 System (Siemens Healthcare, Erlangen, Germany).
Anti-phospholipid antibodies (ß2GP IgG antibodies, ß2GP IgM antibodies, ß2glykoprotein IgG antibodies)	Anti-phospholipid antibodies were analyzed using ELISA (Euro-Diagnostica, Malmö, Sweden).
ANAs (ENA-diff., ds-DNA)	ANA-staining pattern was assessed using indirect immunofluorescence (IIF) on Hep2 cells (NOVA Lite® HEp-2 ANA, Werfen, Barcelona, Spain). Furthermore, patients with positive ANA results were screened for extractable nuclear antigens using a lineblot assay including nRNP/Sm, Sm, SS-A, Ro-52, SS-B, Scl-70, PM-Scl, Jo1, CENP-B, PCNA, ds-DNA, nucleosomes, histones, ribosomal P-proteins, AMA-M2, and DFS70 (ANA-Profile3plusDFS70, Euroimmun, Lübeck, Germany) and an anti-dsDNA-IgG ELISA (Euro-Diagnostica, Malmö, Sweden) and anti-ds-DNA using crithidia-luciliae-IIF (Euroimmun, Lübeck, Germany).
ANCAs (MPO/PR3)	ANCA-staining pattern was assessed using indirect immunofluorescence (IIF) on ethanol and formalin fixed neutrophil specimens (Euroimmun, Lübeck, Germany). Anti-PR3 (Orgentec Diagnostika, Mainz, Germany) or MPO antibodies (Euroimmun, Lübeck, Germany) was measured using ELISA.
AMA/LKM	AMA/LKM autoantibodies were analysed by indirect immunofluorescence (IIF) (Euroimmun, Lübeck, Germany).
SMA	SMA antibodies were analysed by indirect immunofluorescence (IIF) (Euroimmun, Lübeck, Germany).

Abbreviations: AMA-M2, anti-mitochondrial M2 antibody; ANA, anti-nuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; anti-PM/Scl75/100, anti-polymyositis/systemic sclerosis protein 75/100 antibody; ß2GP, ß2glykoprotein; C3/C3d/C4, complement component 3/4/3d; CENP-B, Centromere protein B; CH50, Total complement activity; DFS70, dense Fine Speckled 70; diff., difference; ds-DNA, double stranded deoxyribonucleic acid; ELISA, enzyme-linked immunosorbent assay; ENA, extractable nuclear antigen; HEp-2000 R, epithelioma cancer cell line 200 R; IgA/IgG/IgM, immunoglobulin A/G/M; LKM, liver-kidney microsomal antibody; MPO3, myeloperoxidase; nRNP/Sm, anti-nuclear ribonucleoprotein/Smith; PCNA, proliferating cell nuclear antigen; PR3, proteinase 3; Scl-70, scleroderma 70; Sm, Smith; SS-A, Sjögren's-syndrome-related antigen A; SS-B, Sjögren's-syndrome-related antigen B.

on human epithelioma-2 (HEp-2) cells (Fig. 2), extractable nuclear antigen (ENA) screening and testing for anti-dsDNA antibodies were added (Venhoff et al., 2019). In the case of positive antineutrophil cytoplasmic antibodies (ANCAs), differentiation by proteinase 3 (PR3) and myeloperoxidase (MPO) was conducted (Venhoff et al., 2019). In addition, all patients were offered MRI, EEG, and CSF examinations (Endres et al., 2020b, 2020c). In unclear cases, [^{18}F]fluorodeoxyglucose positron emission tomography (FDG-PET) was performed unsystematically. MRI findings were assessed by senior neuroradiologists and the EEG findings by responsible physicians. Further, MRI and EEG findings were classified as in previous works (Endres et al., 2020b, 2020c), and EEG slowing (intermittent rhythmic delta and theta activity) was analyzed automatically (Endres et al., 2017). Regarding the analyzed patient group, there is an overlap with patients previously published (Endres et al., 2020b, 2020c, 2022). CSF analyses included testing for white blood cell (WBC) count, protein concentration, albumin ratio, immunoglobulin (Ig) G index, and oligoclonal bands (Reiber and Peter, 2001; Engelborghs et al., 2017). In addition, patients were tested for neuronal IgG antibodies against cell surface antigens in serum and CSF using fixed biochip assays (Euroimmun-kits®, Euroimmun, Lübeck, Germany). IgG antibodies against intracellular paraneoplastic antigens in serum were analyzed using immunoblots (Ravo PNS 11 Line Assay®, Ravo Diagnostika, Freiburg, Germany). In addition, serum and CSF samples from 73 patients (32.6 %) were analyzed using tissue-based indirect IIF assays on murine brain sections (Prof. Prüss, Autoimmune Encephalopathies Laboratory, DZNE Berlin and Department of Neurology and Experimental Neurology, Charité Berlin, Germany; Endres et al., 2022; Kreye et al., 2020). In contrast to previous studies, ANA patterns were also analyzed here (Endres et al., 2022).

Secondary rheumatological psychosis cases were checked in all patients with clearly abnormal rheumatoid factor (RF), ANA, ANCA, or APA findings. If brain involvement was identified in these patients on EEG, MRI, CSF, or FDG-PET, a "possible autoimmune psychotic syndrome" was coded; further, if a distinct rheumatological disease was also diagnosed, a "probable autoimmune psychotic syndrome" was assumed. The term "autoimmune psychotic syndrome" was used here (instead of "rheumatological psychosis" or a comparable term), in line with the term autoimmune psychosis, which has been established since 2020 (Pollak et al., 2020).

2.3. Statistics

The statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 27 (IBM Corp., Armonk, NY, USA), and the frequency of alterations in rheumatological screening was presented descriptively. For subgroup comparisons between ANA-positive and ANA-negative patients, the following tests were used: dimensional variables were tested for a normal distribution using the Shapiro–Wilk test, age was compared using an independent sample *t*-test, and categorical variables (e.g., sex) were compared using Pearson's chi-square test or Fisher's exact test. Due to significant group differences in sex, the Wald test for categorical variables and an analysis of covariance (ANCOVA) for dimensional variables, with sex as a covariate, were calculated in further group comparisons. A p-value of < 0.05 was defined as the level of significance, and due to the exploratory nature, correction for multiple testing was not applied.

3. Results

The characteristics of the patient group are summarized in Table 2, while the results of rheumatological screening can be found in Table 3. Patients with clearly abnormal findings in the rheumatological screening approach are demonstrated in Table 4, and the different

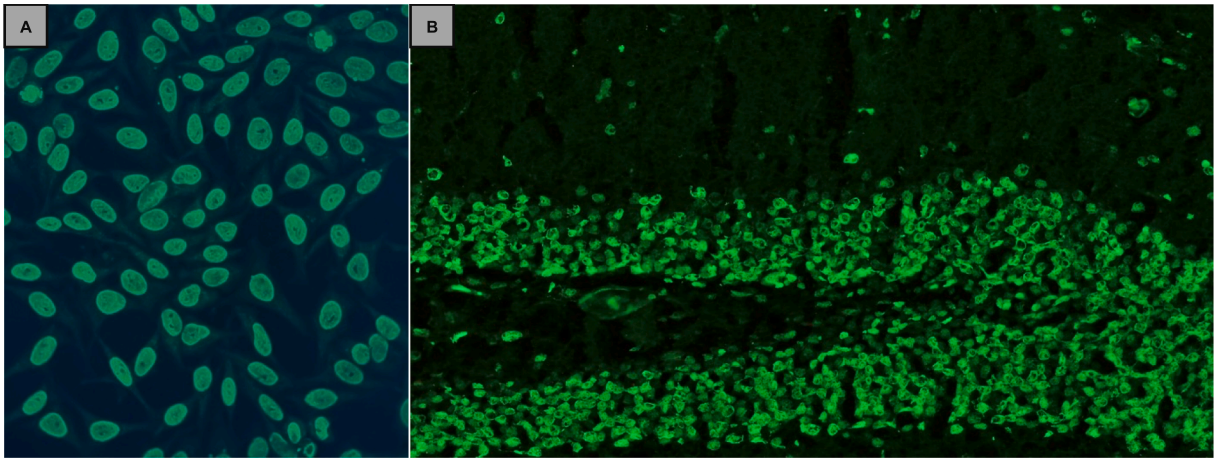

Fig. 2. Antinuclear antibodies analyzed by commonly used indirect immunofluorescence on human epithelioma type 2 cells (A) and additionally used tissue-based indirect immunofluorescence assays on murine brain sections (B).

Table 2
Study cohort. The ICD-10 diagnoses at discharge are shown.

ICD-10	F06.0	F06.1	F06.2	F12.5	F19.5	F20.0	F20.1	F20.2	F20.3	F20.4
Number	1	1	69	3	2	90	7	3	1	1
Percentage	0 %	0 %	31 %	1 %	1 %	40 %	3 %	1 %	0 %	0 %
ICD-10	**F23.0**	**F23.2**	**F25.0**	**F25.1**	**F25.2**	**F29.0**	**F31.2**	**F31.5**	**F32.3**	**F33.3**
Number	1	1	9	19	4	1	3	1	1	6
Percentage	0 %	0 %	4 %	9 %	2 %	0 %	1 %	0 %	0 %	3 %

Abbreviations: ICD-10, International Statistical Classification of Diseases and Related Health Problems; F06.0, Organic hallucinosis; F06.1, Organic catatonic disorder; F06.2, Organic delusional disorder; F12.5, Mental and behavioural disorders due to use of cannabinoids, psychotic disorder; F19.5, Mental and behavioural disorders due to multiple drug use and use of other psychoactive substances; F20.0, Paranoid schizophrenia; F20.1, Hebephrenic schizophrenia; F20.2, Catatonic schizophrenia; F20.3, Undifferentiated schizophrenia; F20.4, Postschizophrenic depression; F23.0, Acute polymorphic psychotic disorder without symptoms of schizophrenia; F23.2, Acute schizophrenia-like psychotic disorder; F25.0, Schizoaffective disorder, manic type; F25.1, Schizoaffective disorder, depressive type; F25.2, Schizoaffective disorder, mixed type; F29.0, Unspecified nonorganic psychosis; F31.2, Bipolar affective disorder, current episode manic with psychotic symptom; F31.5, Bipolar affective disorder, current episode severe depression with psychotic symptoms; F32.3, Severe depressive episode with psychotic symptoms; F33.3, Recurrent depressive disorder, current episode severe with psychotic symptoms.

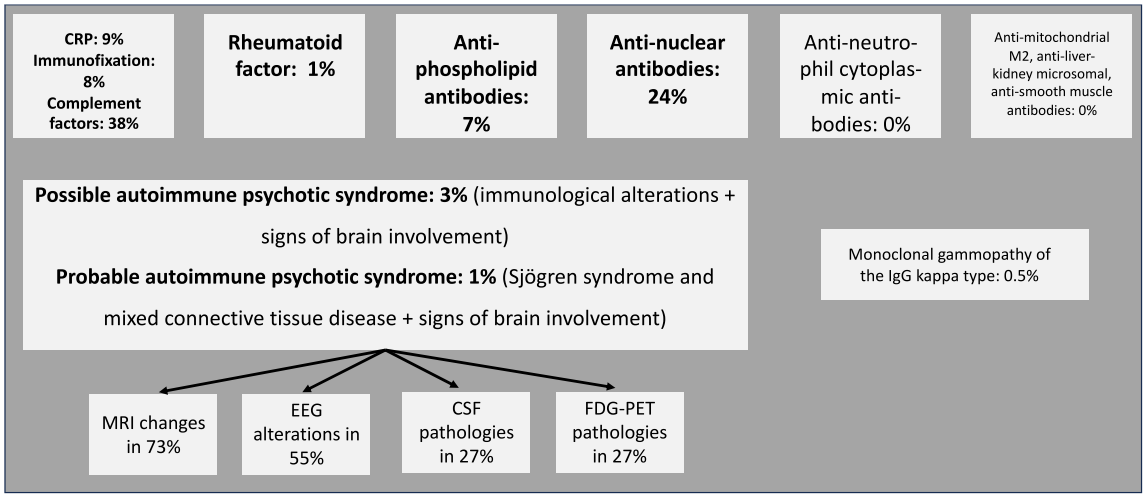

Fig. 3. Graphical illustration of the main alterations in the patient cohort of 224 patients with psychotic syndromes. The frequency of abnormalities in EEG, MRI, CSF, and FDG-PET findings relate to the group of patients with possible and probable autoimmune psychotic syndromes. Abbreviations: CRP, C-reactive protein; CSF, cerebrospinal fluid; EEG, electroencephalography; FDG-PET, [^{18}F]fluorodeoxyglucose positron emission tomography; IgG, Immunoglobulin G; MRI, magnetic resonance imaging.

Table 3
Rheumatological findings.

Biomarker	Alterations in 224 patients with psychosis
Acute phase protein	
Increased C-reactive protein (ref. < 5 mg/l)	20 (9 %)
Immunoglobulins	
Mean IgG levels (and range) (N = 221)	10.45 ± 2.26 (from 6.07 to 27.00)
IgG levels decreased/increased (ref. 7–16 g/l)	8 ↓ (4 %), 2↑ (1 %)
Mean IgA levels (and range) (N = 221)	1.99 ± 0.97 (from 0.49 to 9.09)
IgA levels decreased/increased (ref. 0.70–4 g/l)	5 ↓ (2 %), 7↑ (3 %)
Mean IgM levels (and range) (N = 221)	0.98 ± 0.51 (from 0.23 to 3.01)
IgM decreased/increased (ref. 0.40–2.30 g/l)	14 ↓ (6 %), 7↑ (3 %)
Immunofixation (screening)* (N = 220)	18 altered (8 %) *Pronounced polyclonal IgG/M/A proliferation N = 1* *Polyclonal hypergammaglobulinemia:* *isotype IgG N = 1* *isotype IgM N = 4* *isotype IgA N = 4* *Very trace evidence of a monoclonal gammopathy of the IgG lambda type (as wells as kappa type) N = 2 (1)* *Monoclonal gammopathy of the IgG kappa type N = 1* *Hypogammaglobulinemia (IgG < 7 g/L) N = 4*
Complement factors	
Mean CH50 (range) (N = 214)	102.91 ± 19.17 (from 44.00 to 182.00)
CH50 (ref. 65–115 %)	4 ↓ (2 %), 48↑ (22 %)
Mean C3 (range) (N = 220)	1.12 ± 0.199 (from 0.62 to 1.65)
C3 (ref. 0.90–1.80 g/l)	31 ↓ (14 %), 0↑ (0 %)
Mean C4 (range) (N = 220)	0.22 ± 0.059 (from 0.06 to 0.40)
C4 (ref. 0.10–0.40 g/l)	2 ↓ (1 %), 0↑ (0 %)
Mean C3d (range) (N = 142)	7.21 ± 2.34 (from 4.60 to 28.10)
C3d (ref. < 9 mg/l) (N = 142)	13↑ (9 %)
Complement alterations overall (N = 222)	**85 (38 %)**
Autoantibodies and rheumatoid factor	
Rheumatoid factor (ref. < 16 IE/ml) (N = 218)	2 ↑ (1 %) (28 and 234 IE/ml)
Anti-phospholipid/ß2GP IgG antibodies (ref. < 14 U/ml) (N = 220)	11↑ (5 %) (max. 34 U/ml)
Anti-phospholipid /ß2GP IgM antibodies (ref. < 10 U/ml) (N = 220)	7 ↑ (3 %) (max. 98 U/ml)
ß2glykoprotein 1 IgG antibodies (ref. < 14 U/ml) (N = 220)	0 ↑ (0 %) (max. 8 U/ml)
Anti-phospholipid antibodies overall (N = 220)	**16 (7 %)**
ANA-Hep-2 (against nucleus, ref.: 1:50) (N = 224)	42 (19 %) Trace evidence 17 (+) 18 + 7 ++ – +++ –
ANA-Hep-2 (nucleoli, ref.: 1:50)	2 (1 %) Trace evidence 2 (+) – + – ++ – +++ –
ANA-Hep-2 (chromosomes, ref.: 1:50)	30 (13 %) Trace evidence 11 (+) 14 + 5 ++ – +++ –
ANA-Hep-2 (cytoplasm, ref.: 1:50)	7 (3 %) Trace evidence 6 (+) 1 + – ++ – +++ –
ANA titer mean (range) (available from N = 18)	1716.67 ± 4050.45 (from 100 to 12800)
ANA overall positive (including borderline cases)	51 (23 %)
ANA clearly positive (only including trace of ANA-Hep-2 against nucleus)	**42 (19 %)**
ANA positive findings in tissue-based assays	**26 (out of N = 73; 36 %)**
ANA clearly positive overall (including tissue-based assays)	**54 (24 %)**
ENA-screening (mostly performed if ANAs were clearly positive) performed in 43 cases (19 %)	14 (33 %) clearly positive (+/++/+++), 6 (14 %) borderline positive ("(+)") and 23 (53 %) negative results (N = 43) Positive cases in detail: –- **anti-DFS70:** (+) in N = 1, + in N = 4, +++ in N = 2; in total: N = 8 –- **anti-centromere (CENP B):** (+) in N = 2, + in N = 1; in total: N = 3 –- **anti-PCNA:** (+) in N = 1; + in N = 1; in total: N = 2 –- **anti-snRNP/Sm:** + in N = 1, +++ in N = 1; in total: N = 2 –- **anti-AMA-M2 (IgG):** (+) in N = 1; + in N = 1; in total: N = 2 –- **anti-SS-B/La**: (+) in N = 1; +++ in N = 1; in total: N = 2 –- **anti-PM-Scl75:** + in N = 1 –- **anti-PM-Scl100:** + in N = 1 –- **anti-SS-A/Ro:** +++ in N = 1 –- **anti-Ro-52:** +++ in N = 1 –- **anti-Ku:** ++ in N = 1 –- **anti-Jo-1:** (+) in N = 1 –- **anti-Scl-70:** (+) in N = 1 –- **anti-nucleosom:** (+) in N = 1 –- **anti-SRP:** (+) in N = 1 –- **anti-Histon:** (+) in N = 1
Anti-dsDNA ELISA (ref. < 40 U/ml; only performed if ANAs were clearly positive)	8.66 ± 4.58 (from 3 to 21) (N = 35) 0 ↑ (0 %)
Anti-dsDNA Crithidia-luciliae-IF	All negative (N = 30) 0 ↑ (0 %)
ANCAs (IgG, ref.: 1:10) (N = 222)	6 (2 %) (+) 6 + – ++ – +++ –
MPO/PR3 (performed if ANCAs were borderline positive and there was a clinical suspicion for autoimmunity)	1 (33 %) (N = 3) Positive cases in detail: Anti-MPO 9 U/ml (ref: < 5 U/ml)
AMA/LKM (kidney, ref.: 1:50) (N = 210)	2 (1 %) (+) 2 + – ++ – +++ –
SMA (kidney, ref.: 1:50) (N = 208)	5 (2 %) (+) 5 + – ++ – +++ –
Autoantibodies/rheumatoid factor overall (N = 224)	**71 (32 %)**

Abbreviations: AMA, anti-mitochondrial M2 antibody; ANA, anti-nuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; ds-DNA, double stranded deoxyribonucleic acid; C3/C4/3d, complement component 3/4/3d; CENP B, centromere protein B; CH50, total complement activity; DFS70, dense Fine Speckled 70; ELISA, enzyme-linked immunosorbent assay; ENA, extractable nuclear antigen; Hep-2, epithelioma cancer cell line; IF, immunofluorescence;

IgA/IgG/IgM, immunoglobulin A/G/M; incl., inclusive; LKM, liver-kidney microsomal antibody; MPO, myeloperoxidase; N, number; PCNA, proliferating cell nuclear antigen; PM-Scl75/PM-Scl100, polymyositic/systemic sclerosis associated antigen 75/100; PR3, proteinase 3; ref., reference; Scl 70, sclerosis associated antigen 70; SMA, smooth muscle antibody; snRNP/Sm, small nuclear ribonucleoprotein/Smith; SRP, signal recognition particle; SS-A/SS-B, Sjögren's-syndrome-related antigen A/B; SS-B, Sjögren's-syndrome-related antigen B; ↑, increased; ↓, decreased; (+), borderline positive; +/++/+++, clear positive.

clinical and diagnostic findings in patients with and without ANAs are shown in Tables 5 and 6.

3.1. Characteristics of the study group

Overall, 224 patients were included, most of them (40 %) were diagnosed with paranoid schizophrenia (ICD-10: F20.0). The mean age was 34.71 ± 13.24 years, and 126 patients were female (56 %; Table 2).

3.2. Rheumatological screening approach

Abnormalities in all patients: C-reactive protein (CRP) was elevated (≥5 mg/l) in 9 % of patients, immunofixation identified alterations in 8 %, complement factor C3 was decreased in 14 %, and RF was detectable in 1 %. Further, APAs were elevated in 7 %, ANCAs were not clearly positive (only borderline positive in six cases), and ANAs were clearly positive (including a minimum trace of ANA-Hep-2 against the nucleus, but not against the nucleoli, chromosomes, and cytoplasm) in 19 %. ENA differentiation was performed in 42 patients: six had anti-DFS70 antibodies and two had anti-snRNP/Sm antibodies. Anti-centromere, anti-PCNA, anti-AMA-M2 IgG, anti-SS-B/La, anti-PM-Scl75, anti-PM-Scl100, anti-SS-A/Ro, anti-Ro-52, and anti-Ku antibodies were each individually found in only one patient. In total, the ENA differentiation revealed clear positive results in 14 patients (33 %) and borderline results in six patients (14 %). Further, dsDNA antibodies were negative in all patients tested additionally with ELISA and Crithidia-luciliae-IIF, and AMA/LKM and SMA were never clearly positive (AMA/LKM was borderline positive in 1 %, SMA in 2 %; Fig. 3).

Comparing IIF on HEp-cells and on tissue-based assays: From the 73 patient samples additionally investigated using tissue-based assays, there were 26 positive results for some kind of ANAs (36 %). Based on these findings, 12 additional patients could be considered ANA-positive. In eight cases, there was an overlap in both tests, and in six patients, ANAs were positive in routine testing on Hep2-cells but not detectable in tissue-based assays. Strikingly, fine-dotted anti-nuclear ANAs were frequently found in the CSF in tissue-based assays (in 11 % versus in 4 % in serum), and overall, ANAs using tissue-based assays were found with equal frequency in serum (23 %) as in CSF (in 23 %).

ANA-positive cases overall: In total using both methods of IIF on Hep-2 cells and unfixed murine brain slices, 54 (24 %) patients were considered positive for ANAs.

3.2.1. Autoimmune psychotic syndromes and distinct rheumatological disorders

The findings of patients with clearly abnormal findings (N = 11; 5 %) in our rheumatological screening are summarized in Table 4. Evidence of brain involvement was seen upon EEG in six patients (55 %), upon MRI in eight cases (73 %), and in CSF in three cases (27 %), and FDG-PET was abnormal in three patients (27 %). A neuropsychiatric evaluation revealed a possible autoimmune psychotic syndrome in seven patients (3 %) and a probable autoimmune psychotic syndrome in two patients (1 %). For two patients, there was no evidence of brain involvement. After a multimodal diagnostic work-up and multidisciplinary case discussion, a distinct rheumatological disorder could be diagnosed in two patients (1 %): Sjögren's syndrome and mixed connective tissue disease (thus, both were first diagnoses as a result of our rheumatological screening). In addition, one patient was diagnosed with monoclonal gammopathy of the IgG kappa type (0.5 %; not listed in Table 4, as no inflammatory brain involvement was expected).

Four of the 11 patients (36 %) with probable/possible autoimmune psychotic syndromes (Table 4) ultimately underwent immunotherapy as part of clinical treatment, following a multidisciplinary case discussion. All four patients showed at least partial improvement upon discharge. One patient declined immunotherapy, prompting a scheduled rheumatological follow-up. Another patient had undergone immunotherapy two years earlier, resulting in a clinical improvement at that time.

3.3. Comparison of ANA-positive and ANA-negative patients

More females were identified in the ANA-positive group ($p = 0.007$), among whom seven cases with psychotic depression could be identified (there were no patients with psychotic depression in the ANA-negative group). ANA-positive patients were also more frequently treated with antidepressants ($p = 0.040$) and had a significantly higher number of somatic comorbidities ($p < 0.001$; Table 5). (Chronic) inflammatory MRI lesions ($p = 0.008$) and focal atrophies ($p = 0.012$), as well as overall MRI alterations ($p = 0.017$), were found more frequently in the ANA-positive group, while EEG, neuronal antibody, and FDG-PET changes were not significantly different between the groups. Conversely, CSF total protein levels were higher in the patient group without ANAs ($p = 0.032$; Table 6).

4. Discussion

The main study findings indicate that broad rheumatological screening led to suspicions of possible or probable autoimmune brain involvement in 4 %. In addition, inflammatory and focal atrophic MRI pathologies were more common in ANA-positive patients with psychotic syndromes.

Previous studies focused primarily on the association between SLE and psychosis. In a recent study from Taiwan, 6.2 % of hospitalized chronic schizophrenia patients had concomitant SLE (Chen et al., 2021). However, in this and similar studies, patients did not undergo a multimodal diagnostic work-up to investigate brain involvement. Conversely, a large work-up showed that psychotic symptoms in SLE were found in 6.5 % of all cases. Similarly, cerebrovascular insult (in 7.1 %) and seizures (in 5.3 %) were frequently identified as signs of neuropsychiatric SLE (NPSLE), where 28.1 % had an NPSLE (Meier et al., 2021). Another study from Great Britain found lupus psychosis in 2.5 % of patients with SLE. Overall, combined neuroleptic- and immunotherapy showed complete remission in 66.7 % of patients (Abrol et al., 2021). In our study population, SLE was not identified, but Sjögren's syndrome and mixed connective disorder were newly diagnosed, both of which have previously been reported in case studies associated with psychotic symptoms in the literature (Bennett et al., 1978; Hammett et al., 2020). However, systematic work-ups of rheumatological screening approaches in well-studied cohorts of patients with psychosis are scarce, where a PubMed search of "psychosis AND rheumatic screening" (retrieved 27th of August 2023) yielded only 58 hits and no corresponding patient groups.

Clinical significance is derived from the potential immunotherapeutic consequences for each individual patient with a secondary autoimmune-mediated psychotic syndrome (Abrol et al., 2021; Oldham, 2017). To assess whether immunotherapy will be suggested, it is essential to demonstrate brain involvement in the presence of newly diagnosed rheumatological disorders with psychotic symptoms. Otherwise, a rheumatological systemic disease could "only" represent a comorbidity. A multimodal diagnostic approach using EEG, MRI, and CSF has been established to detect brain involvement and to exclude other brain processes in our special ward ward for psychosis and secondary mental disorders (Endres et al., 2020b, 2020c). In the case of the 11 patients with clear rheumatological alterations in our cohort, 73 % demonstrated MRI, 55 % EEG, and 27 % CSF/FDG-PET abnormalities, respectively. Conversely, two patients had no clear diagnostic

Table 4
Patients with clearly positive findings in rheumatological screening. This included all patients with positive rheumatoid factor, clearly positive anti-phospholipid antibodies (≥40 U/ml) and clearly positive anti-nuclear antibodies (ANA titers ≥ 800 (without anti-DFS70 specification) or positive ENA-screening/ds-DNA antibodies). Patients with monoclonal gammopathy are not presented here.

	Rheumatological screening	Age, sex	Syndrome	MRI	EEG	CSF	Other pathologies laboratory, FDG-PET, etc.)
Pat. 1	**ANAs pos. (titer 12800)**, ANA-Hep-2 (against nucleus) +, **RF pos. (234 U/ml), anti-phospholipid- IgM ↑ (98 U/ml), anti-SS-A/Ro +++, anti-SS-B/La +++; anti-AMA-M2 (IgG) +; anti-Ku ++; anti-Jo-1 (+); anti-Ro-52 +++**	Mid. 60, f	Delusional syndrome	+ (WM changes)	=	n.p.	Pronounced polyclonal hypergammaglobulinemia IgG, Borrelia burgdorferi IgG pos., toxoplasmosis IgG pos. **→Probable autoimmune psychotic syndrome (Sjögren's syndrome)**
Pat. 2	**ANAs pos. (titer 12800),** ANA-Hep-2 (against nucleus) +, **anti-snRNP/Sm +++**	Mid. 30, m	Delusional syndrome, Hashimoto-thyreoiditis	=	=	+ (protein ↑, Q_{Alb}↑)	Raynaud syndrome, CH50↑, ANAs in serum and CSF (tissue testing), FDG-PET: slight bifrontal hypometabolism **→Probable autoimmune psychotic syndrome (mixed connective tissue disease)**
Pat. 3	**RF pos. (28 IE/ml)**	Mid. 20, f	Delusional syndrome	+ (Focal atrophy, micro hemorrhage)	+ (Intermittent focal slowing)	=	ANAs in serum and nuclei of Purkinje cells stained in CSF (in tissue-based assay), Sicca syndrome, pre-diagnosed microcephaly **→Possible autoimmune psychotic syndrome**
Pat. 4	**ANAs pos. (titer 1600),** ANA-Hep-2 (against nucleus) +, ANA-Hep-2 (chromosomes) +	~ 50, f	Delusional syndrome, Hashimoto-thyreoiditis	+ (WM changes)	=	+ (protein ↑)	Anti-TG antibodies ↑, anti-TPO antibodies ↑, C3 ↓ **→ Possible autoimmune psychotic syndrome**
Pat. 5	**ANAs pos. (titer 800),** ANA-Hep-2 (against nucleus) +, ANA-Hep-2 (chromosomes) +	~ 40, f	Recurrent depressive syndrome, currently with psychotic symptoms, Hashimoto-thyreoiditis	+ (WM changes)	+ (Intermittent focal slowing)	=	Anti-TPO-antibodies ↑, C3 ↓, ANAs in serum and CSF (in tissue-based assay) **→Possible autoimmune psychotic syndrome**
Pat. 6	**ANAs pos. (titer: 800),** ANA-Hep-2 (against nucleus) +, ANA-Hep-2 (chromosomes) +	~ 20, m	Delusional syndrome, autism spectrum disorder	+ (WM changes, pineal cyst)	+ (Intermittent general slowing)	=	IgM ↓, CH50↑, C3d ↑, ANAs in serum and CSF (formerly also antibodies against granule cells in tissue-based assays) **→Possible autoimmune psychotic syndrome**
Pat. 7	**Anti-snRNP/Sm +,** ANAs pos. (titer: 100 U/ml)	~ 20, f	Paranoid schizophreniform syndrome	+ (Pineal cyst)	+ (Intermittent general slowing)	+ (WBC count ↑)	**→Possible autoimmune psychotic syndrome**
Pat. 8	**anti-PCNA +**	~ 20, f	Paranoid schizophreniform syndrome	+ (WM changes, inflammatory lesions)	+ (Intermittent general slowing)	=	CH50↑, strong staining of medium-sized vessels in CSF (in tissue-based assay), FDG-PET: hypometabolism on both sights, slight hypermetabolism **→Possible autoimmune psychotic syndrome**
Pat. 9	**Anti-PM-Scl +, anti-PM-Scl100 +,** ANAs pos. (titer: 200)	~ 20, f	Delusional syndrome	=	+ (Intermittent focal slowing, spike waves)	=	FDG-PET: hypermetabolic changes **→Possible autoimmune psychotic syndrome**
Pat. 10	**anti-CENP B +**	~ 20, f	Paranoid schizophreniform syndrome	+ (Pineal cyst)	=	n.p.	Raynaud syndrome, C3 ↓, C4 ↓ →No evidence for brain involvement
Pat. 11	**anti-PM-Scl75 +**	Mid. 40, f	Recurrent depressive syndrome, currently with psychotic symptoms	=	=	=	CH50↑ →No evidence for brain involvement

Abbreviations: AMA-M2, anti-mitochondrial M2 antibody; ANA, anti-nuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; C3/C4/3d, complement component 3/4/3d; CENP B, anti-centromere protein B; CH50, total complement activity; CSF, cerebrospinal fluid; CRP, C-reactive protein; DFS70, dense fine speckled 70; EEG, electroencephalography; ENA, extractable nuclear antigen; f, female; FDG-PET, [^{18}F]fluorodeoxyglucose positron emission tomography; Hep-2, epithelioma cancer cell line; IgA/IgG/IgM, immunoglobulin A/G/M; m, male; Mid, middle; MRI, magnetic resonance imaging; n.p., not performed; Pat, patient; PM/Scl75/100, polymyositis/systemic sclerosis associated protein 75/100; RF, rheumatoid factor; SS-A/Ro, Sjögren's-syndrome-related antigen A/Ro; SS-B/La, Sjögren's-syndrome-related antigen B/La; TG, thyroglobulin; TPO, thyroid peroxidase; WBC, white blood cell; WM, white matter; ~, approximate; ↑, increased; ↓, decreased; +/++/+++, clearly positive.

abnormalities at all, so we judged the immunological findings likely unrelated to psychosis in these patients. Overall, possible or probable autoimmune brain involvement was observed in 4 % of all patients, supporting the use of immunotherapeutic approaches in rare cases with psychotic syndromes (e.g., Lüngen et al., 2019). The optimal therapeutic recommendations for this condition should be investigated in the future.

ANAs were sometimes indicated as an immunological screening tool. To investigate this assumption, patients with and without ANAs were compared. More females were identified in the ANA-positive group, which is consistent with the higher prevalence of connective tissue disorder in women (Hanly et al., 2019). In the ANA-positive patient group, seven cases with psychotic depression were detected, and the rate of patients treated with antidepressants was higher. Thus, our data point to an association between ANAs and psychotic depression.

Table 5
Characteristics of the study cohort and comparison of patients with antinuclear antibodies (ANAs) and ANA-negative patients.

	Total (N=224)	Patients WITH ANAs (N=54)	Patients WITHOUT ANAs (N=170)	Statistics
Sociodemographic and clinical findings				
Age (range) in years	34.71 ± 13.24 (from 18-82)	36.50 ± 14.29 (from 18-76)	34.14 ± 12.88 (from 18-82)	t = 1.144 p = 0.254
Sex	98 male (44 %): 126 female (56 %)	15 male (28 %): 39 female (72 %)	83 male (49 %): 87 female (51 %)	Chi^2 = 7.376 **p = 0.007**
Syndrome overall				
Schizophreniform syndromes	213 (95 %)	46 (85 %)	167 (98 %)	***p*** ***Fisher*** **<0.001**
Depression with psychotic symptoms	7 (3 %)	7 (13 %)	0 (0 %)	
Mania with psychotic symptoms	0 (0 %)	0 (0 %)	0 (0 %)	
Bipolar affective disorder, currently manic or major depressive episode with psychotic symptoms	4 (2 %)	1 (2 %)	3 (2 %)	
Clinical course				
First episode	57 (25 %)	14 (26 %)	43 (25 %)	Chi^2=0.065 p=0.991
Chronic (> 2years)	56 (25 %)	14 (26 %)	42 (25 %)	
Recurrent	107 (48 %)	25 (46 %)	82 (48 %)	
Unknown	4 (12 %)	1 (2 %)	3 (2 %)	
Previous/current comorbid psychiatric disorders				
Depression/affective disorder				
Personality disorder				
Autism	65 (29 %)	21 (39 %)	44 (26 %)	
ADHD				
Tics	17 (8 %)	3 (6 %)	14 (8 %)	
Substance abuse	18 (8 %)	3 (6 %)	15 (9 %)	
OCD/Anxiety	10 (4 %)	2 (4 %)	8 (5 %)	
PTSD	1 (0 %)	1 (2 %)	0 (0 %)	
MCI	39 (17 %)	8 (15 %)	31 (18 %)	
Sleeping disorder	11 (5 %)	3 (6 %)	8 (5 %)	
Eating disorder	3 (1 %)	1 (2 %)	2 (1 %)	
Somatoform disorder	6 (3 %)	1 (2 %)	5 (3 %)	
Overall	1 (0 %)	0 (0 %)	1 (1 %)	
	1 (0 %)	0 (0 %)	1 (1 %)	
	9 (4 %)	6 (11%)	3 (2 %)	Wald = 0.965
	126 (56 %)	**33 (61 %)**	**93 (55 %)**	$p_{overall}$= 0.326
Previous/current comorbid neurological disorders				
Neurovascular	4 (2 %)			
Demyelinating	2 (1 %)			
Dementia	0 (0 %)	1 (2 %)	3 (2 %)	
Chorea Huntington	1 (0 %)	2 (4 %)	0 (0 %)	
Extrapyramidal	5 (2 %)	0 (0 %)	0 (0 %)	
Epilepsy	5 (2 %)	0 (0 %)	1 (1 %)	
Microcephaly	1 (0 %)	2 (4 %)	3 (2 %)	
Infections	17 (8 %)	2 (4)	3 (2 %)	
Tumors	4 (2 %)	1 (2 %)	0 (0 %)	
Tremor	4 (2 %)	7 (13 %)	10 (6 %)	
Paroxysmal	5 (2 %)	0 (0 %)	4 (2 %)	
Traumatic	6 (3 %)	1 (2 %)	3 (2 %)	
Polyneuropathy	5 (2 %)	3 (6 %)	2 (1 %)	
Migraine	12 (5 %)	0 (0 %)	6 (4 %)	
Overall	**62 (28 %)**	3 (6 %)	2 (1 %)	
		4 (7 %)	8 (5 %)	Wald = 2.568
		20 (37 %)	**42 (25 %)**	$p_{overall}$ = 0.109
Internal medicine comorbidity				
Risk factors				
Cardiology/angiology	71 (31 %)	22 (41 %)	49 (29 %)	
Pneumology	31 (14 %)	3 (6 %)	28 (16 %)	
Nephrology	15 (7 %)	8 (15 %)	7 (4 %)	
Hematology	4 (2 %)	0 (0 %)	4 (2 %)	
Endocrinology	6 (3 %)	1 (2 %)	5 (3 %)	
Autoimmune disorder	54 (24%)	20 (37 %)	34 (20 %)	
Gastrology	14 (6 %)	10 (19 %)	4 (2 %)	
Ophthalmology	18 (8 %)	2 (4 %)	16 (9 %)	
ENT	18 (8 %)	7 (13 %)	11 (6 %)	
Urology/Gynecology	3 (1 %)	0 (0 %)	3 (2 %)	
Dermatology	25 (11 %)	11 (20 %)	14 (8 %)	
Rheumatology	18 (8 %)	5 (9 %)	13 (8 %)	
Overall	7 (3 %)	5 (9 %)	2 (1 %)	Wald = 10.932
	154 (69 %)	**48 (89 %)**	**106 (62 %)**	**$p_{overall}$ = < 0.001**
Clinical and psychometric scores				
Clinical Global Impression (CGI)	5.71 ± 0.637 (N=222)	5.58 ± 0.795 (N=53)	5.75 ± 0.575 (N=169)	F = 1.395 p = 0.250
Global Assessment of Functioning (GAF)	39.52 ± 15.503 (N=223)	42.15 ± 16.046 (N=54)	38.67 ± 15.278 (N=169)	F = 1.605 p = 0.203
None	164 (73 %)	39 (72 %)	125 (74 %)	
One	34 (16 %)	7 (14 %)	27 (16 %)	
Two		2 (4 %)	10 (6 %)	
> Two	6 (3 %)	1 (2 %)	5 (3 %)	p_{Fisher} = 0.948
Unclear	8 (4 %)	5 (9 %)	3 (2 %)	
Number of earlier inpatient stays				
None				
One	40 (20 %)	7 (14 %)	33 (22 %)	
Two	36 (18 %)	9 (18 %)	27 (18 %)	
> Two	34 (17 %)	9 (18 %)	25 (16 %)	
Unclear	92 (46 %)	24 (49 %)	68 (44 %)	Chi^2 = 1.263
	22 (10 %)	5 (9 %)	17 (10 %)	p = 0.746
Psychopharmacological treatment (N=224)				
Antipsychotics	185 (83 %)	40 (74 %)	145 (85 %)	Wald = 3.085 p = 0.079
Antidepressants	50 (22 %)	18 (33 %)	32 (19 %)	Wald = 4.233 ***p = 0.040***
Lithium	14 (6 %)	5 (9 %)	9 (5 %)	Wald = 0.370 p = 0.543
Anticonvulsants	17 (8 %)	5 (9 %)	12 (7 %)	Wald = 0.159 p = 0.690
Benzodiazepines	35 (16 %)	9 (17 %)	26 (15 %)	Wald = 0.008

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Table 5 (*continued*)

	Total (N=224)	Patients WITH ANAs (N=54)	Patients WITHOUT ANAs (N=170)	Statistics
Overall	**198 (88 %)**	**45 (83 %)**	**153 (90 %)**	p = 0.931 Wald = 1.944 p = 0.163

Abbreviations: ADHD, Attention deficit hyperactivity disorder; ANA, Antinuclear antibody; ENT, Ear, Nose and Throat; MCI, Mild cognitive impairment; N, number; OCD, Obsessive–compulsive disorder; PTSD, Post-traumatic stress disorder.

The higher number of somatic comorbidities in ANA-positive patients and the more frequent MRI pathologies with (post-)inflammatory and focal atrophic processes suggest that ANAs could be a biomarker of the "organicity" of psychotic syndromes. Consistent with this, *meta*-analytical findings recently showed significantly lower volumes in SLE patients of the hippocampus, corpus callosum, and total gray matter (Cox et al., 2023). However, the ANA-positive group did not show more frequent neuronal antibodies or inflammatory CSF signals. Thus, no evidence was obtained to confirm that ANAs predict other inflammatory brain processes. Conversely, CSF protein levels, which are markers for blood–-brain barrier (BBB) (dys)function, were higher in the patient group without ANAs, which suggests that ANAs do not cause dysfunction of the BBB, as is assumed for thyroid antibodies (Endres et al., 2021).

From a methodological viewpoint, it should be mentioned that the commonly available assay for the detection of ANAs by IIF on Hep-2 cells was less sensitive (ANA rate of 19 %) than the use of tissue-based assays (detection of antinuclear patterns in serum and CSF at 36 %). Thus, it is possible that ANAs with novel antigens may be found in a subset of patients with psychosis but may be overlooked in current routine diagnostics. Antibodies targeting nuclear antigens have been mostly considered clinically irrelevant, because they are unlikely to reach their target in vivo. However, in some patients of our cohort, high antibody titers in CSF with a strong binding to mouse brain tissue were observed. In such constellations, especially if further distinct signs of neuroinflammation are identified in the CSF or brain imaging (cf. Endres et al., 2023), small amounts of ANAs could possibly induce psychotic symptoms after several years of brain exposure. This hypothesis should be investigated in the future, as its proof could initiate a paradigm shift in the interpretation of ANAs detected in the CSF of some patients with psychosis.

It is important to note the **limitations of this study**. It involved a retrospective analysis performed in a tertiary psychiatric center focusing on organic causes of psychosis, which implies a pre-selected patient population. Hence, the results cannot be considered representative for all patients with psychotic syndromes. Due to the retrospective nature of the study, which was conducted in a naturalistic setting, complete findings from each patient were not available (Fig. 1). Due to the lack of a healthy control group, false-positive rheumatological findings in the patient group cannot be excluded. However, an optimal control group for this approach would have been healthy individuals who, in addition to rheumatological blood screening, underwent supplementary diagnostics, including MRI, EEG, and CSF analysis. To the best our knowledge, such control groups are not yet available. In addition, it must be mentioned that due to the retrospective design, only 73 patients received a tissue-based assay. It is conceivable that a subgroup of the other patients whose ANA findings were negative for Hep2 cells would have been positive for ANAs in the tissue-based assay. Therefore, the results of the subgroup analyses should be considered preliminary and will need to be replicated in future studies. The pathological diagnostic findings indicative of CNS inflammation in patients with abnormal rheumatological screening (Table 4) could have arisen independently of a rheumatological process. This consideration is crucial, especially given

Table 6
Comparison between antinuclear antibody (ANA) positive and ANA negative psychotic patients in diagnostic findings.

	Total (N=224)	**Patients WITH ANAs (N=54)**	**Patients WITHOUT ANAs (N=170)**	**Statistics**
Rheumatological blood screening				
CRP increased	20 (9%)	3 (6%)	17 (10%)	Wald = 0.847
	n.a.: 6	n.a: 3	n.a.: 3	p = 0.357
Immunglobin alterations	36 (16%)	7 (13%)	29 (17%)	Wald = 0.541
(IgG/IgA/IgM)	n.a.: 5	n.a.: 1	n.a.: 4	p = 0.462
Complement alterations (C3/C4/CH50/C3d)	85 (38%)	25 (46%)	60 (36%)	Wald = 1.202
	n.a.:2		n.a.: 2	p = 0.273
Routine cerebrospinal fluid parameters				
WBC counts	1.55 ± 1.016	1.62 ± 1.248	1.52 ± 0.910	F = 1.125
(Mean ± SD, range)	(from 1 to 7/µl)	(from 1 to 7// µl)	(from 1 to 6/ µl)	p = 0.327
	n.a.: 67	n.a.: 9	n.a.: 58	
Increased WBC counts	5 (3%)	3 (7%)	2 (2%)	Wald = 1.514
(ref. < 5 /µl)	n.a.: 67	n.a.: 9	n.a.: 58	p = 0.218
Protein concentration (Mean ± SD, range)	444.26 ± 262.921 (from 132 to 2520 mg/l)	390.50 ± 151.719 (from 132 to 785 mg/l)	466.74 ± 295.073 (from 175 to 2520 mg/l)	F = 3.532 ***p = 0.032***
	n.a.: 68	n.a.: 8	n.a.: 60	
Increased protein concentration (ref. < 450 mg/l)	57 (37%)	13 (28%)	44 (40%)	Wald = 0.790
	n.a.: 68	n.a.: 8	n.a.: 60	p = 0.374
Albumin quotients (Mean ± SD, range)	5.64 ± 3.890 (from 2 to 36 x 10^{-3})	5.00 ± 1.974 (from 2 to 10 x 10^{-3})	5.91 ± 4.425 (from 2 to 36 x 10^{-3})	F = 2.473 p = 0.088
	n.a.: 66	n.a.: 8	n.a.: 58	
Increased albumin quotients (ref.: <40y.: < 6.5 x 10^{-3}; 40-60y.: < 8 x 10^{-3}; >60y.: < 9.3 x 10^{-3})	28 (18%)	8 (17%)	20 (18%)	Wald = 0.063
	n.a.: 66	n.a.: 8	n.a.: 58	p = 0.802
IgG-Index (Mean ± SD, range)	0.5175 ± 0.07613 (from 0.33 to 1)	0.5143 ± 0.08539 (from 0.37 to 1)	0.5187 ± 0.07236 (from 0.33 to 0.95)	F = 0.079 p = 0.924
	n.a.: 66	n.a.: 8	n.a.: 58	
Number of patients with increased IgG indices (ref. <0.7)	4 (3%)	1 (2%)	3 (3%)	Wald = 0.123
	n.a.: 66	n.a.: 8	n.a.: 58	p = 0.726
Isolated OCB in CSF	6 (4%)	3 (7%)	3 (3%)	Wald = 0.542
				p = 0.461
OCBs in CSF and Serum	7 (5%)	4 (9%)	3 (3%)	Wald = 1.333
				p = 0.248
	n.a.: 71	n.a.: 9	n.a.: 62	
Overall basic CSF alterations	60 (37%)	18 (38%)	27 (25%)	Wald = 1.116
	n.a.: 63	n.a.: 7	n.a.: 56	p = 0.882
Anti-neuronal and anti-thyroid autoantibodies				
Biochip assays for antibodies against cell surface antigens				
■ serum	3 (2%)	2 (4%)*	1 (1%)**	Wald = 1.698
	n.a.: 49	n.a.: 5	n.a.: 44	p = 0.193

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Table 6 (*continued*)

	Total (N=224)	Patients WITH ANAs (N=54)	Patients WITHOUT ANAs (N=170)	Statistics
■in CSF				
	0 (0%) n.a.: 63	0 (0%) n.a.: 6 (one patient with expired anti-NMDA-R encephalitis)	0 (0%) n.a.: 57 (two additional cases with anti-MOG antibodies)	
Immunoblots for serum antibodies against intracellular antigens	1 (1%) n.a.: 45	0 (0%) n.a.:3	1 (1%)*** n.a.: 42	Wald = 0.000 p = 0.997
Tissue-based assays				
Novel anti-CNS antibodies in serum	10 (14%)	1 (3%)	9 (22%)	Wald = 3.036 p = 0.081
Novel anti-CNS antibodies in CSF	19 (26%) n.a.: 151	5 (16%) n.a.: 22	14 (34%) n.a.: 129	Wald = 2.506 p = 0.113
Overall positive anti-neuronal antibodies	21 (12%)	5 (10%)	16 (12%)	Wald = 0.034 p = 0.853
Thyroid antibodies in serum				
Overall	28 (13%)	11 (22%)	17 (11%)	Wald = 2.568 p = 0.109
TPO	23 (11%)	8 (16%)	15 (9%)	Wald = 1.110 p = 0.292
TG	14 (7%)	7 (14%)	7 (4%)	Wald = 3.426 p = 0.064
TSH-R	0 (0%) n.a.: 13	0 (0%) n.a.: 3	0 (0%) n.a.: 10	-
MRI changes (N=208)		**(N=52)**	**(N=156)**	
Non-specific white matter changes	80 (38%)	21 (40%)	59 (38%)	Wald = 0.000 p = 0.993
(Chronic) inflammatory lesions	15 (7%)	9 (17%)	6 (4%)	Wald = 6.959 ***p = 0.008***
Limbic encephalitis	0 (0%)	0 (0%)	0 (0%)	-
Global atrophy	4 (2%)	2 (4%)	2 (1%)	Wald = 0.555 p = 0.456
Focal atrophy	7 (3%)	5 (10%)	2 (1%)	Wald = 6.341 ***p = 0.012***
Macroangiopathic vascular alterations (post-ischemic changes)	3 (1%)	1 (2%)	2 (1%)	Wald = 0.706 p = 0.401
Microhaemorrhage	13 (6%)	4 (8%)	9 (6%)	Wald = 0.295 p = 0.587
Pineal cyst changes	20 (10%)	9 (17%)	11 (7%)	Wald = 3.114 p = 0.078
Others	33 (16%)	7 (13%)	26 (17%)	Wald = 0.267 p = 0.605
Overall MRI alterations	**127 (61%)**	**40 (77%)**	**87 (56%)**	Wald = 5.673 ***p = 0.017***
EEG pathologies (N=220)		**(N=54)**	**(N=166)**	
Focal slowing	27 (12%)	5 (9%)	22 (13%)	Wald = 0.392 p = 0.529
Generalized slowing	66 (30%)	15 (28%)	51 (31%)	Wald = 0.323 p = 0.570
Epileptic pattern	2 (1%)	0 (0%)	2 (1%)	Wald = 0.000 p = 0.997
Spike wave	18 (8%)	6 (11%)	12 (7%)	Wald = 1.290 p = 0.256
EEG overall alterations	**88 (40%)**	**22 (41%)**	**66 (40%)**	Wald = 0.002 $p_{overall}$ = 0.964
IRDA/IRTA rate before HV (Mean ±SD)	0.78 ± 1.30 (N=206)	0.78 ± 1.52 (N=50)	0.77 ± 1.22 (N=156)	F = 1.761 p = 0.175
IRDA/IRTA rate after HV (Mean±SD)	1.09 ± 1.63 (N=188)	1.04 ± 1.69 (N=49)	1.10 ± 1.61 (N=139)	F = 0.397 p = 0.673
IRDA/IRTA difference (Mean ±SD)	0.32 ± 1.15 (N=188)	0.25 ± 0.89 (N=49)	0.34 ± 1.23 (N=139)	F = 0.422 p = 0.656
IRDA/IRTA rates overall (Mean±SD)	0.85 ± 1.29 (N=206)	0.83 ± 1.54 (N=50)	0.85 ± 1.21 (N=156)	F = 1.289 p = 0.278
FDG-PET alterations (N=42)		**(N=19)**	**(N=23)**	
FDG-PET metabolism				
Hypermetabolism	8 (19%)	2 (11%)	6 (26%)	Wald = 1.637 p = 0.201
Hypometabolism	14 (33%)	9 (47%)	5 (22%)	Wald = 2.489 p = 0.115
Overall FDG-PET alterations	**19 (45%)**	**10 (53%)**	**9 (39%)**	Wald = 0.520 p = 0.471

*Anti-contactin associated protein (CASPR2) antibodies, anti-leucine–rich-glioma-inactivated 1 (LGI1) antibodies, **anti-N-methyl D-aspartate receptor (NMDA-R) antibodies, ***anti-Yo antibodies. Abbreviations: ANA, anti-nuclear antibody; C3/C4/C3d, complement component 3/4/3d; CH50, total complement activity; CNS, central nervous system; CRP, C-reactive protein; CSF, cerebrospinal fluid; EEG, electroencephalography; FDG-PET, ^{18}F] fluorodeoxyglucose positron emission tomography; HV, Hyperventilation; IgA/IgG/IgM, Immunoglobulin A/G/M; IRDA, intermittent rhythmic delta activity; IRTA, intermittent rhythmic theta activity; MRI, magnetic resonance imaging; n., number; n.a., not available; OCBs, oligoclonal bands; ref, reference; SD, standard deviation; TG, thyroglobulin; TPO, thyroid peroxidase; TSH-R, thyroid-stimulating hormone receptor; WBC, white blood cells; ↑ = increased, ↔ = normal.

that ANAs are detectable in the sera of some healthy people, with a frequency of up to 16 % in the United States (Dinse et al., 2022). Notably, there was a significant sex difference between ANA-positive and ANA-negative patients, which was statistically corrected for. The criteria for possible and probable autoimmune psychotic syndrome were

pragmatically defined on a clinical basis but lack a foundation in established diagnostic criteria. Optimal criteria for diagnosing "rheumatological autoimmune psychotic syndromes" have yet to be developed. Finally, frequent medication (in 88 %) with psychotropic drugs in this patient sample may have influenced the results.

5. Conclusion

In summary, psychotic syndromes rarely occur in the context of rheumatological diseases. The screening for rheumatological parameters like ANAs might help identifying these cases. For the detection of brain involvement, a multimodal diagnostic work-up using EEG, MRI, and CSF analysis could be beneficial. Optimal diagnostic screening approaches for the detection of an underlying rheumatological disease in patients with psychosis must be further studied in the future.

Availability of data and material

This is a descriptive analysis. All necessary data can be found in the paper.

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CRediT authorship contribution statement

Dominique Endres: Conceptualization, Supervision, Visualization, Writing – original draft, Funding acquisition. **Katharina von Zedtwitz:** Writing – original draft, Data curation, Visualization, Formal analysis, and Methodology. **Kathrin Nickel:** Data curation, Writing – review & editing. **Kimon Runge:** Data curation, Writing – review & editing, Formal analysis, Methodology. **Alexander Maier:** Data curation, Writing – review & editing. **Katharina Domschke:** Writing – review & editing, Resources. **Ulrich Salzer:** Investigation, Methodology, Software, Supervision, Writing – review & editing, Visualization. **Harald Prüss:** Investigation, Methodology, Supervision, Visualization, Writing – review & editing. **Nils Venhoff:** Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing. **Ludger Tebartz van Elst:** Conceptualization, Data curation, Funding acquisition, Investigation, Supervision, Writing – review & editing, Resources.

Declaration of Competing Interest

Potential competing interests KD: Formerly: Steering Committee Neurosciences and speaker honoraria, Janssen-Cilag, within the last three years. LTvE: Advisory boards, lectures, or travel grants within the last three years: Roche, Eli Lilly, Janssen-Cilag, Novartis, Shire, UCB, GSK, Servier, Janssen and Cyberonics. All other authors declare that they do not have any conflicts of interest.

Data availability

This is a descriptive analysis. All necessary data can be found in the paper.

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