212, 318–320. doi: 10.1192/bjp.2018.24

Short report

Absence of cerebrospinal fluid antineuronal antibodies in schizophrenia spectrum disorders

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Summary

Antibody-mediated encephalitis has been discussed as one possible cause for isolated psychotic syndromes. Mostly based on serum samples, findings have been controversial. We present the results of a retrospective study of 124 clinically diagnosed psychotic patients without documented relevant neurological symptoms. All were tested for different antineuronal antibodies in cerebrospinal fluid (CSF) while 81 received serum testing. Antineuronal antibodies in CSF were negative across the sample. 3.7% showed low positive serum antibodies. Our findings highlight the importance of a deeper discussion about the relevance of low positive serum antibodies without concurrent findings in CSF or clinical signs for autoimmune encephalitis.

Declaration of interest

None.

Usually patients with autoimmune encephalitis develop overt neurologic symptoms.[1] However, autoimmune encephalitis can also lead to severe psychiatric symptoms, such as psychosis, mania, and cognitive impairment. Interestingly, encephalitis caused by IgG-type antibodies to the NR1 subunit of the *N*-methyl-D-aspartate-receptor (NMDAR) may present exclusively with psychotic symptoms,[2] but other autoantibodies (e.g. anti-Contactin-associated protein-2 (CASPR2) and anti-Leucine-rich glioma inactivated 1 protein (LGI1)) have also been linked to psychotic syndromes.[3,4] These observations have led to the hypothesis that autoimmune encephalitis may be the primary aetiology in a currently unidentified subgroup of patients with psychotic disorders. Because autoimmune encephalitis can be treated with immunosuppressants and its outcome depends on the time lag to treatment,[1] prompt recognition of this cause of psychosis may have important clinical implications. Although findings to date have been heterogeneous, the prevalence of pathogenic antineuronal antibodies is low in blood samples of patients with psychotic disorders.[3] In rare cases where neuronal antibodies are detected, the titres are usually low, and similar titres may also be found in patients with other neuropsychiatric syndromes or even in healthy people.[3,4] However, pathogenic neuronal autoantibodies can be negative in serum but positive in cerebrospinal fluid (CSF) in patients with autoimmune encephalitis, especially in patients with better outcomes.[5] Analysing CSF may therefore increase the likelihood of detecting patients with isolated psychosis and presence of pathogenic neuronal autoantibodies. To the best of our knowledge, only one retrospective study examined the presence of different neuronal autoantibodies in CSF of 142 patients with psychotic disorders (125 had surface antibody testing), showing positive results in nine patients (four patients with antibodies against surface and five patients with antibodies against intracellular antigens).[6] However, titres were not reported and five out of nine patients with positive titres had significant neurological abnormalities. Here, we present the prevalence of neuronal antibodies in serum and CSF of patients with a first or recurrent episode of psychosis without major neurological symptoms that could indicate an underlying autoimmune encephalitis.[7]

Methods

We report a naturalistic cohort of 124 patients with schizophrenia spectrum disorders (first episode and recurrent course) who underwent a lumbar puncture and were tested for different antineuronal antibodies in CSF and serum as part of the clinical routine in the Department of Psychiatry and Psychotherapy at the Klinikum der Universität München between July 2012 and May 2017. Medical data were manually extracted from the electronic clinical documentation system and retrospectively analysed for the presence of antineuronal antibodies as well as abnormalities in routine CSF parameters (white blood cell count, protein levels, oligoclonal bands [OCBs] and albumin quotient). We included patients with documented ICD-10 diagnoses of schizophrenia spectrum disorders and excluded patients with a diagnosis of organic psychotic disorders (F06.0/F06.1/F06.2), drug-induced psychotic disorder (F1X.5) or clinical signs that could indicate the presence of an underlying autoimmune encephalitis[7] (e.g. seizures, movement disorders, autonomic instability), based on thorough screening of all available data on clinical and physical examination. We were able to detect a total of 332 patients with lumbar puncture. Of these, 124 patients were tested for CSF neuronal antibodies, a decision made by the treating physicians according to best clinical judgement. The offer to carry out a lumbar puncture is usually made in every patient with a first episode and to patients with a recurrent disease course who had not previously received a lumbar puncture. The CSF samples were analysed in the laboratory of our hospital by a cell-based assay from EUROIMMUN (Lübeck, Germany) for autoimmune encephalitis (antibodies tested: NMDAR [$n = 119$], α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor-1 (AMPAR-1) [$n = 114$], α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor-2 (AMPAR-2) ([$n = 114$], CASPR2 [$n = 111$], LGI1 [$n = 110$] and γ-amino-butyric acid receptor B1/B2 [$n = 112$]) and a paraneoplastic neurological syndrome panel from ravo Diagnostika (Freiburg, Germany) (antibodies tested: Amphiphysin [$n = 93$], Yo [$n = 59$], HuD [$n = 94$], Ri [$n = 94$], CV2 [$n = 93$], Ma1 [$n = 93$] and Ma2 [$n = 93$]). In ten patients, analyses were performed with the EUROIMMUN assay elsewhere (Clinical Immunological Laboratory, Lübeck, Germany). Serum results were available only for 81 patients. The power was at least 95% to detect one or more positive anti-NMDAR CSF titres for any true rate for positive CSF titres of $r_0 \geq 2.5\%$. However, as we detected no positive CSF titres, with a probability of only $P < 5\%$, we have $r_0 \geq 2.5\%$. For anti-Yo titres, we had at least 95% power to detect at least one positive CSF titre for any true rate of $r_0 \geq 5.0\%$. Again, we had no positive CSF titres, and therefore with $P < 5\%$

Table 1 Descriptive data of our cohort

Cohort Description ($N = 124$)	*N*
Epidemiologic and demographic information	
Gender (female/male)	60/64
Average age at the time of the lumbar puncture (years ± s.d.)	36.85 ± 15.29
Positive family history for psychiatric illnesses ($n = 119$)	47.1%
Prevalence of any neurological diagnosis	3.2%
Illegal substance misuse ($n = 123$)	19.5%
Alcohol misuse ($n = 122$)	26.2%
Information about psychiatric illness	
Duration of illness at the time of lumbar puncture (months ± s.d.) ($n = 109$)	61.58 ± 97.99
First episode at the time of lumbar puncture ($n = 122$)	44.3%
Recurrent psychotic episode ($n = 122$)	55.7%
Documented treatment with clozapine	24.2%
Cerebrospinal fluid basic panel	
White blood cell count (cells/μl ± s.d.)	1.58 ± 2.04
Prevalence of pleocytosis (>5 cells/μl)	4.8%
Protein level (mg/dl ± s.d.)	40.01 ± 16.72
Albumin quotient (±s.d.) ($n = 123$)	5.98 ± 2.98
Prevalence of oligoclonal bands ($n = 123$)	41.5%
Intrathecal oligoclonal bands	14.6%
Mirrored	26.8%
Diagnosis	
Schizophrenia (ICD-10: F20)	62.1%
Schizotypal disorder (ICD-10: F21)	3.2%
Persistent delusional disorders (ICD-10: F22)	5.6%
Acute and transient psychotic disorders (ICD-10: F23)	13.7%
Schizoaffective disorders (ICD-10: F25)	12.9%
Unspecified nonorganic psychotic disorders (ICD-10: F29)	2.4%

Items with missing data are noted by the description of the available sample size in parentheses. Percentages are calculated based on the available data for each item.

the true rate of positive CSF titres is $r_0 \geq 5.0\%$. Approval for this retrospective analysis was obtained from the Ethikkommission bei der Medizinischen Fakultät der Ludwig-Maximilians-Universität München, the approval number for this study is 463-16.

Results

Table 1 outlines the descriptive statistics. None of the 124 patients with CSF autoantibody analyses showed positive results in any of the tested antibodies. Three out of 81 patients (3.7%; one female; mean age, 36 ± 27.78 years) did have low-titre neuronal antibodies in serum (CASPR-2 antibodies: 1:10; CASPR-2 antibodies: 1:50; Yo antibodies: low band intensity). All three patients had ≤1 cell/μl in CSF and unspecific white matter lesions, whereas only one of these three had positive intrathecal OCBs. Overall, 18 (14.6%) patients showed intrathecal OCBs and 6 (4.8%) patients showed pleocytosis within a range of 6–14 cells/μl. None of the patients showed major abnormalities on neurological examination suggestive of autoimmune encephalitis.

Discussion

In our cohort of patients with schizophrenia spectrum disorder with no major neurological abnormalities we were unable to detect positive CSF titres of any of the commonly tested neuronal autoantibodies. This seems in contrast with a previous publication.[6] However, in that study three out of four patients with surface autoantibodies had severe neurological symptoms,[6] whereas we retrospectively selected patients with isolated psychotic symptoms.

We identified three patients with low-level serum autoantibody titres of whom only two had antibodies against surface antigens. This low rate of 3.7% conflicts with some studies, but is in line with others.[3,4,6,8] Reasons for these contradicting results have been discussed in detail before, but the most important are the selection of patients and the method of antibody testing.[9] Because we did not find antineuronal antibodies in the CSF of these three patients, we assume that these low-level serum antibodies do not play a causal role in their psychotic disorders. This is in line with the observation that first-episode patients with positive serum autoantibodies against different surface antigens did not show a poorer outcome compared with seronegative patients and did not develop encephalitis during a 6-month follow-up period.[4]

Interestingly, 14.6% of our patients showed intrathecal OCBs and 4.6% showed a mild pleocytosis, which is comparable with previous reports,[10] but significantly below the rates reported for full-blown autoimmune encephalitis.[11] These findings may point to a possible not yet fully understood central nervous system inflammatory or immune process in schizophrenia.[10]

The limitations of our study are its retrospective and open design, the use of a single-screening method and the lack of a control group and longitudinal data. Because of the retrospective nature of our study we had to rely upon the documented physical examinations and may have missed less overt neurological signs or subtle autonomic instability. In addition, we cannot determine how many patients rejected a lumbar puncture. Moreover, as we only included patients with documented F2X diagnoses, we may have missed patients with isolated psychiatric symptoms[2] who received a different ICD-10 diagnosis. To address this, we also analysed all patients with primary or secondary diagnoses of organic psychoses (F06.0/F06.1/F06.2) or encephalitis (G04/G05) and did not find any isolated psychotic syndrome with positive CSF autoimmune antibodies. Finally, there is ongoing debate about the sensitivity of the EUROIMMUN assay.[9]

In conclusion, our findings highlight the need for a balanced discussion about the relevance of low-level serum antibody titres in patients with psychotic disorders without major clinical signs of autoimmune encephalitis. They do not invalidate the often urgent clinical need to offer comprehensive serum and CSF analyses to all patients presenting with either a combination of psychotic symptoms and major neurological signs or a combination of psychotic symptoms and clinical criteria for autoimmune encephalitis.[7]

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First received 21 Sep 2017, final revision 7 Dec 2017, accepted 17 Jan 2018

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