The clinical relevance of serum versus CSF NMDAR autoantibodies associated exclusively with psychiatric features: A systematic review and meta-analysis of individual patient data

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Introduction

Patients with NMDAR antibody encephalitis (NMDARE) can present purely with psychiatric symptoms.

Consensus criteria[1] for diagnosis of definite NMDARE requires rapid onset (< 3 months) of one, or more major groups of symptoms coinciding with detection of IgG antibodies in the cerebrospinal fluid (CSF).

However, antibody testing in psychiatric settings is often limited to serum samples[2]. In addition, the clinical relevance of the NMDAR antibody when present only in the serum without accompanying CSF NMDAR antibodies is unclear.

Aim

We aimed to investigate if patients with an isolated psychiatric syndrome with CSF NMDAR antibodies can be distinguished from patients with serum-only NMDAR antibodies based on clinical features and investigation findings.

Methods

We performed a systematic review and meta-analysis of case reports and series of patients aged 18 years and older with psychiatric symptoms and NMDAR antibodies in the serum and/or CSF.

Electronic databases MEDLINE, EMBASE, PubMed, and PsycINFO were searched for studies published between January 2006 and May 2020.

Patients with neurological or dysautonomic features were excluded.

Patients with CSF NMDAR autoantibodies were compared to patients with serum-only NMDAR autoantibodies using a patient level meta-analytic approach. Analysis was restricted to patients who had undergone CSF antibody testing to confirm the presence or absence of detectable CSF autoantibodies.

Using R statistical software, crude odds ratios (OR) with 95% confidence intervals (CI) were estimated for dichotomous variables. A Mann–Whitney U Test was performed for continuous variables.

Results

A total of 42 studies were included (Fig 1) reporting a total of 79 patients (Fig 2). Of these, 61 patients were included in meta-analysis.

There were 41 patients with CSF NMDAR autoantibodies and 20 patients with serum-only NMDAR autoantibodies.

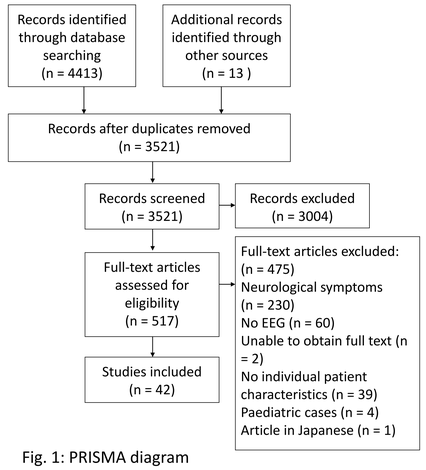

Fig. 1: PRISMA diagram

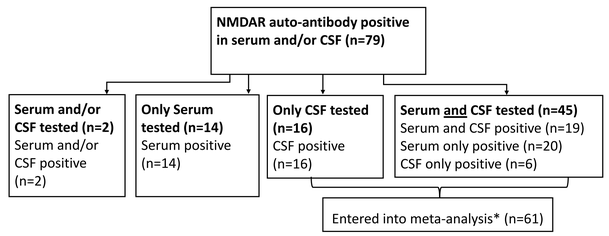

Fig. 2: Overview of antibody detection.

The key findings of this study are presented in the forest plots on the right (Fig 3).

Compared to the serum-only group, patients in the CSF positive group were significantly more likely to be female (p <0.001) and have a rapid (<3 month) onset of symptoms (p =0.02). They were also more likely to present with psychosis (p <0.001).

Patients in the CSF positive group were significantly more likely to exhibit abnormal EEG (p =0.006) and MRI findings (p=0.002), as well as CSF abnormalities (p=0.001) such as elevated protein, pleocytosis and oligoclonal bands.

However, patients in the CSF positive group were less likely to present with insomnia (p= 0.04).

In patients with CSF autoantibodies, the most common MRI abnormality was signal hyperintensity, while the most common EEG abnormality was generalised slowing.

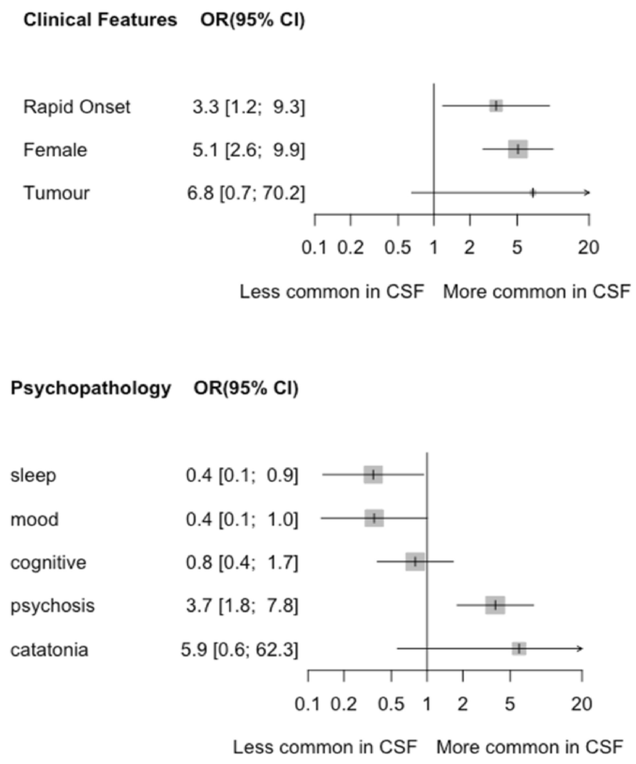

Fig. 3: Forest plot of random-effects odds ratios (OR) and 95% confidence intervals comparing patients with CSF NMDAR autoantibodies to those with serum-only NMDAR autoantibodies.

Conclusion

Patients with an isolated psychiatric symptom with CSF NMDAR antibodies may be distinguished from those with serum-only antibodies based on clinical features and investigations findings.

Patients with CSF NMDAR antibodies are significantly more likely to be female, have a rapid onset of symptoms and present with psychosis, as well as exhibit EEG, MRI and CSF abnormalities.

These clinical characteristics should raise the index of suspicion for the presence of NMDAR antibodies in the CSF, and nudge clinicians towards further investigations beyond serum antibodies.

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Full Text

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