Prevalence of neuronal membrane target antibodies in first-episode psychosis: abridged secondary publication

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KEY MESSAGES

1. Psychosis related to anti-N-methyl-D-aspartate (NMDA) antibodies is uncommon in Hong Kong, with a prevalence of 1.5%.
2. It is clinically difficult to differentiate first-episode psychotic patients with or without anti-NMDA antibodies.
3. A high index of suspicion of psychosis related to anti-NMDA antibodies is needed for cases with unexplained abnormal electroencephalography findings.
4. Future studies may include only patients presenting as schizophrenia, owing to a potentially higher yield.

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Introduction

Patients with unexplained neurological syndromes of the central nervous system carry autoantibodies in their blood. These conditions can occur in patients of all ages. Two such autoantibodies target voltage-gated potassium channel (VGKC)–complex proteins and N-methyl-D-aspartate (NMDA) receptors. Patients with such autoimmune diseases usually present with cognitive symptoms and seizure, but unexplained psychiatric presentation mimicking schizophrenia and other psychosis is not uncommon.[1] Common psychiatric symptoms include agitation, paranoia, psychosis, and violent behaviours. Cognitive impairments, memory deficits, speech problems, and motor symptoms can also occur. Some patients may progress to widespread encephalopathy with movement disorders, autonomic disturbance, and hypothalamic dysfunction. A pilot study in the United Kingdom explored the prevalence of the anti-VGKC and anti-NMDAR antibodies in psychotic patients who would otherwise be diagnosed with schizophrenia.[2] Of 47 patients who fulfilled DSM-IV criteria of schizophrenia, two carried anti-NMDAR antibodies, and one carried anti-VGKC antibodies, with a proportion being 6.38% (95% confidence interval=1.9%–18.9%).[2]

In addition, there is a time-sensitive response to immunotherapy in antibody-mediated cases of encephalitis.[3] If antibodies are identified and removed early, treatment response is excellent. If the disorder is associated with ovarian or testicular teratoma, the treatment response with removal of the teratoma is even better. If patients with schizophrenia caused by antibodies can be treated early, there is potential to significantly improve patient outcomes and costs associated with the disorder.

Antibody-mediated psychosis may represent a new form of mental illness requiring specific treatment. It is pertinent to determine its prevalence in patients initially diagnosed with psychosis, in whom the treatment and prognosis is completely different. We can inform health care planners of the resource implications. Associated features are highlighted to alert physicians of the possibility of autoimmune psychosis.

Methods

The study was approved by the Research Ethics Committee of Kowloon West Cluster (Ref: KW/EX-14-054(73-09)). Consecutive subjects were recruited from the Early Intervention Team in Kwai Chung Hospital. Inclusion criteria were age of 15 to 64 years, ethnically Chinese, first-episode psychosis, with a Positive and Negative Syndrome Scale score of ≥4 on any of the positive symptoms 1, 3, 5, 6 or general symptoms 9, duration of untreated psychosis of <3 years, and <6 weeks of continuous antipsychotic medications. Subjects were excluded if they had any other neurological disorders, primary drug-induced psychosis, or failed to provide informed consent.

Basic demographic information, history of medication use, family history of autoimmune and psychotic illness, and the duration of untreated psychosis were assessed. Diagnosis was documented according to the DSM-IV-TR criteria. Blood tests including complete blood count, liver and renal function test, antinuclear antibody, and C-reactive protein were performed.

Primary outcome measurements were antibody tests for anti-NMDAR and anti-VGKC at baseline and 6 months. Secondary outcome measurements were the Positive and Negative Symptoms Scale, Catatonia Rating Scale, Addenbrookes Cognitive Examination-III, and the Social and Occupational Functioning Assessment Scale at baseline and 6 months.

Results

A total of 341 subjects were recruited; 267 (78.3%) of them completed the second assessment at 6 months. Their mean age was 36.0 (standard deviation [SD], 13.1) years. About 64.4% of subjects were female; 50% of subjects were never married; and 51.3% of subjects were unemployed. They had a mean of 10.9 (SD, 5.1) years of education. The most common diagnosis was schizophrenia (n=136, 39.9%), followed by psychotic depression (n=79, 23.2%) and acute and transient psychosis (n=44, 14.4%). Most subjects never used illicit substances (92.7%), alcohol (89.6%), or cigarettes (82.9%). Six of them reported a history of other autoimmune disorders, namely autoimmune thyroiditis. In 52.2% of subjects, antipsychotic medications were prescribed for a mean duration of 2.3 (SD, 1.4) weeks. At baseline, the mean scores for positive, negative, and general subscales of the Positive and Negative Symptoms Scale were 17.4 (SD, 5.9), 11.3 (SD, 5.6), and 33.2 (SD, 9.1), respectively. The mean scores for Social and Occupational Functioning Assessment, Addenbrookes Cognitive Examination-III, and Catatonia Rating Scale were 47.5 (SD, 10.2), 78.5 (SD, 17.5), and 0.4 (SD, 1.1), respectively.

Only five subjects were found to be positive of anti-NMDA antibodies (Table); the overall prevalence of antineuronal antibodies in our study population was 1.5%, whereas the prevalence of antineuronal antibodies in schizophrenia and severe depressive episode with mood-congruent psychotic symptoms were 2.2% and 2.5%, respectively. No cases of anti-VGKC positivity were found.

Discussion

The prevalence of autoimmune psychosis related to antineuronal target antibodies in our sample is much lower than that reported in overseas studies. There are several possible reasons to explain the difference. Owing to genetic and environmental differences, prevalence of autoimmune conditions varies greatly in Chinese and western populations. For example, the prevalence of rheumatoid arthritis in Hong Kong was much lower than that of European Caucasians, with a standardised morbidity ratio of 0.27 only.[4] As such, the prevalence of autoimmune psychosis may also show geographical and racial differences.

Our clinic is a tertiary referral centre for treatment of first-episode psychosis. Most patients had been assessed by other medical practitioners, with thorough organic workups. Patients with features suggestive of organic psychosis may have been referred to other specialties.

We included all cases of first-episode psychosis to better study the pattern of seropositivity. As such, we have included cases from a range of different psychiatric diagnosis. The prevalence of antineuronal antibodies has been reported to vary among different psychiatric diagnoses.[5]

In one case, positive findings were only shown at follow-up. The patient had received high-dose antipsychotic treatment for several weeks. This finding suggests that antipsychotic medication might affect the immune response and reduce antibody levels.

There are several limitations to our study. The lack of a control group limited the calculation of the relative risk of the condition. Cerebrospinal fluid samples were not collected because of the invasive procedure. Some cases with antineuronal antibodies might be missed, as around 15% of patients have antibodies only in their cerebrospinal fluid. Patients who were referred after a period of treatment elsewhere were excluded owing to possible interference of results with antipsychotic medications.

TABLE. Characteristics of the five seropositive subjects

Sex/age of onset, y	Diagnosis	Cognitive impairment, Addenbrookes Cognitive Examination-III score	Organic workup	Electroencephalography	Antipsychotic treatment response
F/45	Schizophrenia	Yes, 62	Unremarkable	Generalised slow waves, frontal prominent	Good
F/31	Depression with psychosis	Yes, 74	Unremarkable	Bi-frontal slow waves	Partial
M/31	Schizophrenia	Yes, 78	Low calcium level	Spike activity over frontopolar and anterior temporal area	Partial
F/49	Depression with psychosis	No	Unremarkable	-	Good
F/31	Schizophrenia	-	Unremarkable	Unremarkable	Good

Conclusion

Electroencephalography is an important diagnostic tool for first-episode psychosis. Almost all antibody-positive cases were found to have unexplained slow activities on electroencephalography, especially in the frontal regions, while having unremarkable imaging findings.[5]

Further studies are needed to validate our findings. Future studies should include different centres in secondary and tertiary referral settings or even the emergency settings (where a number of our patients presented initially) to reduce sampling bias. Blood tests should be performed prior to the initiation of treatment, and more assessment time points may help delineate changes in antibody levels after antipsychotic treatment. A control group can help determine the prevalence of seropositivity in the general population. More proper comparison of different diagnostic groups should be performed.

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