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Anti-glutamate receptor ε2 antibodies in psychiatric patients with anti-thyroid autoantibodies – A prevalence study in Japan

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HIGHLIGHTS

- This is the first report on the prevalence of anti-GluRε2 antibodies in PPATs.
- Anti-GluRε2 antibodies were frequently observed in the CSF of PPATs.
- Anti-GluRε2 antibodies would relate to the neuropsychiatric manifestations of PPATs.

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ABSTRACT

Patients with anti-thyroid antibodies (ATAs) present various kinds of psychiatric conditions. When these psychiatric patients with ATAs (PPATs) show responsiveness to immunotherapy, they are frequently diagnosed with a diffuse progressive type of Hashimoto's encephalopathy (HE). Anti-glutamate receptor ε2 subunit (GluRε2) antibodies have previously been reported in HE patients. However, it is unclear whether there is any relationship between PPATs, including HE patients, and anti-GluRε2 antibodies. We investigated anti-GluRε2 antibodies in the serum and cerebrospinal fluid (CSF) of 15 PPATs, and we compared the results with those of 11 patients with neuropsychiatric systemic lupus erythematosus (NPSLE), an anti-glutamate receptor antibody-related disease. We then compared the neuropsychiatric symptoms between the PPATs with and without anti-GluRε2 antibodies. The prevalence of anti-GluRε2 antibodies was significantly higher in the CSF than in the serum of PPATs (41.7% versus 6.7%; $p = 0.040$). The prevalence of anti-GluRε2 antibodies was slightly higher in the CSF of PPATs than NPSLE patients. PPAT-GluR(+)s showed a significantly higher prevalence of emotional instability (100% versus 33.3%; $p = 0.03$) and also showed a significantly lower prevalence of delusions (0% versus 100%; $p = 0.001$) and hallucinations (17% versus 83%; $p = 0.038$) than PPAT-GluR(−)s. Our results suggest that anti-GluRε2 antibodies may be associated with the neuropsychiatric manifestation of PPATs.

1. Introduction

A number of psychiatric disorders have been reported to have autoimmune factors in their etiologies [23]. Except for the possible effects of thyroid hormonal dysfunction, anti-thyroid antibodies (ATAs) have attracted interest because of their association with psychiatric disorders such as mood disorder [23,32], anxiety disorder [4], schizophrenia [23], and dementia [10]. The ATAs were reported to be found in 9.2% of the admitted psychiatric inpatients. [16] When psychiatric patients with ATAs (PPATs) show responsiveness to immunotherapy, they are frequently diagnosed with a diffuse progressive type of Hashimoto's encephalopathy (HE) [5,12,21,26]. The definition of HE is still unclear, as it involves some unknown autoimmune mechanisms, and the detailed prevalence of HE is still unknown. A diagnosis of HE is usually based on a combination of neuropsychiatric findings and the presence of ATAs and/or responsiveness to immunotherapy. Recently Shindo et al. [27] reported a case of HE with anti-glutamate receptor ε2 subunit (GluRε2) antibodies in the serum and cerebrospinal fluid (CSF). GluRε2 is a subunit of N-methyl-D-aspartate (NMDA) glutamate receptor, which is believed to play an important pathogenic role in schizophrenia and dementia [3,6,24].

Like HE, neuropsychiatric systemic lupus erythematosus (NPSLE) is a well-known autoimmune disease. The overall

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prevalence of neuropsychiatric feature of patients with SLE is varied widely between 37% and 95%. [17] Recently anti-NMDA receptor antibodies in the CSF of NPSLE patients have received particular attention because of their association with psychiatric symptoms [2,9,14,22,25,34]. Among NPSLE patients, the relatively high prevalence of anti-NMDA receptor antibodies in the CSF was reported by Fragoso-Loyo et al. [14] and Arinuma et al. [2] and those were 35% and 69.6%, respectively. Anti-NMDA receptor antibodies in the CSF are believed to represent an important mechanism of cerebral dysfunction in NPSLE. However, it is unclear whether there is any relationship between PPATs, including HE patients, and anti-GluRε2 antibodies.

The purpose of the present study was to clarify the prevalence of anti-GluRε2 antibodies in PPATs. We compared the findings with a control group of patients with NPSLE, an anti-glutamate receptor antibody-associated disease. Additionally, we compared psychiatric features between PPATs with and without anti-GluRε2 antibodies.

2. Materials and methods

2.1. Patients

We evaluated 15 PPATs and 11 NPSLE patients who had been tested for serum and/or CSF anti-GluRε2 antibodies between 2006 and 2011 at Yokohama City University Hospital, Yokohama, Japan. In these cases, some organic psychiatric or autoimmune disease, such as HE or NPSLE, was suspected because of the atypical course of their psychiatric symptoms and/or cognitive dysfunctions, and resistance to psychotropic agents.

All the PPATs visited the Department of Psychiatry at our hospital for treatment of their psychiatric symptoms. They were evaluated for anti-thyroid peroxidase (anti-TPO) antibodies and anti-thyroglobulin (anti-TG) antibodies because of mild thyroid dysfunction found by a screening test or past history of thyroid disease. Some of them had been treated for thyroid dysfunction, and all patients were confirmed to have almost normal thyroid-stimulating hormone (TSH) levels. For this study, "almost normal TSH" was defined by their euthyroid status (TSH: 0.3–5.0 mIU/L) or subclinical hypothyroidism (TSH: 5.1–20.0 mIU/L), which would not account for myxoedema encephalopathy associated with hypothyroidism. Psychiatric diagnoses were based on the Diagnostic and Statistical Manual of Mental Disorders-4th Edition-Text Revision (DSM-4-TR) published by the American Psychiatric Association [1]. Exclusion of SLE was made on the basis of the revised American College of Rheumatology (ACR) criteria of 1997 [19]. Some patients received immunotherapy after anti-GluRε2 antibody evaluation, and their responsiveness was checked.

All NPSLE patients visited the Department of Psychiatry at our hospital for treatment of psychiatric symptoms or for neuropsychological evaluation required by rheumatologists. They had been diagnosed with SLE by rheumatologists, based on the 1997 ACR criteria. They had also been routinely tested for thyroid function, anti-TPO antibodies and anti-TG antibodies in order to check for complications of autoimmune thyroid disease. All patients with NPSLE were confirmed not to have ATAs. The immunotherapy they received after anti-GluRε2 antibody evaluation was checked, and their responsiveness was checked. All NPSLE patients were classified using the ACR consensus document published in 1999 [31].

All PPATs and NPSLE patients were evaluated to exclude any opportunistic infection, other mental disorder, other abnormal metabolic condition, or drug-induced disorder. For this study, the responsiveness to the immunotherapy was evaluated by the psychiatrists, rheumatologists and neurologists, and was defined that the patients show any clinical improvements on the neuropsychiatric symptoms after the immunotherapy. Informed consent was obtained from all patients or their guardians after oral and written explanations according to the ethical principles of the Declaration of Helsinki. The Institutional Ethics Committee of Yokohama City University Hospital approved the study protocol.

2.2. Evaluation for autoantibodies

Anti-GluRε2 antibodies were investigated in the serum and CSF. Serum samples were available for 15 PPATs and 11 NPSLE patients. CSF samples were available for 12 PPATs and 5 NPSLE patients. Anti-GluRε2 antibodies were investigated according to the technique previously reported by Takahashi et al. at the Shizuoka Institute of Epilepsy and Neurological Disorders, Shizuoka, Japan [29]. After establishing stable NIH3T3 transformant cell lines expressing full-length GluRε2 (B18), the supernatants of the cell extracts from B18 and the control cell line (A1) were subjected to sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), and the gels were transferred to nitrocellulose membranes. Each membrane was cut into strips after blocking with a buffer. The strips of B18 and A1 were reacted with 20-fold-diluted serum or CSF and were stained by alkaline phosphatase-labeled second antibodies. The presence of autoantibodies to GluRε2 was judged by a positively stained band with a molecular size of about 180 kD.

Anti-TPO and anti-TG antibodies were investigated by radioimmunoassay (RIA) with a cut-off value of 0.3 IU/ml. Anti-amino terminal of α-enolase (NAE) antibodies, which have been reported in the serum of HE patients, were investigated in the PPATs according to the technique previously reported by Yoneda et al. [33] and Fujii et al. [15].

2.3. Evaluation of neuropsychiatric symptoms

The psychiatric symptoms of PPATs were evaluated concerning hallucinations, delusions, anxiety, depression, emotional instability, and personality change. These symptoms were examined by psychiatric specialists during routine interviews at our hospital. Hallucinations and delusions were defined as positive if any symptoms were observed. Other psychiatric symptoms such as anxiety, depression, emotional instability or personality change were defined as positive if the symptoms persisted for at least one month and if these symptoms caused clinically significant distress or impairment in social functioning. Cognitive functions were evaluated by using the mini-mental state examination (MMSE).

2.4. Statistical analysis

The prevalence of anti-GluRε2 antibodies in the serum and CSF of PPATs was compared to that of the NPSLE patients by using Fisher's exact test. The prevalence of anti-GluRε2 antibodies in the PPATs and NPSLE patients was compared again between the serum and the CSF by using Fisher's exact test. The PPATs with anti-GluRε2 antibodies in their serum or CSF were classified as PPAT-GluR(+)s, and the PPATs without anti-GluRε2 antibodies in their serum and CSF were classified as PPAT-GluR(−)s. The psychiatric symptoms were compared between the PPAT-GluR(+)s and PPAT-GluR(−)s by using Fisher's exact test. Data were analyzed with the SPSS version 20.0 statistical package. The significance level was set at $p < 0.05$.

3. Results

3.1. Patients and autoantibodies

The clinical profiles of the PPATs and NPSLE patients are shown in Tables 1 and 2, and the demographics are shown in Table 3.