Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.4196-24
Intern Med 64: 1249-1252, 2025
http://internmed.jp

【 CASE REPORT 】

# Anti-N-methyl-D-aspartate Receptor Encephalitis in Turner Syndrome with 45,X/46,X,idic(X)(p11.4) Mosaics

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**Abstract:**

A 46-year-old woman with Turner syndrome (TS) (45,X/46,X,idic(X)(p11.4) mosaic) presented with a fever, unresponsiveness, hyperhidrosis, and rigidity approximately one month after episodes of confusion and suicide attempts, prompting a diagnosis of schizophrenia. Cerebrospinal fluid (CSF) showed mild hypercellularity with oligoclonal bands. Brain and abdominal magnetic resonance imaging showed no abnormalities. Bizarre upper-extremity movements and spasms followed the trial administration of acyclovir, and autoimmune encephalitis was suspected. Intensive immunotherapy was initiated, and the symptoms improved. Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis was diagnosed based on the presence of anti-NMDAR antibodies in her spinal fluid. This case represents a rare presentation of anti-NMDAR encephalitis in TS, which is susceptible to autoimmune disease complications.

**Key words:** anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis, Turner syndrome, autoimmune disorder, mosaicism

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**(DOI: 10.2169/internalmedicine.4196-24)**

## Introduction

Turner syndrome (TS) is characterized by short stature, pterygium colli, and other physical malformations, as well as gonadal abnormalities in individuals assigned female at birth, typically caused by deletion of all or part of an X chromosome. The karyotypic variation is large, encompassing 45,X, and mosaic XX (e.g. 45,X/46,XX) karyotypes with isochromosomes (either consisting of p or q arms) and even mosaic compositions with a Y chromosome or fragments thereof (1). Autoimmune diseases are among the most prominent types of TS-associated diseases. Since the risk of autoimmune diseases in TS is approximately twice as high as that in women of the general population, TS-specific factors have been suggested to play a role in the development of autoimmune diseases (2). Under these circumstances, TS is associated with a variety of autoimmune disorders, such as Hashimoto thyroiditis, celiac disease, type 1 diabetes, alopecia areata, inflammatory bowel disease, juvenile rheumatoid arthritis, idiopathic thrombocytopenic purpura, psoriasis, and vitiligo (2). However, there are very few reports of patients with TS who develop autoimmune encephalitis (3, 4).

We herein report a case of anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis that developed in a patient with mosaic TS [45,X/46,X,idic(X)(p11.4)]. This rare case reinforces the fact that a background of TS should increase suspicion of autoimmune diseases, including rare autoimmune diseases, when diagnosing such individuals.

## Case Report

A 46-year-old Japanese woman visited a local clinic for a behavioral episode in which she repeatedly called her mother to say, “I’m sorry.” The following day, other abnormal behaviors were observed, including an attempt to jump out of the mother’s car. As a result, she was diagnosed with schizophrenia and admitted to a psychiatric hospital. Treatment with olanzapine and blonanserin was then initiated. On day 17, she developed a fever. On day 20, unresponsiveness, abnormal sweating, and muscle rigidity were observed. The

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Received: May 27, 2024; Accepted: July 18, 2024; Advance Publication by J-STAGE: September 4, 2024
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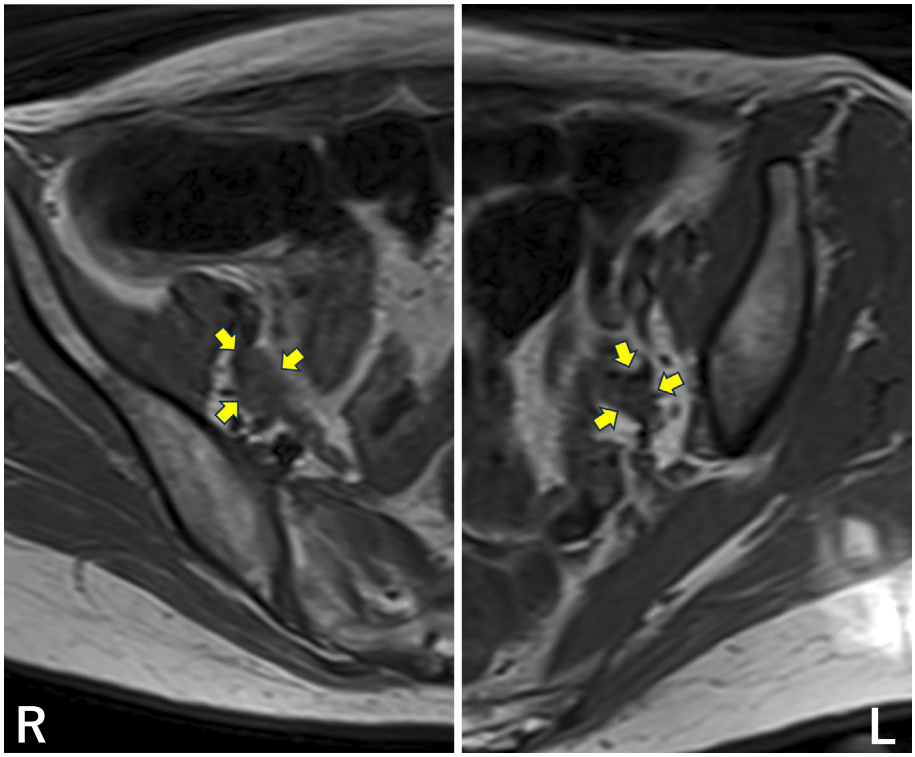


**Figure 1.** **Magnetic resonance imaging in the pelvis (T2-weighted imaging). The bilateral ovaries were atrophic (arrows). No obvious pelvic masses were observed.**

patient was tentatively diagnosed with neuroleptic malignant syndrome. Antipsychotic drugs were tapered off, and dantrolene sodium hydrate was administered. However, her symptoms continued to gradually worsen, and she was referred to our hospital on day 24.

The patient's history revealed that she had graduated from a junior college and had worked as a childcare worker at a day-care center ever since. In her 20s, she had been diagnosed with TS due to amenorrhea. Except for amenorrhea, she had no malformations characteristic of TS, such as short stature or pterygium collis. The karyotype examined on admission was 45,X/46,X,idic(X)(p11.4) mosaic [20 cells observed: 9 with 45,X; 11 with 46,X,idic(X)(p11.4)].

Her consciousness was E4V1M1 on the Glasgow Coma Scale. Horizontal nystagmus was observed in the frontal gaze. She failed to follow the moving indicators. Hypertonus was observed in the extremities. There were no involuntary, abnormal limb, or truncal movements. Tendon reflexes were increased in the bilateral biceps and patellar tendons, and plantar responses were extensor on the right side. Drooling, elevated sweating, and severe fluctuations in pulse rate were observed.

Laboratory findings were as follows: white blood cell 5,640/μL, C-reactive protein 1.62 mg/dL, aspartate aminotransferase 49 U/I, alanine aminotransferase 67 U/I, lactate dehydrogenase 431 U/I, creatine phosphokinase 779 U/I, interleukin-2 receptor 374 U/mL, thyroid-stimulating hormone 1.30 IU/mL, free T4 1.26 ng/dL, antithyroglobulin antibody 167 IU/mL (N: <28 IU/mL), anti-thyroid peroxidase antibody 9 IU/mL (N: <16 IU/mL). The results for rapid plasma reagin, β-D-glucan, and T-SPOT were negative. Serum antibodies (IgM) for herpes simplex virus type 1, cytomegalovirus, and varicella zoster virus were negative. Cerebrospinal fluid (CSF) showed a cell count of 6/μL (only mononuclear cells) and a protein level of 80 mg/dL. No herpes simplex virus type 1 or varicella zoster virus DNA was detected in the CSF by polymerase chain reaction. The oligoclonal bands were positive. The IgG index was 0.67. Pelvic magnetic resonance imaging showed bilateral atrophic ovaries consistent with the formation of streak gonads observed in TS (5) but no neoplastic lesions (Fig. 1).

Acyclovir (ACV) 1,500 mg/day was started day 24 because of suspected viral meningoencephalitis. Immediately after ACV initiation, lip self-bite and indiscriminate arm swinging were observed. Several episodes of tonic convulsions occurred on days 29 and 30 but were controlled by the administration of 10 mg of diazepam. The electroencephalogram could not be adequately evaluated owing to the large amount of electromyographic activity introduced by involuntary arm movements. The bizarre movements and seizures not associated with infection suggested autoimmune encephalitis; thus, ACV was terminated on day 32, and steroid pulse therapy (methylprednisolone 1.0 g/day for 3 days) was initiated. On day 34, the patient developed aspiration pneumonia. Therefore, immunoglobulin (400 mg/kg/day for 5 days) was initiated as an alternative treatment to steroid pulse therapy. On day 44, anti-NMDAR antibody was detected in the CSF that had already been submitted (cell-based assay; titer 1x), and she was confirmed to have definite anti-NMDAR encephalitis based on the criteria of Graus

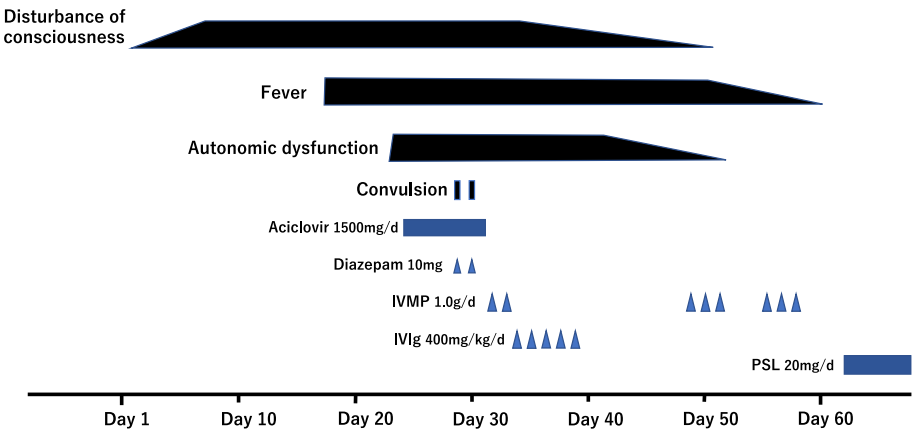


**Figure 2.** **Clinical course. IVIg: intravenous immunoglobulin, IVMP: intravenous methylprednisolone, PSL: prednisolone**

**Table.** **Clinical Findings of Autoimmune Encephalitis Developed in Turner Syndrome.**

| Case | Age | Sex | Karyotype | Antibody | Clinical symptoms | Therapy | Outcome |
|---|---|---|---|---|---|---|---|
| (3) | 65 | F | Not mentioned | NMDAR | Hallucinations memory disturbances agitation | Steroids IVIg | Improvement |
| (4) | 20 | F | 45,XO/46Xr(x) | AMPAR | Anxiety inner tension confusion mutism bizarre behavior paranoid | Memantine Valproic acid | Improvement |
| Our case | 46 | F | 45,X/46,X, idic(X) (p11,4) | NMDAR | Confusion unresponsiveness muscular tonicity | IVMP IVIg | Improvement |

NMDAR: N-methyl-D-aspartate receptor, AMPAR: α-Amino-3-hydroxy-5-mesoxazole-4-propionic acid receptor, IVMP: intravenous methylprednisolone, IVIg: intravenous immunoglobulin

et al. (6). After day 52, when the second course of steroid pulse therapy was completed, a fever, impaired consciousness, and autonomic symptoms improved. On day 63, she was started on oral prednisolone 0.5 mg/kg/day. On day 107, she was transferred to another hospital for rehabilitation. Although a childish demeanor remained, normal conversation became possible at this point, and her physical function was equivalent to a modified Rankin Scale of 2 (7). Nine months after hospitalization, she returned to her former daycare center as a childcare worker without any sequelae. No relapse or higher brain dysfunction was observed (Fig. 2).

## Discussion

This is a rare case of anti-NMDAR encephalitis in a patient with TS. The results of blood, CSF, and imaging studies revealed neither tumors (including ovarian teratomas) nor viral infections, which are potential immunologic triggers of anti-NMDAR encephalitis (8). Therefore, in this case, the development of anti-NMDAR encephalitis may have involved other immunological triggers.

The susceptibility of TS patients to autoimmune diseases has been suggested to be due to X chromosome haploinsufficiency, maternal origin of the X chromosome, overproduction of inflammatory cytokines, decreased anti-inflammatory cytokines, or hypogonadism (2). Since numerous genes located on the X chromosome, including a major histocompatibility complex locus in the long arm, are involved in regulating immune responses and altering immune tolerance, X-linked gene dosage may play a role in the loss of tolerance (9). In addition, discrete, genetically based disturbances in both humoral and cellular immune responses (10), the PTPN22 C1858T polymorphism (11), and alterations in X-linked FOXP3 gene polymorphism expression (12) have been reported as important factors in autoimmune susceptibility in TS.

A meta-analysis reported thyroid autoimmune diseases, including Hashimoto's thyroiditis, in 38.6% of patients with TS (13). While many autoimmune diseases, including Hashimoto's thyroiditis and type 1 diabetes mellitus, show high standardized incidence ratios (14), to our knowledge, only two other cases of TS-related autoimmune encephalitis have been reported (3, 4) (Table). Since anti-NMDAR and anti-AMPAR antibodies cause symptoms similar to schizophrenia, dementia, and sleep disorders (15), there may be cases in which the development of psychiatric symptoms is not diagnosed as a complication of autoimmune encephalitis but is rather misdiagnosed as a complication of schizophrenia or other psychiatric disorders, as previously reported (4). Further research is needed to determine whether there is a causal relationship between TS and autoimmune encephalitis.

Most comorbidities between TS and schizophrenia have a

mosaic karyotype (45,X/46,XX). This is probably due to the effect of the gene dosage (16). Interestingly, the only reported karyotype of TS cases complicated by autoimmune encephalitis is mosaicism [45,XO/46Xr(x)] (4), as in our case [45,X/46,X, idic(X) (p11,4)]. Although the risk of developing an autoimmune disease is high in TS regardless of karyotype (X monosomy, isochromosome Xq, and all others) (14), schizophrenia in TS is largely limited to mosaics with numerical abnormalities. Therefore, when TS cases with mosaics with structural abnormalities present with psychiatric symptoms, autoimmune encephalitis should be considered rather than schizophrenia. Treatable autoimmune encephalitis can be diagnosed by focusing on the neurological features and resistance/side effects of antipsychotics within days to weeks of onset (17).

In summary, psychological episodes in patients with TS may have an autoimmune origin, as TS confers susceptibility to autoimmune diseases. As TS with mosaicism has been associated with schizophrenia, the psychiatric symptoms that develop in TS should be carefully differentiated from autoimmune encephalitis caused by anti-NMDAR or anti-AMPAR antibodies, and a CSF analysis of such cases should be considered early. Compared to schizophrenia, autoimmune encephalitis is relatively curable; thus, it is especially important to note the development of neurological features and resistance/side effects of antipsychotics after the onset of psychiatric symptoms.

**The authors state that they have no Conflict of Interest (COI).**

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