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Anti-N-Methyl-D-Aspartate Receptor Encephalitis with Serum Anti-Thyroid Antibodies: A Case Report and Literature Review

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Patient: Female, 16-year-old
Final Diagnosis: Anti NMDA receptor encephalitis
Symptoms: Epilectic seizure • irritability • memory decline • psychomotor retardation • psychosis
Medication: —
Clinical Procedure: —
Specialty: Neurology

Objective: Rare disease

Background: Anti-N methyl D-aspartate receptor encephalitis (anti-NMDArE) is a disorder in which triggers such as infectious agents or neoplastic disease can lead to an autoimmune response against the nervous system, although this disorder is usually idiopathic. Some patients with anti-NMDArE have evidence of other autoimmune alterations. Here, we present a case of non-paraneoplastic anti-NMDArE with elevation of serum anti-thyroid antibodies and a literature review of this association.

Case Report: A 16-year-old girl was admitted in the University Hospital of Bari for a new onset of tonic-clonic seizures. Progressively, the patient manifested also psychomotor agitation, language difficulties, memory impairment, psychotic symptoms, autonomic dysfunction, and psychomotor retardation. Blood evaluation revealed the presence of anti-thyroglobulin, anti-thyroperoxidase, and anti-NMDAr antibodies. Cerebrospinal fluid analysis confirmed the diagnosis of anti-NMDArE. No tumors were found. Treatment with intravenous immunoglobulin, steroids, and plasma exchange relieved symptoms and decreased levels of serum anti-NMDAr antibodies. After 12 months, the patient had full recovery of communicative capacity, with the persistence of slight difficulty of memory and mild tendency to irritability. Blood exams shown persistence of anti-NMDAr positivity and absence of anti-thyroid antibodies.

Conclusions: We report a rare case in which an autoimmune involvement of thyroid gland was concurrent with an anti-NMDArE. It would be useful for clinical practice to clarify whether the presence of anti-thyroid antibody an characterize the clinical course, prognosis, and response to treatment of the idiopathic type of anti-NMDArE.

Keywords: Thyroiditis • Anti-N-Methyl-D-Aspartate Receptor Encephalitis • Adolescent

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Background

Anti-N-methyl-D-aspartate receptor encephalitis (anti-NMDArE), first described by Dr. Josep Dalmau and colleagues at the University of Pennsylvania in 2007 [1], is an autoimmune disorder with a wide spectrum of neuropsychiatric symptoms. This disorder usually occurs in young women [2-4] with a female-to-male ratio of approximately 4: 1 [5]. It is the second most common autoimmune encephalitis in children and adolescents following acute disseminated encephalomyelitis (ADEM) [6].

The NMDA receptor is ligand-gated cationic channel mainly located in the forebrain and hippocampus and activated by glutamate. It is involved in synaptic transmission and neuronal plasticity, and has a role in learning, judgment, perception of reality, memory, and autonomic functions [7]. In the anti-NMDArE, the immune system produces immunoglobulins, with the prevalence of G1 subclass, against the GluN1/NR1 subunit of the NMDA receptor [8,9].

These antibodies (Abs) are produced in response to an autoimmune reaction, but the cause of this process is not entirely understood. Previous infections from other agents, such as Herpes Simplex Virus (HSV), Epstein-Barr Virus (EBV) and neoplastic disease with ectopic expression of neuronal proteins are thought to trigger a misdirected immune response against the nervous system [10]. The anti-NMDArE associated with a tumor is identified as a paraneoplastic encephalitis. The most common tumor associated with anti-NMDArE is ovarian teratoma [11], which is diagnosed in 6-50% of female patients with paraneoplastic encephalitis [12], while testicular germ cell tumors, lung cancer, thyroid cancer, breast cancer, colon tumors, mediastinal teratoma, neuroblastoma and Hodgkin's lymphoma are less frequent [13-16]. Nevertheless, most cases of anti-NMDArE are idiopathic [7]. Possible risk factors for idiopathic anti-NMDArE are viral comorbidities, a family history for autoimmunity, and possible genetic and ethnic predisposition [10].

Several studies showed that patients with autoimmune encephalitis have contemporary evidence of other autoimmune alterations and syndromes (eg, anti-nuclear Abs (ANA), thyroid peroxidase (TPO) Abs, Graves' disease, neuromyelitis optica, type I diabetes) [17-20], according to the hypothesis that an autoimmune disorder increases the risk of an additional autoimmune disorder [21]. Over the past decade, several authors have pointed out the coexistence of anti-thyroid (Thy) Abs in non-paraneoplastic anti-NMDArE [21], but the clinical and pathogenetic significance of this association needs to be further explored. In the context of this ongoing debate, we present the present case report of an adolescent girl affected by a non-paraneoplastic anti-NMDArE associated with positive anti-TPO and anti-thyroglobulin (TG) circulating Abs; then, we discuss this finding together with other case reports selected through a brief review of the literature on the association between anti-NMDArE and serum anti-Thy Abs.

Case Report

A 16-year-old girl was admitted in the Child Neuropsychiatric Unit of the University Hospital of Bari for the onset, during the previous week, of 3 tonic-clonic seizures, with loss of consciousness followed by falling and characterized by severe tonic muscle spasms, upward rolling of the eyes, loss of saliva from the mouth, bluish/gray face, wheezing sounds, and jerky movements of the face, arms, and legs, which gradually disappeared after 1-5 minutes. She had no personal history for previous medical conditions, but had a family history for Hashimoto's thyroiditis. The first neurologic examination was positive for inconstant gait and balance abnormalities. Moreover, the patient reported paresthesia of the left side her body.

During the first 24 hours following admission, we performed blood exams (blood count, electrolytes, creatinine, urea, glucose, bilirubin, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transpeptidase, albumin, cholesterol, triglycerides, lactate dehydrogenase, creatine phosphokinase, fibrinogen, thyrotropin, free thyroxin, free triiodothyronine, C reactive protein), showing normal values. An electroencephalogram (EEG) showed alpha waves with anterior spreading and discontinuous sharp waves in the parietal and temporal regions on the right side of the brain. Brain magnetic resonance imaging (MRI) results were normal.

Our first hypothesis was epilepsy, so we started treatment with carbamazepine (20 mg/kg/day), with a partial intensity and frequency reduction of the seizures.

At 2 weeks after admission, the patient presented psychotic symptoms characterized by psychomotor agitation, fearfulness, and auditory/visual hallucinations with an intermittent course during the day. In addition, other clinical manifestations appeared, such as discuss autonomic disorders (lability of blood pressure, cold extremities, and pale skin), night insomnia, cognitive deterioration, and worsening of motor and language abilities, so the patient had prolonged bed rest. In this phase, a neurological examination showed mild dysmetria, dysdiadochokinesia, and dysfunctions of dynamic postural control and balance. Furthermore, epileptic seizures increased again in frequency, occurring as focal impaired awareness, focal motor movements, and/or generalized tonic-clonic seizures. Carbamazepine was suspended on the 19th day of hospitalization due to the onset of thrombocytopenia and leukopenia and was changed to levetiracetam (17 mg/kg/day).

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According to the modification of the patient's clinical conditions and the presence of epileptic seizures, psychomotor agitation and psychotic symptoms, an encephalitis syndrome was suspected. Microbiological [Herpes Simplex Virus (HSV) 1/2, Epstein-Barr Virus (EBV), Human Herpes Virus (HHV) 6, Rubella Virus, Cytomegalovirus (CMV), Varicella Zoster Virus (VZV), Measles Virus Immunoglobulins] and immunological blood evaluations [anti-nuclear Abs (ANA), anti-neutrophil cytoplasmic Abs (ANCA), extractable nuclear antigens (ENA) Abs, Rheumatoid Factor (RF), LG11 and CASPR2 potassium channels Abs, myelin-associated glycoprotein (MAG) Abs, gamma-amino butyric acid (GABA) receptor Abs] were performed. Based on the young age of the patient, the acute onset of the disease, and the anamnestic data, we did not perform tests searching for viral and bacterial agents responsible for encephalitis in advanced stage of infection such as HIV virus and *Treponema pallidum*. All listed blood investigation results were within normal ranges, except for anti-NMDAr Abs (titer 1: 3200), anti-TG (110 IU/mL, normal range 15-60 UI/mL), and anti-TPO (203 IU/mL, normal range 28-60 UI/mL). Thy function was normal. Cerebrospinal fluid (CSF) analysis revealed normal protein concentration, but the presence anti-NMDAr Abs. The diagnosis of anti-NMDArE was confirmed on the 18th day of hospitalization.

Further blood and radiological exams were performed to exclude the paraneoplastic etiology of encephalitis: serum dosage of cancer antigen (CA)-125, carcino embryonic antigen (CEA), α-fetoprotein and tissue polypeptide antigen (TPA), abdominopelvic, lymph nodes and thyroid ultrasound, positron emission tomography with fluorine-18 fluorodeoxyglucose (FDG PET) of total body without evidence of tumors.

According to the positivity for anti-NMDAr Abs in both the serum and CSF, the patient received intravenous immunoglobulin (IVIG, 0.4 g/kg/day) for 5 days, followed by high-dose methylprednisolone (1 g/day for 7 days, and then 0.5 g/day for 3 days), with no significant clinical improvement. A slow alleviation of encephalitis symptoms started only after she underwent the third session of plasma exchange (PLEX) (2 cycles with 5 sessions per cycle, on alternate days). At the same time, a decrease of serum level of anti-NMDAr Abs was found (titer 1: 320). At the time of hospital discharge, the patient showed only occasional language difficulties (comprehension and formulation of complete sentences), short memory impairment, and some buccal automatisms [modified Rankin Scale (mRS) [22] score passed from 4 to 2]. The anti-epileptic therapy with levetiracetam was confirmed.

Later, the patient was followed up through close outpatient check-ups. After 12 months, she was admitted to the same hospital to re-perform clinical and instrumental tests. She showed full recovery of communicative and expressive ability, mild short-term memory difficulties, and a slight tendency to irritability. The neurologic examination revealed no focal signs. Blood exams still showed positivity for anti-NMDAr Abs (weak reactivity to titer 1.10) and decrease of anti-Thy Abs serum levels (TG Ab 12 IU/mL, TPO Ab < 9 IU/mL). Brain MRI, chest X-ray, abdominopelvic, and lymph nodes ultrasound were free of pathological signs. An EEG study showed slight excess of slow activity in the left temporal side of brain. Anti-epileptic therapy was confirmed.

Review of Anti-NMDArE with Serum Anti-THY ABS

An electronic literature search was conducted for all articles published up to April 2020, with a range of databases searched including PubMed, Scopus, and Web of Science. The following combinations of keywords were used: "NMDAr/NMDA encephalitis", "Thyroid", "Thyroid Peroxidase/TPO", "Thyroglobulin/TG". Research articles, case reports, and reviews in free full-text format and in English language were included.

We identified 35 records through the database search; after removing duplicates, there were 24 records. As inclusion criteria, papers needed to provide enough information about thyroid involvement in non-paraneoplastic anti-NMDArE cases, so 6 publications were selected for inclusion in this review.

Discussion

We described the case of an adolescent girl with a definite diagnosis of non-paraneoplastic anti-NMDArE and the coexistence of anti-TPO and anti-TG circulating Abs. The acute onset of epileptic seizures, psychotic symptoms, and abnormal speech and behavior and the progressive clinical worsening despite treatment with anti-epileptic and anti-psychotic drugs justified the Abs testing on CSF, confirming the diagnosis of anti-NMDArE. We observed good results with immunomodulatory therapy, with progressive improvement of clinical conditions and no episode of relapse over a 12-month follow-up.

To our knowledge, this is one of the few cases reported in the literature of an autoimmune involvement of the thyroid gland concurrent with an anti-NMDArE. We know that Thy Abs are found in 10-12% of healthy populations [23], with different ranges according to age and sex [24], so the detection of anti-Thy Abs in patients with anti-NMDArE could be considered as an occasional finding. A recent retrospective cohort study of 517 patients with different types of antibody-positive autoimmune encephalitis (AE) showed that Hashimoto's thyroiditis was the most commonly diagnosed autoimmune comorbidity, with a frequency of 5.42%, opposed to 1% in the general population [25]. This finding supported the hypothesis, previously suggested by Tuzun et al [26], that patients with Thy Abs are inclined to develop anti-neuronal-immune response and acute idiopathic encephalitis. A literature search of patients with the

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Table 1. Literature review on anti-NMDArE cases with serum anti-Thy Abs.

Authors	Type of study	Patients (Number, sex, age in years)	Abs (type and serum level)	Therapy	Outcome
Tuzun E et al (2011) [26]	Research article	2, F, 37 and 53	TPO and TG >200 IU/mL	Steroids+ IVIG or PLEX or Cyclophosphamide	Neurological improvement with return to work and daily activities
De Leu N et al (2012) [27]	Case report	1, F, 16	TPO >600 IU/mL	Methylprednisolone+ thyroidectomy	After 3 days of corticoid administration, gradual and complete neurological relapse
Lu J et al (2015) [28]	Case report	1, F, 36	TPO 585 IU/mL	Methylprednisolone+ prednisone + PLEX	Improvement of psychosis and hypersexuality. At about 5 months, recurrence of Graves' disease (treated with Methimazole and radioactive iodine ablation) and subjective memory impairment
Jung Y et al (2016) [29]	Case report	1, F, 70	TPO >3000 IU/mL TG 92.52 IU/mL	Steroids+ IVIG+ Rituximab	Gradual improvement of confusional mentality and psychiatric symptoms. After 12 months complete resolution of the symptoms
Zhang W et al (2017) [30]	Research article	1, F, 18	TPO 58.43 IU/mL TG 920.33 IU/mL	Methylprednisolone+ IVIG	Partial recovery of psychological and behavioral disorders (mRS score: 4) after 10 months
Wang X et al (2018) [31]	Case report	1, F, 20	TPO and TG (no data on serum levels)	Steroids+ IVIG	Marked improvement of mental status without motor or behavioral abnormality

F – Female patient; TPO – thyroperoxidase antibodies; TG – thyroglobulin antibodies; IVIG – intravenous immunoglobulins; PLEX – plasmapheresis.

co-occurrence of anti-NMDArE and increased level of serum anti-Thy Abs is presented in **Table 1** [26-31]. In particular, De Leu et al [27] and Lu J et al [28] described 2 patients with Graves' disease; the remaining 5 patients had variable and different titers for Anti-Thy Abs, ranging from 58 IU/mL to 3000 IU/mL for TPO and from 92 IU/mL to 920 IU/mL for TG. In addition, our patient had a family history of Hashimoto's thyroiditis.

It should be noted that each anti-NMDArE case considered was the non-paraneoplastic form, as was the case we described. Although anti-NMDArE is often categorized as a paraneoplastic syndrome, more frequently it is a non-paraneoplastic condition, especially in children [7]. The co-occurrence of both anti-NMDAr-Abs and Anti-TPO/Anti-TgG Abs in idiopathic forms of anti-NMDArE could suggest that T cell activation and the loss of immune self-tolerance, probably as a consequence of a complex interaction between genetic and environmental factors, could contribute to development of autoimmune disorders [25]. Juvenile age and female sex could be considered 2 adjunctive factors which increase the risk of auto-Abs production against both Thy and the brain.

Our patient and the cases listed in the table were young women, with a mean age of 33.2 years. The high frequency of anti-NMDArE and autoimmune thyroiditis reported in reproductive age woman suggested that sex hormones could act as factors increasing risk to develop both of these autoimmune disorders [7,32].

In addition, the pathogenetic role of anti-Thy Abs in AE, which has already been established for Hashimoto's encephalitis (HE), should be considered. It would be better to classify HE as a probable AE [33], because the underlying pathogenetic mechanism of HE is currently not clear. In fact, the theory that self-Abs against neural antigens cross-reacts with Thy antigens as the pathogenetic basis of HE needs further investigation. The following pathogenetic mechanisms have been suggested: a) a shared target antigen between the thyroid gland and central nervous system; b) a neurotoxic effect of Thy hormones and Abs interference on neurotransmission; c) an effect of other Abs as enolases, dimethylargininase-I, aldehyde reductase-I, myelin-oligodendrocyte glycoprotein, gangliosides, and a few onco-neuronal antigens; and d) a consequence of vasculitic processes, primary demyelination, and immune complex-mediated processes [34]. Because of these considerations, we are not

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able to exclude a direct effect of anti-Thy Abs on the brain or a second autoimmune mechanism in some patients with presumed HE. According to the diagnostic criteria for AE, if anti-Thy Abs and anti-neuronal Abs exist simultaneously, AE should be diagnosed with priority. Otherwise, before diagnosing HE, anti-neuronal Abs should be detected to avoid misdiagnosis. In line with these considerations, the case we reported had a definite diagnosis of anti-NMDArE with associated detection of anti-Thy Abs of unclear significance. The hypothesis that the association between anti-NMDAr and anti-Thy Abs could be suggestive of a co-shared pathogenetic mechanism of autoimmune encephalitis needs more intensive investigation.

We know of no specific clinical phenotype to discriminate NMDArE with serum anti-Thy Abs from no-serum Thy Abs ones. Guan et al [35], studying the clinical NMDArE evolution in several female patients, explored the hypothesis that the presence of serum anti-Thy Abs and their titers could predict a shorter disease duration and a better treatment response [36-38]. Because very little is known about this topic, further studies are required to determine the utility of anti-Thy Abs titers predicting clinical manifestations, prognosis, and eventual relapses [39]. Anti-NMDArE is certainly a severe disease in which the prognosis remains obscure, but early diagnosis and intervention could reduce the incidence of complications and relapses.

Conclusions

The case we reported showed a classic presentation of anti-NMDArE, but with the presence of anti-Thy Abs. To date, the coexistence of anti-NMDAr Abs and anti-Thy Abs is still unclear. The detection of high titers of anti-TG and anti-TPO in an adolescent female with anti-NMDArE and a positive family history for Hashimoto's thyroiditis we described, together with previous evidence reported by other authors, suggests the hypothesis that this association cannot be just occasional. Further studies about these mechanisms are needed to determine if anti-Thy Abs has a pathogenetic role in the context of idiopathic anti-NMDArE. Moreover, it would be useful for clinical practice to clarify, through longitudinal studies on a larger number of patients, whether the presence of anti-thyroid antibody can characterize the clinical course, prognosis, and response to treatment of the idiopathic type of anti-NMDArE.

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Conflict of Interests

None.

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