

Single Case – General Neurology

Anti-NMDA Receptor Encephalitis in a Patient with Tuberous Sclerosis-Related Brain Tumor: A Case Report

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Keywords

NMDA receptor encephalitis · Tuberous sclerosis complex · Primary brain tumor · Case report

Abstract

Anti-NMDA receptor (NMDAR) encephalitis (NMDARE) is an important treatable cause of autoimmune psychosis in all age-groups, which is sometimes associated with tumors, especially ovarian teratomas. Tuberous sclerosis complex (TSC) is an autosomal dominant inherited neurocutaneous disease predisposing for development of benign tumors. We present a case of a 35-year-old woman with recurrent episodes of schizophrenia-like symptoms. Accidentally, MRI revealed TSC-related brain tumors. NMDAR antibody titers were strongly positive in serum and cerebrospinal fluid. This is the first case describing an overlap of NMDARE and TSC-related brain tumors. A review of brain tumors and NMDARE is given in the supplementary material. Although a causal link seems interesting from a pathophysiological point of view, we are in favor of a coincidence.

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Introduction

Anti-NMDA receptor (NMDAR) encephalitis (NMDARE) is an autoimmune disorder caused by self-reactive IgG antibodies against the NR1 subunit of the NMDA receptor. First described in 2007 by Dalmau et al. [1], NMDARE is today recognized as a leading cause of encephalitis, especially in young female adults, although it can affect male patients and all age-groups [2, 3]. While initial symptoms vary with respect to different patient groups, most patients develop a relatively similar spectrum of symptoms, regardless of age, which consists of seizures, memory deficits, movement disorders, autonomic dysregulation, central hypoventilation, and psychiatric disorders [2, 3]. Psychiatric disorders are upon the most common symptoms in NMDARE but vary in their clinical presentation, often misleading physicians to a primary psychiatric diagnosis [4]. The most common psychiatric manifestation is behavioral disorders, psychosis, mood disorders, catatonia, and sleep disturbances [5]. While earlier studies suggested a strong association with ovarian teratomas, only in 38% of all patients with NMDARE neoplasms can be found but are particularly common in young female adults [1–3].

Tuberous sclerosis complex (TSC) is an autosomal dominant inherited neurocutaneous disease with extremely heterogeneous phenotypes affecting about 1:6,000–10,000 live births or 1:20,000 adults [6]. Loss of function mutations in hamartin (TSC1, chromosome 9) or tuberlin (TSC2, chromosome 16) results in a disinhibition of the mammalian target of rapamycin (mTOR) [6, 7]. Diagnosis of definite TSC can be established genetically or clinically according to the recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference [6]. Overactivation of mTOR leads to development of benign tumors, the so called hamartomas, and can affect almost any organ, especially the brain, skin, kidney, heart, and lung [6–8]. In the brain, TSC manifests with subependymal nodes or subependymal giant cell astrocytomas (SEGA) – which represent a continuum of the same tumor [9] – cortical and subcortical tubers and radial migration lines. Two-thirds of patients have their first seizure before their first birthday, and patients are prone to TSC-associated neuropsychiatric disorders (TANDs) with cognitive impairment and autism spectrum diseases which can be assessed using the specific TAND checklist [7, 10]. To date, there are no validated data on psychosis and schizophrenia in TSC [10]. To our knowledge, there are no previous case reports of coincidence of NMDARE and TSC.

Case Report

A 35-year-old woman consulted our neurologic outpatient department in January 2019 because of at least 2 episodes of psychotic symptoms and an incidental diagnosis of TSC. She did not show any symptoms in a thorough neurological examination, and she was remitted from psychiatric symptoms.

She reported 2 episodes of psychotic symptoms in December 2017 and September 2018. In the first episode, she had not sought medical help because symptoms ameliorated soon without medical intervention.

In September 2018, she had flu-like symptoms. Three weeks later, she again heard a voice that told her to commit suicide. She had delusions and disorganized and paranoid thinking. In addition, she reported diffuse visual disturbances, especially double vision, and did not recognize her parents' faces. CT and MRI (Fig. 1) displayed 2 subependymal tumors, radial migration lines and cortical tubers, which proves the diagnosis of TSC according to the current guidelines [6]. An EEG revealed no pathology. Laboratory findings were unremarkable, and ultrasound of the heart and abdominal organs displayed

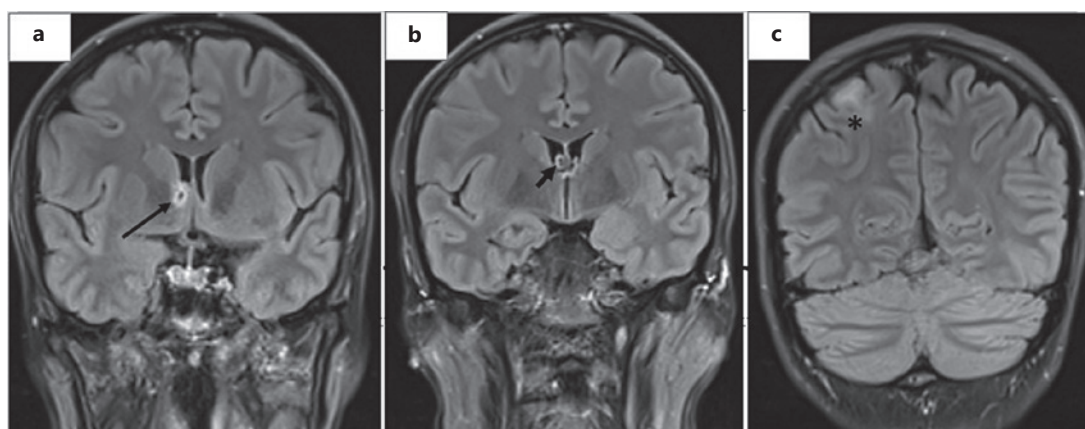


Fig. 1. Brain MRI: T2-TIRM with contrast agent showing a subependymal tumor with enhancement (large arrow in **a**), another subependymal tumor (small arrow in **b**), and a cortical tuber next to a radial migration line (* in **c**).

no further TSC-related tumor. An ophthalmologic examination found no correlate for the visual disturbances and especially no retinal hamartomas. A lumbar puncture was recommended, but the patient refused at this time. She was diagnosed with organic delusional disorder and treated with olanzapine, risperidone, and aripiprazole. Symptoms completely resolved, and she remained free of symptoms for more than a year, although she stopped medication only a few days after discharge.

In February 2019, we performed blood sampling and a lumbar puncture and found elevated serum (1:10,000) and cerebrospinal fluid (CSF) titers (1:3) of IgG anti-NMDAR antibodies but no antibodies against AMPAR1/2, DPPX, GABA-B-receptor, LGI1, or CASPR2. Interestingly, tissue-based immunofluorescence of CSF showed IgG antibodies binding to cerebral blood vessels with an undetermined epitope. There were no other alterations in CSF parameters, for example, no elevated cell count, no oligoclonal bands, no increase in protein, and blood-brain barrier (BBB) function was not compromised.

An MRI displayed (again) the 2 subependymal tumors, radial migration lines, and cortical tubers, showing no growth of the subependymal tumors but contrast enhancement in one of them. We therefore confirmed the diagnosis of a TSC according to the recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference [6]. We screened the patient for TSC-related neuropsychiatric disorders according to the TAND checklist, but there were no findings in either of the 12 dimensions. The patient refused genetic testing of TSC. EEG revealed no pathological findings, and another abdominal ultrasound exhibited no teratoma. We agreed with the patient on an active surveillance strategy with regard to the incidental TSC and – despite the detection of NMDAR-antibodies – the previous psychotic symptoms because she was asymptomatic at that time.

In May 2020, the patient was transferred to our hospital because of a stupor. Retrospectively, the patient reported being delusional (megalomania, delusion of reference) for about 1 week before hospital admission and complained about sleep disturbances. She ameliorated under treatment with benzodiazepines within a few hours but remained delusional and showed harmful behavior toward others; therefore, we transferred her to an external psychiatry department, where she was treated intermittently between May and August of 2020. Blood sampling and lumbar puncture showed the same NMDAR antibody titers as in February 2019 (1:3 in CSF and 1:10,000 in serum). Again, CSF revealed neither pleocytosis nor oligoclonal bands. Laboratory results yielded no further pathologic result.

Table 1. Timeline of clinical, diagnostic, and therapeutic management of the current case

Timeline	Symptoms	Therapy
December 2017	First episode with command auditory hallucinations and delusional symptoms	No therapy (spontaneous recovery)
September/ October 2018	Second episode with command auditory hallucinations and suicidal thoughts, and formal thought disorder	Aripiprazole and risperidone (both only for few days)
February 2019	No symptoms	First proof of NMDAR antibodies; no therapy
May–July 2020	Third episode with stupor, delusional symptoms, harmful behavior, sleeping disorder, and formal thought disorder	Lorazepam, zuclopenthixol, and olanzapine
August 2020		
Before immunosuppressive treatment	Concentration problems, formal thought disorder, and sleeping disorder	Lorazepam, zuclopenthixol, and olanzapine
2 cycles of rituximab	Initially delusional thinking	Lorazepam, zuclopenthixol, olanzapine, and 2 cycles of rituximab (with prednisolone premedication)
September 2020	Concentration problems, marked subjective improvement, and patient again taking up her study	Lorazepam, zuclopenthixol, and olanzapine
December 2020	Depressive symptoms, anxiety, leading to inpatient treatment	Lorazepam, zuclopenthixol, and olanzapine
January 2021	Suicide	

CSF, cerebrospinal fluid; NMDAR encephalitis, NMDA receptor encephalitis.

Especially, thyroid levels were in a normal range, and urinalysis was negative for drugs (methadone, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates). She was negative for HIV, hepatitis virus B and C, and tuberculosis. Nevertheless, in a neurological in-hospital re-evaluation in August 2020, she still complained of disturbed circadian rhythm and noticed difficulty concentrating, so she was not able to manage her daily life alone. Moreover, she felt that sleep disturbances were worsening. As she was symptomatic and fulfilled the criteria for NMDARE (oligosymptomatic-psychiatric) according to the criteria of Graus et al. [11], we started a therapy with 2 cycles with rituximab (and premedication with prednisolone). One day after the first treatment with prednisolone and rituximab, her symptoms deteriorated as she became delusional and showed inadequate, agitated behavior as well as signs of thought disorders. We added 1 cycle of intravenous immunoglobulins and reinitiated her antipsychotic and sedative treatment with olanzapine, lorazepam, and zolpidem. Upon discharge about 1 week later, her condition had improved significantly as she was now less delusional and showed an improving organization of thinking. She agreed to continue the antipsychotic treatment as well as further immunotherapy with rituximab. In September 2020, NMDAR antibody titers had declined (1:1 in CSF, 1:100 in serum). After an initial stabilization and overall improvement of her clinical status to the extent that she had taken up her studies again, the patient began suffering from depressive symptoms and anxiety, ultimately resulting in committing suicide in January 2021 during an ongoing inpatient treatment in a psychiatric hospital. Table 1 summarizes the case in a timeline.

Discussion/Conclusions

To the best of our knowledge, this is the first case reporting a coincidence of NMDARE and TSC. In a follow-up period of 3 years, the patient exhibited delusional symptoms, mood changes, complex neurological deficits (visual disturbances, prosopagnosia), sleep disturbances, and stupor. This is in line with the typical clinical symptoms described in patients with NMDARE [5]. The patient showed a subacute onset of psychiatric symptoms in <3 months. From an epidemiological point of view, the patient belongs to the main risk group for NMDARE [2, 3]. In the presence of one of the 6 major group symptoms (i.e., abnormal psychiatric behavior, speech dysfunction, seizures, movement disorders, decreased level of consciousness, and autonomic dysfunction), the detection of IgG anti-GluN1 antibodies and after exclusion of other diseases diagnosis of definite NMDARE can be made according to the guideline of Graus et al. [11]. It is remarkable that neither EEG nor CSF (except of the NMDAR antibodies) and the MRI showed any pathologic feature regarding NMDARE. Although the sole detection of NMDAR antibodies in patients with psychosis seems not to have an influence of the course of disease [12], in the current case, the high serum antibody titers and the typical clinical presentation together with the intrathecal antibody detection corroborate the diagnosis of NMDARE.

Despite the patient's refusal for genetic testing, diagnosis of TSC could be established because of 2 cortical tubers, radial migration lines, and 2 subependymal tumors according to the recommendations of the International Tuberous Sclerosis Complex Consensus Group [6]. In the current case, one of the subependymal tumors showed uptake of contrast agent but did not show growth within 6 months. Thus, this tumor only fulfilled 3 of 4 criteria for SEGAs, and definite diagnosis of SEGAs could not be established. Subependymal tumors like subependymal nodules and SEGAs are different from other astrocytomas regarding histology, therapy, and prognosis and are of mixed glio-neuronal origin [7].

Because of the relapsing remitting course of the psychiatric symptoms of the patient, we discussed if psychiatric symptoms may alternatively result from a TSC-associated neuropsychiatric disorder. However, psychotic symptoms are no classical symptom of TSC, and screening for other neuropsychiatric impairment abnormalities using TAND checklist remained normal [10].

In NMDARE pathogenesis, an established hypothesis concerning the triggering of antibody production is the ectopic expression of neuronal tissue, especially NMDAR subunits, in teratomas, leading to an impaired immune tolerance [1]. Despite our thorough literature review, we did not find any case report of subependymal tumors and NMDARE. Therefore, due to missing evidence, we do not suspect a triggering of NMDAR-antibody production via subependymal tumors in the given case. The literature review for primary brain tumors and NMDARE is presented in detail in online suppl. material; for all online suppl. material, see www.karger.com/doi/10.1159/000518642.

Alternatively to triggering NMDAR antibody production, subependymal tumors might lead to impairment of BBB function as indicated by contrast enhancement. Previous studies suggest that impaired BBB function plays a crucial role for NMDARE [13, 14]. In the current case, one of the subependymal tumors did indeed show uptake of contrast agent. It seems possible that transient leakage of the BBB may allow passive transfer of serum-dominated IgG NMDAR antibodies with consecutive clinical symptoms. This would be in line with the high gradient between serum (1:10,000) and CSF antibody titers observed in our patient. The relatively low CSF antibody titer (1:3) furthermore suggests that NMDAR antibodies in the brain compartment are bound to neuronal tissue (immunoprecipitation) [14]. However, in the given case, BBB impairment could also be due to NMDARE innate phenomena independent of the TSC-related tumors.

In general, tumor removal is emphasized in paraneoplastic NMDARE as the most important therapeutic step [3]. Since a causal connection between her subependymal tumors and the NMDARE in this case seemed unlikely, we decided not to surgically remove the TSC-related tumors. Moreover, the tumors were stable in size (<2 cm) and most likely asymptomatic, neither did they cause a ventriculomegaly therefore not showing any indication for treatment of TSC-related tumors by resection and/or mTOR inhibition (8) independent of the presence of NMDARE.

Furthermore, surgical interventions in brain tumors are often difficult and can lead to significant brain tissue damage, reinforcing our surveillance strategy in the given case. When the first immunomodulatory treatment with rituximab was started, the patient had suffered at least 3 episodes of NMDA-RE, and those episodes had become longer in duration and more severe. We suspected that the clinical course indicated a more severe form of NMDARE. In an analysis by Titulaer et al. [2], 47% did not improve under first-line therapy in the first 4 weeks, had a poor mRS, and had better outcomes if treated with rituximab. Hence, we decided with the patient using a case-by-case strategy to immediately start a therapy with rituximab and added intravenous immunoglobulins.

Naturally, since we only found a report of a single case of TSC and NMDARE, no conclusions regarding the association of both diseases could be made. Moreover, the patient refused genetic testing, so we could not determine the TSC subtype, showing one of the limitations of this case report.

Another limitation concerns the known association of NMDAR encephalitis with other tumors such as ovarian (micro)teratomas. In the given case, neither a positron emission tomography nor a thoraco-abdominal MRI was performed in order to rule out further neoplasms. On the other hand, we did not find classical TSC- or NMDARE-related tumors using ultrasound of the heart and of abdominopelvic organs. Furthermore, an ophthalmologic evaluation did not show any TSC-related tumor. Unfortunately, a postmortem autopsy was not carried out, showing another limitation of the given case report. Taken together, the current case presents a new type of brain tumor co-occurring with NMDARE, although further investigations are needed to distinguish a causal connection between TSC and NMDARE from a coincidence of the diseases. Furthermore, it underlines the need for thorough exclusion of encephalitis in any new onset psychiatric patient.

Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from the patient for the publication of this case report and accompanying images and figures before her death. This case report did not require IRB approval.

Conflict of Interest Statement

The authors confirm that this article content has no conflict of interest.

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The current report describes a clinical case and all analyses were part of a routine clinical evaluation, hence there was no need for any funding.

Author Contributions

Names	Locations	Roles	Contribution
T. Ihl	Charité Universitätsmedizin Berlin	Author	Acquisition of data. Carried out the literature review. Interpreted the data. Drafted the manuscript for intellectual content
F.A. Arlt	Charité Universitätsmedizin Berlin	Author	Acquisition of data. Revised the manuscript for intellectual content
M.-L. Machule	Charité Universitätsmedizin Berlin	Author	Revised the manuscript for intellectual content
H. Prüss	Charité Universitätsmedizin Berlin	Author	Interpreted the data. Revised the manuscript for intellectual content
H.J. Audebert	Charité Universitätsmedizin Berlin	Author	Interpreted the data. Revised the manuscript for intellectual content

Data Availability Statement

The most important aspects of the case are presented in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

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