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NMDA-RECEPTOR ASSOCIATED ENCEPHALITIS IN A WOMAN WITH MATURE CYSTIC OVARIAN TERATOMA

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Introduction – N-methyl-D-aspartate receptor (NMDA-R) antibody-associated encephalitis has been reported in the international neurological literature to be associated with mature or immature ovarian teratomas (OTs). However, few cases of encephalitis were diagnosed in Hungary. In 2011 Hollody et al. described the first case of anti-NMDA receptor associated encephalitis in Hungary.
Objective – Our aim was to present a case of NMDA-R antibody-mediated encephalitis in a woman with OT thereby providing information facilitating diagnosis of OT in women, who present with symptoms of encephalitis.
Case – We report the case of a 25 year-old women, who developed NMDA-R -antibody associated autoimmune encephalitis and who displayed confusion, disorientation, a behavioural disturbance with agitation and features of paranoia and at least one reported generalized tonic clonic seizure and orofacial dyskinesia. Magnetic resonance imaging revealed a functional ovarian cyst measuring 3.3 cm, which was removed surgically and demonstrated histologically to be a mature cystic OT. The serum was positive for antibodies to NMDA receptors. Following intravenous immunoglobulin treatment, oophorectomy and a 5-day course of plasma exchange, followed by corticosteroid and azathioprine immunosuppressive therapy, the patient displayed a significant clinical improvement.

N-METIL-D-ASZPARTÁT-RECEPTOR (NMDA-R) -ELLENES ANTITEST KÖZVETÍTETTE ENCEPHALITIS ÉRETT OVARIALIS TERATOMÁVAL

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Bevezetés – Az N-metil-D-aszpartát-receptor (NMDA-R) -ellenes antitest közvetítette encephalitis és az érett, illetve éretlen ovarialis teratoma (OT) kapcsolata ismert a nemzetközi neurológiai szakirodalomban, azonban Magyarországon kevés ilyen esetet diagnosztizáltak. Hollody és munkatársai 2011-ben voltak az elsők, akik leírták az anti-NMDA-receptor-asszociált encephalitis esetét Magyarországon.
Célkitűzések – Célunk volt bemutatni egy NMDA-R-ellenes antitest-közvetített encephalitisben szenvedő nőbeteg esetét, akinél neurológiai tüneteinek hátterében ovarialis teratoma igazolódott. Ezáltal szeretnénk felhívni a kollégák figyelmét és elősegíteni a hasonló tüneteket produkáló nőbetegeknél a mihamarabbi diagnózist.
Eset – A 25 éves nőbeteget NMDA-R-ellenes antitest-közvetített autoimmun encephalitis tüneteivel kezeltük. A betegnél dezorientáció, agitáció, viselkedési zavar, paranoia és orofacialis dyskinesia, valamint generalizált tónusos-clonusos roham jelentkezett. Az MR-vizsgálat kimutatta a 3,3 cm-es funkcionális petefészekcisztát a klinikai tünetek hátterében, melyet műtétileg eltávolítottunk. A szövettani vizsgálat igazolta az érett OT diagnózisát. A kért szérumantitest-vizsgálatok közül az NMDA-receptor-ellenes antitest bizonyult pozitívnak. Az intravénás immunglobulin-kezelés, a petefészek-eltávolítás és az ötnapos plazmaferézis, majd a kortikoszteroid-, azatioprintartalmú immunszuppresszív terápia a beteg jelentős klinikai javulását eredményezte.

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Conclusion – Cystic teratomas are common benign ovarian lesions in women of reproductive age. Although the association of OTs and NMDA-R antibody-associated encephalitis has been described in the international neurological literature, this relationship needs to be considered from on the interdisciplinary aspect by the health care providers.

Keywords: *ovarian teratoma, NMDA-receptor antibody-associated encephalitis*

Megbeszélés – A cisztás teratoma gyakori jóindulatú petefészek-elváltozás a fertilis korú nőkben. Bár az OT és az NMDA-R-ellenes antitestek által közvetített encephalitis ismert a nemzetközi neurológiai szakirodalomban, az antitest-reakció által kiváltott neuropszichiátriai tünetek interdiszciplináris megközelítést igényelnek az egészségügyi személyzet részéről.

Kulcsszavak: *ovarialis teratoma, NMDA-receptor antitest-közvetített encephalitis*

N-methyl-D-aspartate receptor (NMDA-R) antibody-associated encephalitis has been reported in the international neurological literature to be associated with mature or immature ovarian teratomas (OTs). However, few cases of encephalitis were diagnosed in Hungary. In 2011 Hollody et al. described the first case of anti-NMDA receptor associated encephalitis in Hungary[1]. The traditional concept of the paraneoplastic limbic encephalitis (PLE) was first described more than 30 years ago by *Corsellis* et al.[2]. In this case the antigen is intracellular, the detected onconeural antibodies are just biomarkers and not mediators, and prognosis is poor. As opposed to these, there is the newly described group of truly antibody-mediated paraneoplastic *or* autoimmune encephalitis with favourable prognosis, including the anti-NMDA-R encephalitis and others presenting as typical limbic encephalitis (LGI1, CASPR2, AMPAR, $GABA_BR$).

In the review by *Gultekin* et al.[3] 137 patients with PLE associated ovarian teratoma (OT) and germ-cell tumours of the testis have been reported. Although this first reports described a high incidence of ovarian teratoma associated with the disease (app. 60%), it is now becoming clear that the majority of patients do not have any tumours and their disease is of autoimmune nature.

Some papers have described that the majority of patients suffering from PLE had limbic structures and brainstem involvement[2, 3]. But in the case of anti-NMDA-R encephalitis the symptoms are different from those of limbic encephalitis that typically starts with an amnestic syndrome, whereas anti-NMDA-R encephalitis has a more widespread and frontal symptomatology. The differential diagnosis of PLE or autoimmune encephalitis is often difficult: similar symptoms (seizures, an acute confusional state, psychiatric abnormalities, a cognitive dysfunction, brainstem abnormalities and other clinical features[2]) can be caused by infections (especially type 2 herpes simplex encephalitis), brain metastasis, toxic or metabolic encephalopathies and cancer-related complications or side-effects of cancer therapy[4]. The presence of antibodies in the serum and cerebrospinal fluid (CSF), facilitates the diagnosis of PLE or autoimmune encephalitis and the associated tumours[4, 5].

ABBREVIATIONS

CNS: central nervous system
CRP: C-reactive protein
CSF: cerebral spinal fluid
EEG: electroencephalography
MRI: magnetic resonance imaging
NMDA: N-methyl-D-aspartate
OT: ovarian teratoma
PLE: paraneoplastic limbic encephalitis

Neurologists, obstetricians and gynaecologists are the primary care providers for women during the reproductive life cycle, and as such can play a role in the identification of OT-associated PLE in females. We report here the differential diagnostic and treatment efforts of our multidisciplinary team to clarify the origin of NMDA-R antibody associated encephalitis in a young woman.

Objective

Our aims are to present a case of NMDA-R antibody-associated encephalitis in a woman of reproductive age with OT and to provide information relating to the connection between OT and encephalitis.

Case report

A 25-year-old nulliparous woman with a 3 week history of encephalopathy, including confusion, disorientation, a behavioural disturbance with agitation and features of paranoia and at least one report-

Table 1. *Diagnostic algorithm of patients with NMDA-receptor antibody mediated encephalitis*

Diagnostic procedure	Results
Lumbar punction and analysis of cerebrospinal fluid (CSF)	A glucose level was 3.7 mmol/L. The protein level was 0.18 g/L. No pathogenic organism was detailed
Blood test (general hematology and general biochemistry)	A white cell count was 10.2×10^9 L. The C-reactive protein level was CRP<0.2 mg/L
Brain Magnetic Resonance Imaging (MRI)	Bilateral hyperintense hippocampal lesions were detected.
Electroencephalography (EEG) assessment	Normal record, age 25 years. Posterior l0-l2 sec alpha rhythm. Good blocking response to eye opening and reactivation of alpha rhythm with eye closure.
Staging computer tomography (CT) of chest and abdomen	There were no evidence of metastatic lesion
Vaginal ultrasound examination	There were no evidence of metastatic lesion
NMDA-R and voltage gated potassium channel antibodies examination from CSF and serum samples	NMDA-R antibodies were found positive in two samples
Pelvis MRI	A 3.3 cm functional follicle was seen within the left ovary. Adjacent to it, there was a 5 mm high T1 signal intensity, high T2 signal intensity lesion. This demonstrated a signal intensity loss with peripheral enhancement on the T1 fat-saturated sequences with gadolinium, suggestive of a small dermoid cyst. No other ovarian disease was observed. There were no lymph nodes within the pelvis or para-aortic region and no pelvic free fluid.
Histological examination of the teratoma (citology and immunology)	Macroscopy: A previously opened cystic ovary measuring 660×30×20 mm. Sectioning revealed sebaceous type material and fatty tissue along with cystic ovarian tissue. Microscopy: The cyst wall contains various type of tissue including skin, fat, cartilage and sweat glands. Immature elements are not identified. There was no somatic dysplasia or malignancy. Normal ovarian stromal was present at the periphery.

ed generalized tonic-clonic seizure, was treated and cured with diagnosis of vulvovaginal candidiasis in the Outpatient Unit of Department of Obstetrics and Gynaecology in Szeged. The patient lives in Hungary permanently and was visiting London for a 3 week course when she became unwell. In consequence of the neurological symptoms she was admitted to Whipps Cross University Hospital in London, followed by treatment at the Departments of Rheumatology, Neurology and Psychiatry, in Szeged.

PAST MEDICAL HISTORY

The patient had a past medical history of hypothyroidism on treatment with Thyroxine. She was a smoker and drank alcohol occasionally.

MEDICAL EXAMINATIONS

The patient was admitted initially on 18/11/2012 to Whipps Cross University Hospital with a 3 week history of encephalopathy, including confusion, disorientation, behavioural disturbance with agitation and features of paranoia and at least one reported generalised tonic chronic seizure on 19/11/2012. *Neurological examination* at presentation revealed confusion and disorientation. The general medical examination was unremarkable.

DIAGNOSTIC ALGORITHM AND TREATMENT

The lumbar puncture on 18/11/2012 revealed an increased number of white blood cells (49; 100% lymphocytes) in the CSF, a glucose level (3.7 mmol/L and a protein level of (0.18 g/L), with no pathogenic organism. The blood test showed a white cell count of 10.2×10^9 /L and the urea and electrolyte levels, liver function tests and full blood count were otherwise normal, including a C-reactive protein (CRP<0.2 mg/L) (**Table 1**). She was treated empirically with acyclovir to cater for the possibility of atypical viral encephalitis. Phenytoin and lamotrigine were also given to prevent the generalised tonic-clonic seizures.

The brain MRI scan indicated bilateral hyper intense hippocampal lesions (**Table 1**). The radiologist suggested a tentative diagnosis of autoim-

mune encephalitis, probably mediated by NMDA-R antibodies. NMDA-R and voltage gated potassium channel antibodies were measured. Prednisolone (60 mg) was started on 22/11/2012.

The cognitive status of the patient gradually deteriorated further, her level of consciousness fluctuated [Glasgow Coma Scale (GCS): 8 to 14] and she was markedly agitated, requiring risperidone and haloperidol.

She developed *acute kidney injury (*creatinine: 169 µmol/L), which improved in response to adequate intravenous hydration and eventually normalised (creatinine: 74 µmol/L) The lumbal puncture was repeated on 23/11/2012, the CSF was found to be acellular (glucose: 4.1 mmol/L, protein 0.23 g/L) and no organism was detailed. The neurological review raised the possibility of a complex partial status epilepticus, and the dosage of lamotrigine was increased to 50 mg.

The patient was transferred to the Royal London Hospital for further treatment on 29/11/2012. On examination, eyes were open spontaneously, tracking and blinking to menace. Pupils were equal and reactive to the light, corneal and vestibule-ocular reflexes were intact. There was incomprehensible vocalisation. The patient did not follow the simple 1-step commands. Reflexes were symmetrical and plantars were bilaterally flexor. Examinations of the chest and abdomen were unremarkable and the result of electroencephalography (EEG) was normal. Further blood test results demonstrated that the included Thyroid Stimulating Hormone (TSH) was moderately elevated at 5.8 (fT4: 18.7) because of the hypothyroidism. The ammonia (9 mmol/L) and complement levels were in the normal ranges. A normal pattern was seen on serum protein electrophoresis. A 5-day course of intravenous immunoglobulin was administered because of the suspected autoantibody-mediated encephalitis.

Staging computer tomography of the chest and abdomen did not provide any evidence of metastatic lesions **(Table 1)**. NMDA-R antibodies were found positive in several serum and CSF samples and the diagnosis of NMDA-R antibody- mediated autoimmune PLE was confirmed on 29/11/2012. The pelvis MRI on 04/12/2012 suggested *an OT in the left ovary*. The patient underwent left *oophorectomy on* 08/12/2012 *a*nd the left ovary containing a cystic tumour was removed. Histological examinations revealed a mature cystic OT **(Table 1)**. In the meantime, the patient suffered several generalized tonic clonic seizures, and also several episodes of dysautonomia, with cardiovascular lability. Admission to a high dependency unit became necessary. During this time she contracted aspiration pneumonia, which was treated and resolved on treatment. She also manifested the typical orofacial dyskinesia characteristic of this disorder. She completed a 5-day course of plasma exchange. Following removal of the OT and plasma exchange, she displayed a significant clinical improvement. She remained stable from a cardiovascular aspect. She is now seizure-free, her level of consciousness is stable, her cognition is improving and the orofacial dyskinesia has subsided, but she still requires cognitive rehabilitation and neurology follow-up in the Department of Psychiatry. Her corticosteroid treatment gradually has been tapered off as indicated by the immunology follow-up at the Department of Rheumatology, whereas the azathioprine treatment is still continuing in order to prevent a relapse of the neurological symptoms. The azathioprine therapy is planned to last for one year.

Discussion

OTs are among the most common benign ovarian tumours in young women. Both mature and immature OTs have been associated with anti-NMDA-receptor encephalitis. These antibodies of NR1 and NR2 subunits circulate in the serum or CSF where they may bind to the NMDA receptors located in the cell membrane of the neuron. It is speculated that either this ectopic expression of the NR1/NR2 subunits causes a failure of immune tolerance, or a viral like illness causes the abnormal immune response[5–7]. The interaction of the NMDA receptor and antibody is thought to involve antagonistic GABA release, which has been suggested as the reason for many of the symptoms such as the psychotic behaviour, autonomic dysfunction and dystonia/orofacial movements[8]. *Iizuka* et al. concluded that, the clinical features generally follow a progression categorized into four phases[8]. In the prodromal phase (a) numerous cold or viral-like symptoms are observed. The unresponsive phase (b) usually involves a mute, akinetic catatonic-like state. The hyperkinetic phase (c) includes orofacial-limb dyskinesias ranging from jaw movements and lip chewing to athetoid distonic movements and choreiform motion of the arms. The final phase (d) is a gradual improvement over a period of months with full recovery within three or more years[9]. Other common symptoms include loss of the short-term memory, an acute confusional state, psychiatric abnormalities, a hypothalamic and cognitive dysfunction, cerebellar symptoms, brainstem abnormalities etc.[3].

The differential diagnostic examinations include

analysis of anti-NMDA and voltage-gated potassium channel antibodies in the serum and CSF, an EEG assessment, CSF analysis for pleocytosis, elevated protein level and oligoclonal bands, MRI with abnormal signalling in the medial temporal lobe, gynaecological bimanual examination and vaginal ultrasound examination[10]. Among the cases diagnosed by *Dalmau* et al. with anti-NMDA-R mediated encephalitis, 77% gave EEG findings of generalized slowing with non-epileptic discharges, 91% yielded evidence of pleocytosis in the CSF, in 55% the MRI findings were abnormal. Fifty-nine percent had newly discovered OT[4]. Imaging modalities assist in determining the diagnosis prior to potential surgical treatment[5, 11]. The treatment outcomes have tended to vary. In some women, surgical removal of the OT was associated with a more rapid recovery than in those who did not participate in surgical treatment. Surprisingly, a rapid improvement was experienced in both operated and non-operated patients[8]. There are no data specifying as to whether ovarian cystectomy or oophorectomy is preferred. Total removal of the OT is recommended.

Various types of immunotherapy have been used including intravenous immunoglobulin, plasmapheresis and corticosteroids[5, 8, 11]. In patients who have not responded to these treatment options, cyclophosphamide and rituximab have been administered because of their effectiveness in other immune-mediated CNS disorders[4]. The selection of immunosuppressive treatment modalities can depend on the parity and what kinds of drugs are available from primary care.

In our case azathioprine proved to be a good choice in general. The prognosis is favourable with many reports of a clinical improvement occurring after 6-9 months without surgical tumour removal to a significant clinical improvement within days after the procedure[5, 8]. As relapses may occur, especially when an underlying tumour cannot be identified or is not removed, immunosuppressive therapy for at least one year is generally recommended. Our case followed a very similar clinical picture as presented in the current literature. Diagnostic testing included anti-NMDA R antibody testing. The lumbar puncture demonstrated the presence of pleocytosis in the CSF. The EEG findings were in the normal range. MRI imaging revealed bilateral hyperintense hippocampal lesions. A left OT was diagnosed. The patient is now seizure-free and her orofacial dyskinesia has subsided, but steroid treatment and cognitive rehabilitation in the Department of Psychiatry are ongoing. In contrast with the report by *Dabner* et al.[12] the MRI scan did not indicate metastasis or lymphoid infiltrates in our case. It should be emphasized that the most typical presentation at onset is short prodromal symptoms followed by an acute psychotic state and/or repetitive epileptic seizures or status epilepticus in patients without history of drug abuse, psychiatric disease and epilepsy. These symptoms in young females should immediately raise the suspicion of anti-NMDA-R encephalitis.

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