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ANTI-N-METHYL-D-ASPARTATE RECEPTOR ENCEPHALITIS - CHALLENGES IN DIAGNOSIS AND MANAGEMENT (CLINICAL CASE)

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Introduction

Encephalitis represents a severe inflammatory disorder of the brain (1).

Anti-N-methyl-D-aspartate receptor encephalitis (anti-NMDARE) is an autoimmune encephalitis, caused by immunoreactivity against the GluN1 subunit of the NMDAR (2). It was first described as a clinical syndrome of acute onset psychosis followed by progressive, and treatable encephalopathy in 2005 (3), then linked to the NMDAR in 2007 by Dalmau et al.(4), and now represents one of the most common nonviral encephalitis (5, 6), which often remains unrecognized.

Initially it was associated with ovarian teratomas in women, but there are cases without paraneoplastic association (7). It can affect all age groups, with lower prevalence in individuals greater than 50 years old, and it affects females more than males (80% are women) (8, 9). The disease is rare, with an estimated incidence of 1·5 per million population per year (10).

Patients develop a polymorphism of symptoms, which may be variable and make diagnosis difficult. Initially, in 70% of patients, there are an unnoticed prodromal phase, which is similar to a viral flu-like illness (11, 12).

The condition is often recognized in the psychotic phase, with delusions, hallucinations, paranoia and agitation, that can be difficult to differentiate from a primary psychiatric disease (13), or substance-induced psychosis (8). Then the disease progress to a state in which catatonia, impaired attention, dyskinesias (especially orofacial), seizures (11), and autonomic dysfunction(may develop) (8). Self-injuries of the tongue, lips, or teeth are common (14).

Purpose

The assessment of challenges that intervene in the diagnosis and management of anti-N-methyl-D-aspartate receptor encephalitis based on a clinical case presentation and literature review.

Keywords

anti-NMDA-R encephalitis, autoimmune encephalitis, ovarian teratoma

Figure 1. Anti-NMDA-R antibodies result

thank you for your order. Hereby we advise you the following findings:

Analysis	Result	Unit	Ref.Range	GOÄ
1 Serum from 22.05.2019				
NMDAR AAB	↑ 1: 160		1: < 10	

Material and methods

We present a case report of a 27 years old female hospitalized with confusion, after 2 focal epileptic seizures, with impaired awareness and evolution to bilateral tonic-clonic, first life event. She was afebrile, without focal neurologic deficits or meningeal signs. Medical history without neurological, psychiatric pathology or seizures. From medical recordings, 3 days before the admission, the patient was discharged from the gynecology department, where she underwent laparoscopic left ovarian cystectomy.

Laboratory parameters were normal. Brain computerized tomography (CT) was normal. Electroencephalographically identified focal slowing F-T on left at the hyperventilation provocation (Fig.2). Histological - mature ovarian cystic teratoma

During hospitalization she developed psychiatric symptoms with confusion, agitation, self-aggression, auditory hallucinations, orofacial dyskinesias and involuntary movements of the upper extremities were observed. Performed EEG excluded non-convulsive status epilepticus.

Subsequently, as the psychiatric symptoms progressed even to catatonia, she was referred to a psychiatric hospital, preventively collecting serum anti-NMDA-R antibodies (given the constellation of personality changes, psychiatric symptoms, orofacial dyskinesia and seizures.).

Anti-NMDA-R antibodies were detected in serum (Fig. 1), so she was readmitted to our department, reevaluated by EEG, excluded the specific *delta brush pattern* or non-convulsive seizures, performed brain (Fig. 3) and pelvic MRI without abnormalities.

The patient was treated with plasmapheresis (she already had Laparoscopic left cystectomy; pathology confirmed mature cystic teratoma.), with improvement of the psychoneurological condition, then given oral corticosteroids, later tapered, also she received antiepileptic drugs – Valproate, taking in count the possible temporal lobe involvement.

At discharge she presented only cognitive disorders (Raven Standard IQ test = 75) and difficulties in identifying words.

Behaviorally and emotionally stable.

Figure 2. EEG result of our patient - focal slowing F T left

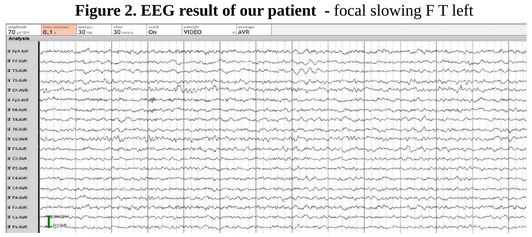

Figure 3. Normal brain MRI scan of our patient

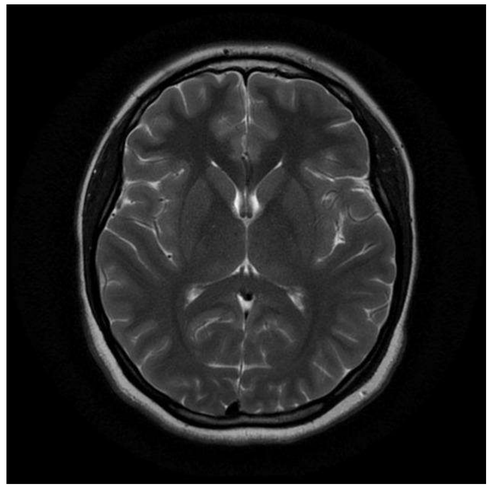

Figure 4. Diagnostic criteria for anti-NMDA receptor encephalitis (1)

Diagnostic criteria for anti-NMDAR Encephalitis

Probable anti-NMDA receptor encephalitis* (three of the following criteria)

- Rapid onset (less than 3 months) of at least four of the major groups of symptoms:
  - Abnormal (psychiatric) behaviour or cognitive dysfunction
  - Speech dysfunction (pressured speech, verbal reduction, mutism)
  - Seizures
  - Movement disorder, dyskinesias, or rigidity/abnormal postures
  - Decreased level of consciousness
  - Autonomic dysfunction or central hypoventilation
- At least one of the following laboratory study results:
  - Abnormal EEG (focal or diffuse slow or disorganised activity, epileptic activity, or extreme delta brush)
  - CSF with pleocytosis or oligoclonal bands
- Reasonable exclusion of other disorders.

!!!Diagnosis can also be made in the presence of three of the above groups of symptoms accompanied by a systemic teratoma.

Definite anti-NMDA receptor encephalitis*

Diagnosis can be made in the presence of one or more of the six major groups of symptoms and IgG anti-GluN1 antibodies,† after reasonable exclusion of other disorders.

*Patients with a history of herpes simplex virus encephalitis in the previous weeks might have relapsing immune-mediated neurological symptoms (post-herpes simplex virus encephalitis).
†Antibody testing should include testing of CSF. If only serum is available, confirmatory tests should be included (eg, live neurons or tissue immunohistochemistry, in addition to cell-based assay).

Results/ Discussions

We determined that this patient had definite anti-NMDAR encephalitis.

Central nervous system tissue in the teratoma might be a trigger of the immune reaction. The majority of teratomas are mature cystic ones. Immature teratomas (constituting 1% of all teratomas) were present in 29% of anti-NMDAR related cases. Bilateral teratomas were present in 14% of cases, comparable to 12% described in general.

Seizures, that are common in anti-NMDARE (57–82%) (2, 5, 15-18), can take place at any time during the disease, but tend to occur earlier in males (19) and can be confused clinically with movement disorders(20). The presence of seizures early in the illness course should raise diagnostic suspicion. Complex and generalized seizures are reported in the majority of cases (2), distinguishing anti-NMDARE from most causes of viral encephalitis and suggesting that seizures are part of the natural history of this syndrome(21). For patients with only one seizure and no temporal lobe involvement, antiepileptic medication may not be strictly needed(22). Prolonged follow-up indicates that, in most patients, the seizures resolve after the encephalitis subsides (9). Valproate, levetiracetam, and carbamazepine can be selected (18).

It is important to note that anti-NMDARE cases may not follow a strict phasic progression and may not include all of the symptomatology mentioned, thereby complicating diagnosis (8).

Diagnostic criteria for probable and definite anti-NMDARE are presented in Figure 4.

Objective assays in anti-NMDARE usually are nonspecific or normal (2).

The only specific diagnostic test of anti-NMDARE is serum and cerebrospinal fluid(CSF) IgG antibodies (23), but serum antibodies assays are not as sensitive as CSF studies (8, 24), with false negative results in up to 14% of cases (24). These results are often delayed.

Brain MRI is abnormal in 30-35% of affected patients, mainly showing increased fluid-attenuated inversion recovery (FLAIR) signal involving the cortical, subcortical, or cerebellar regions (17).

Electroencephalography (EEG), as a corollary objective test (25), is often pathologic in anti-NMDARE, but with nonspecific abnormalities such as diffuse or focal slowing (26). Focal slowing was localized in the fronto-temporal (2, 27), and in the temporal region (28). Normal EEG were described in 7–14% of cases (15, 23), in the early stage of disease or later in the recovery phase (26). EEG may reveal extreme versions of the "*delta brush pattern*" - transient patterns characterized by a slow delta wave at 1-3 Hz (15) with superimposed fast activity (29). The *extreme delta brush* that appears to be unique and specific to anti-NMDARE may suggest a more prolonged illness, but they are not so frequent (15). Also EEG can reveals epileptiform activity (2, 15, 23, 28, 30, 31) and sinusoidal alpha rhythm as an ictal phenomenon (32).

The majority of patients with teratoma improved after tumor resection, also immunotherapy is the treatment of choice and involves trials of corticosteroids, intravenous immunoglobulins, or plasma exchange (8). If patients show minimal improvement, the next line of therapy is immunosuppression, using rituximab or cyclophosphamide, with continued immunosuppression (mycophenolate mofetil or azathioprine) for at least 1 year (33). The recovery could take up to 18 months (17).

Early identification and treatment has been associated with better outcomes (17), less frequently associated hippocampal damage (34), but, however, up to 25% of patients may have severe deficits or die (2).

Conclusions

Anti-NMDAR encephalitis is an increasingly recognized, potentially lethal syndrome of psychiatric and neuromotor dysfunction in patients, often younger in age, who have an underlying tumor.

It is a challenging condition requiring greater emphasis of clinical and paraclinical manifestations, antibodies panel determination, to prevent misdiagnosis and to expect a better outcomes.

The case illustrates the importance of suspecting autoimmune encephalitis, although the results of antibody testing are delayed.

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