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*Published in:*  
 Netherlands Journal of Critical Care

**IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.**

*Document Version*  
 Publisher's PDF, also known as Version of record

*Publication date:*  
 2020

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Ghijsselings, I. E., Hoogland, I. C. M., Brouwer, M. C., van der Voort, P. H. J., & Horn, J. (2020). The broad differential diagnosis of encephalitis: a case report. *Netherlands Journal of Critical Care*, 28(2), 103-106. <https://nvc.nl/node/3277>

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## CASE REPORT

# The broad differential diagnosis of encephalitis: a case report

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**Keywords** - autoimmune encephalitis, anti-N-methyl-D-aspartate receptor encephalitis, differential diagnosis, tuberculous meningitis

## Abstract

A 31-year-old previously healthy woman presented with hallucinations and altered mental status, which was eventually found to be due to anti-N-methyl-D-aspartate receptor encephalitis. In this case report, we discuss the broad differential diagnosis of encephalitis with infectious and autoimmune causes. Furthermore, we consider empirical treatment options in case a definite diagnosis is hard to be made.

## Introduction

When a patient presents to the emergency department with clinical signs of meningoencephalitis, a bacterial or viral cause is often initially suspected. As time to treatment is an important prognostic factor in bacterial meningitis, treatment with amoxicillin and a third-generation cephalosporin plus dexamethasone is initiated immediately.<sup>[1]</sup> Acyclovir is frequently added to treat herpes simplex encephalitis, while awaiting cerebrospinal fluid (CSF) culture and polymerase chain reaction results. However, the differential diagnosis of encephalitis also includes other infectious and autoimmune causes, which may be difficult to diagnose.

We describe a case of a patient presenting with encephalitis, who deteriorated clinically despite antibiotic and antiviral therapy. Intensive care unit (ICU) admission was required because of severely altered mental status, loss of consciousness and autonomic instability. We discuss the broad differential diagnosis and consequences in terms of treatment. The patient's family consented to the publication of this case report.

## Case report

A 31-year-old Caucasian woman without a medical history was brought to the emergency department with headache, dizziness, tinnitus, vomiting and fever for two weeks. The day

of presentation, she developed diplopia, echolalia and auditory hallucinations. Upon physical examination she was obese (body mass index of 38.6 kg/m<sup>2</sup>) and had a right-sided abducens nerve palsy. Cranial CT showed no abnormalities after which a lumbar puncture was performed. The CSF showed an elevated leucocyte count (98% mononuclear cells), slightly elevated protein and slightly decreased CSF/blood glucose ratio (*table 1*). The patient was admitted and treated for meningoencephalitis with amoxicillin, ceftriaxone, dexamethasone and acyclovir (*figure 1*). Additional hetero-anamnesis revealed no allergies, no alcohol or drug abuse and no recent foreign travel. She had a dog, but no other contact with animals. She smoked five to ten cigarettes a day. She was a social worker and had close contact with homeless people including a recent relationship with a homeless person.

In the following two days she developed anxiety, agitation and involuntary urinary loss. The level of consciousness fluctuated, and she developed orofacial dyskinesias and rhythmic contractions of her right hand, for which midazolam was given with good effect. The electroencephalogram (EEG) showed no epileptic activity. Repeated lumbar punctures revealed a high opening pressure, an increase in leucocyte count and a normal protein (*table 1*). On day 3 after admission her consciousness deteriorated (Glasgow Coma Scale (GCS) E1M4V1) after which she was transferred to the ICU and intubated.

At the ICU, the patient had a GCS of three, had opisthotonic posturing, intact brainstem reflexes, adduction position of her right eye, regular non-rhythmic vertical movements of the eyes with a rotatory component and regular, simultaneous, supinating movements of both arms with extension of the fingers. MRI of the brain showed enhancement of the leptomeninges, both supratentorially and infratentorially. EEG was repeated three times during admission showing a slow background pattern but

**Table 1.** Cerebrospinal fluid (CSF) characteristics

CSF	Day 0	Day 3	Day 5	Day 8
Opening pressure (cmH <sub>2</sub> O)	x	48	37	29
Leukocytes (x10 <sup>6</sup> cells/l)	238	417	251	179
Total protein (g/l)	0.6	0.3	0.5	0.2

no epilepsy. CT scan of the thorax and abdomen showed no abnormalities, HIV test was negative.

Autoimmune encephalitis (e.g. anti-NMDA, anti-AMPA, leucine-rich glioma-inactivated protein, Hashimoto) was deemed to be likely at that moment. However, given her social contacts, bacterial meningitis due to uncommon pathogens such as *M. tuberculosis* or *L. monocytogenes*, cryptococcal meningitis and

herpes encephalitis was still a possibility. Awaiting results the patient was given methylprednisolone for three days to treat autoimmune encephalitis; amphotericin B and flucytosine to treat cryptococcal meningitis; ethambutol, isoniazid, pyrazinamide and rifampicin to treat tuberculous meningitis (TBM) (figure 1).

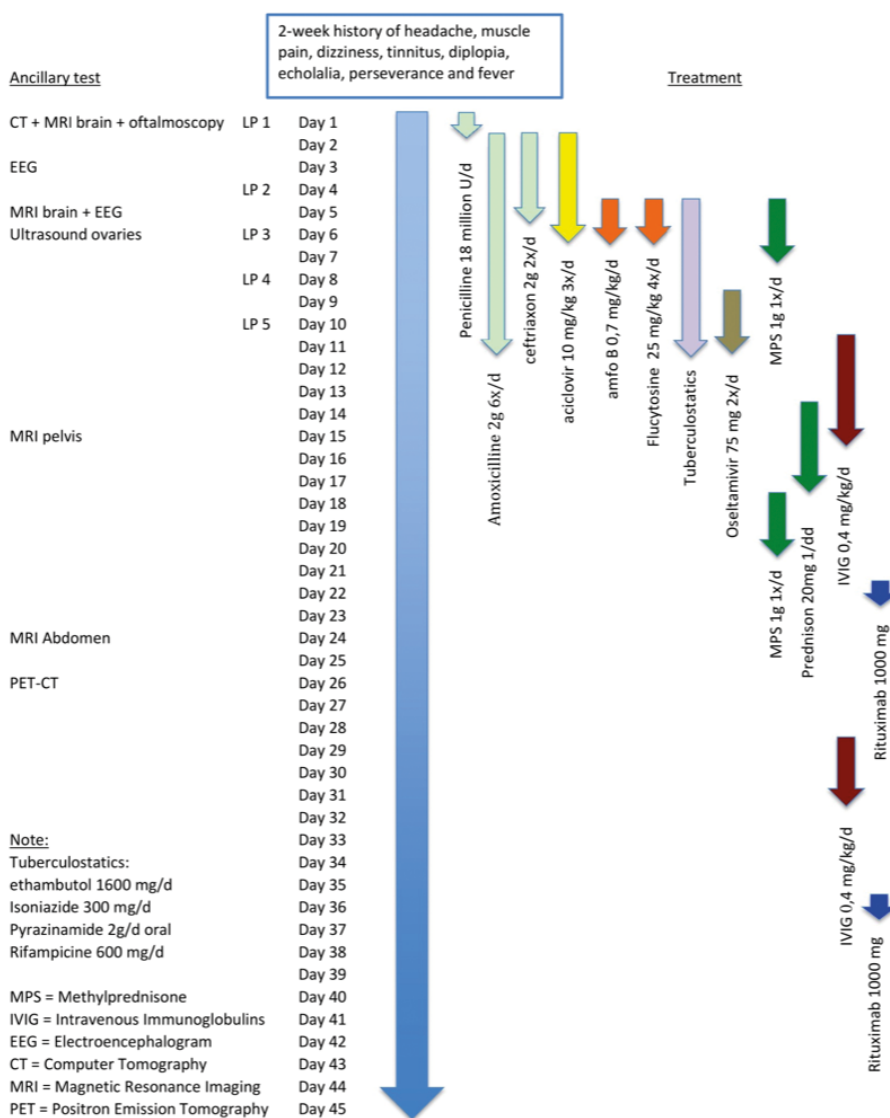
On day 10 after admission, CSF and serum tests came back positive for NMDA antibodies, leading to a diagnosis of anti-NMDA receptor encephalitis. A course of intravenous immunoglobulin was started and antimicrobial treatment was stopped (figure 1). As the patient did not recover, a high-dosed methylprednisolone pulse treatment was repeated and rituximab was started. Further tumour screening was performed including MRI of the ovaries, whole body 18-Fluorodeoxyglucose PET-CT scan and biopsy of

a mass in the breast. No malignancies were found.

During admission to the ICU, the patient developed severe autonomic dysfunction including hypersalivation, bradycardia and tachycardia, hypotension and hypertension and hyperthermia.

The hyperthermia posed a clinical challenge because of the differential diagnosis of infections in a now immunocompromised patient. Cultures of blood, urine and sputum were done every three days and were all negative. Hyperthermia above 41°C was treated with extracorporeal cooling. The hypersalivation was treated with botulinum toxin injections in the parotid glands. The bradycardias and tachycardias spontaneously normalised, frequently within 30 minutes. The orofacial dyskinesias and the dyskinesias of her arms were severe and responded well to propofol and midazolam treatment.

The patient slowly improved and on day 21 all sedative medication could be discontinued after which she was successfully weaned from mechanical ventilation. The dyskinesias diminished after which midazolam boluses could be tapered. On day 35 she opened her eyes when spoken to and she intermittently performed tasks at request.



**Figure 1.** Timeline of ancillary tests and treatment

(MPS = methylprednisone; IVIG = intravenous immunoglobulins; EEG = electroencephalogram; CT = computed tomography; MRI = magnetic resonance imaging; PET = positron emission tomography)

On day 43 she could be discharged from the ICU to the neurology department. There she improved further. She made eye contact, showed emotion and tried to speak. Because of the severity of the disease and the very slow improvement, she was treated with intravenous cyclophosphamide on day 54 after admission (figure 1).

On day 60 after admission the patient was readmitted to the ICU because of hyperthermia and respiratory distress. Shortly after arrival to the ICU she collapsed and cardiopulmonary resuscitation was started due to cardiac arrest with pulseless electric activity. Thrombolysis was given for a tentative diagnosis of pulmonary embolism, but the patient ultimately died.

## Discussion

A young patient with a highly likely autoimmune receptor encephalitis but also a possible infectious meningoencephalitis leads to a complex situation. Ideally, immune suppressive treatment is started as soon as possible to prevent further neurological deterioration. But high-dosed methylprednisolone or other immune suppressive therapies will likely lead to an acute aggravation of the infectious disease. It often takes several days for the results of the diagnostic tests to become available, so a strategy has to be developed while awaiting the results.

At presentation to the emergency department our patient had a two-week history of flu-like symptoms, had been in contact with several homeless people, had unprotected sexual contact and had cranial nerve palsy. Her CSF characteristics were more typical for TBM than for autoimmune encephalitis. An increased intracranial pressure, a high leucocytosis and a low CSF/blood glucose ratio are uncommon in autoimmune encephalitis. Furthermore, the MRI of the brain showed pachymeningitis. Because the definite diagnosis remained uncertain, lumbar puncture was repeated several times and empirical treatment was started as soon as possible.<sup>[2]</sup> Treatment with corticosteroids reduces the mortality and morbidity of HIV-negative patients with TBM.<sup>[3]</sup> The advised dosage to start with is prednisone 60 mg/day. We decided to change this to methylprednisolone 1g/day to simultaneously treat the suspected autoimmune encephalitis. For suspected bacterial meningitis, a third-generation cephalosporin combined with amoxicillin is the standard therapy.<sup>[4]</sup> When cultures are negative after 48 hours, the cephalosporin can be stopped. As *Listeria monocytogenes* is notoriously difficult to culture, the amoxicillin should be continued for 14 days. Other infectious causes for meningoencephalitis are rare but should be kept in mind. Due to the complex social situation of this patient, TBM was one of the possibilities.

TBM typically presents as subacute meningitis where symptoms often precede for seven days or longer.<sup>[5]</sup> Non-specific symptoms such as fever, headache, nausea and vomiting are common. Also epileptic seizures and cranial nerve palsy are relatively common. Risk factors for TBM are contact with patients with

open tuberculosis, tuberculosis in the past medical history, HIV infection, drug addiction and being homeless. CSF characteristics of TBM are a lymphocytic leucocytosis (usually 100-2000 x 10<sup>6</sup> cells/l), an increased protein and a low CSF/blood ratio. We repeated the CSF testing to increase the sensitivity.

In our patient we combined a treatment with immune suppression with antibiotic therapy for tuberculosis. This led to a combination of an impressive number of drugs. When the results were positive for anti-NMDA antibodies and enough certainty was obtained to rule out TBM, all antibiotics except amoxicillin were stopped.

Anti-NMDA receptor encephalitis is an autoimmune receptor encephalitis that is more frequent in young women and is associated with ovarian teratomas or other tumours, and viral infections.<sup>[6,7]</sup> Specific IgG antibodies are formed as a paraneoplastic phenomenon against neurological tissue in teratomas and target the NMDA receptor in the brain. This results in internalisation of the receptor and reduced NMDA effect. Low activity of NMDA receptors has been associated with psychiatric symptoms such as schizophrenia.<sup>[8]</sup>

The clinical course of anti-NMDA encephalitis typically consists of different phases.<sup>[9]</sup> About 70% of patients have a nonspecific flu-like prodrome, with symptoms as fever, headache and fatigue. Within a few days, this is followed by psychiatric and behavioural symptoms (psychotic phase) such as confusion, anxiety, fear, insomnia, paranoid thoughts, disorientation, visual and auditory hallucinations, stereotypical behaviour and short time memory loss. A rapid disintegration of language, varying from reduction of verbal output and echolalia to mutism, is frequent in this phase. The next phase consists of decreases of consciousness, epileptic seizures, hypoventilation, autonomic instability and dyskinesia.

Multiple ancillary investigations may provide valuable information for diagnosing anti-NMDA receptor encephalitis. CSF tests can show a mild-to-moderate lymphocytic leucocytosis, a mild increase of protein concentration and CSF-specific oligoclonal bands. Abnormal MRI findings are present in 30 to 50% of cases and are often mild, transient and nonspecific.<sup>[7,10,11]</sup> Most often, the EEG shows focal or generalised slow activity with or without epileptic discharges. An extreme delta brush is rather rare (30% of cases) but regarded a unique EEG pattern of anti-NMDA receptor encephalitis.<sup>[12]</sup> The definite diagnosis can be made by positive anti-NMDA receptor antibodies in serum or CSF by immunohistochemistry or cell-based assay, but test results may take a couple of days until known.<sup>[9]</sup>

Treatment consists of three modalities: first- and second-line immunotherapy, if applicable tumour resection and treatment of complications such as autonomic instability, epileptic seizures, hypoventilation and dyskinesia.<sup>[13,14]</sup>

This case of encephalitis is characterised by a broad differential diagnosis and a subsequent therapeutic dilemma.

Although the probability of cryptococcal meningitis was low,

we decided to treat awaiting the CSF cryptococcal test result. Furthermore, the immunological status of the patient was not clear since haematological malignancy was still in our differential diagnosis. Similarly, the probability of TBM was low. Nevertheless we decided to treat for several reasons. First, the diagnosis of TBM is often made too late since a previous tuberculous infection is known in only 10% of patients with TBM, and the presentation of TBM is often atypical. Second, the prognosis of untreated TBM is poor: 25-50% of patients die or have severe neurological damage.<sup>[15]</sup>

### Conclusion

We present a case report of a young woman with autoimmune encephalitis. The presenting symptoms were typical, but due to the patient's social history and absence of positive test results other causes had to be taken into account. When the differential diagnosis remains broad, all possible causes of meningoencephalitis should be treated empirically until a definitive diagnosis can be made. Waiting until tests become positive may result in a harmful delay in necessary treatment.

### Disclosures

All authors declare no conflicts of interest. No funding or financial support was received.

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