Headache, Delirium or Encephalitis?

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Case Series – Headache

Headache, Delirium or Encephalitis? A Case of Residual Mutism Secondary to Anti-NMDA Receptor Encephalitis

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Keywords
Anti-N-methyl-D-aspartate receptor encephalitis · Delirium · Headache disorders · Mutism

Abstract
Encephalitis is a heterogeneous syndrome that is diagnosed through clinical assessment and the assistance of laboratory, neuroimaging and electroencephalographic workup. Over the past 10 years, autoimmune encephalitis has been more frequently recognized; however, most reports come from highly specialized hospital settings. Anti-N-methyl-D-aspartate receptor

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(NDMAR) encephalitis has been associated with paraneoplastic encephalitis syndromes and was first recognized in 2005. We present the case of a 34-year-old male patient who debuted clinically with a headache associated with neuropsychiatric symptoms (i.e., visual and auditory hallucinations, anxiety, aggressiveness) and memory deficits, progressing to autonomic dysfunction (i.e., tachycardia and hypertension), seizures, and stupor with catatonic features. Initially, infectious, metabolic, and toxicological etiologies were excluded; followed by the assessment of immunological and paraneoplastic etiologies, yielding positive IgG levels for anti-NMDAR antibodies. The patient was treated successfully with systemic steroid therapy and therapeutic plasmapheresis, while mutism was the only sequela. Although large case series reporting on paraneoplastic and autoimmune anti-NMDAR encephalitis have been reported in the literature in recent years, this case is of particular importance due to the stepwise differential diagnosis and treatment management procedure that was used in a regional but not highly specialized hospital setting.

Background

Encephalitis refers to the inflammatory process of the cerebral parenchyma which can produce neurological deficits [1, 2]. Encephalitis is a heterogeneous syndrome that is diagnosed through clinical assessment and the assistance of laboratory, neuroimaging and electroencephalographic workup [2]. Etiologically, encephalitis can be divided into infectious and noninfectious (e.g., autoimmune, paraneoplastic) origins [2–4]. Over the past 10 years, recognition of autoimmune encephalitis has been more frequent as a cause of noninfectious encephalitis. Autoimmune encephalitis affects more often young adults and children [5]. Autoimmune encephalitis is associated with antibodies against neuronal antigens such as brain surface proteins, ion channels and protein receptors [3, 5–7]. Examples of autoimmune encephalitis were mediated by protein receptor antibodies against N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis, anti-gamma-aminobutyric acid (anti-GABA) receptor encephalitis, and encephalopathy with antibodies against glial fibrillary acidic protein, among many others [3, 5, 6]. Autoimmune encephalitis must fulfill three criteria: (1) subacute onset of clinical signs (i.e., rapid progression in less than 3 months) and symptoms (e.g., memory loss, altered mental state, movement disorders, and neuropsychiatric symptoms); (2) onset of focal neurologic deficits or seizures that are not explained by a previous medical condition; and (3) exhaustive altered state of consciousness diagnosis for other common etiological causes (e.g., infectious, metabolic, paraneoplastic, and toxicological) must be performed [3].

Anti-NDMAR encephalitis has been associated with paraneoplastic encephalitis syndromes, first recognized in a series of case studies in 2005 [8]. In a single-site retrospective study of patients with a previous diagnosis of encephalitis of unknown origin, 7 out of 505 cases fulfilled criteria for suspicion of autoimmune encephalitis: (1) encephalitic signs with psychiatric symptoms such as agitation, paranoid thoughts, irritability, or hallucinations; (2) seizures; (3) cerebrospinal fluid (CSF) inflammation; and (4) exclusion of viral or bacterial infection and 6 of the analyzed CSF samples were positive for anti-NMDAR antibodies [9]. Furthermore, anti-NMDAR encephalitis has previously been reported to be more prevalent than viral encephalitis [10]. Immunoglobulin G (IgG) NMDAR antibodies are highly specific for anti-

NMDAR encephalitis [11]. However, although serum anti-NMDA levels can be detected in patients with NMDAR encephalitis, the sensitivity of NMDAR antibody testing is higher in CSF than in serum, reaching a sensitivity of 100.0% [95% CI, 98.5–100] compared to 85.6% [95% CI, 80.7–89.4] [12]. Clinically, anti-NMDAR encephalitis is associated with fever, headache, and general malaise resembling a virial infection. After this prodromal stage, patients develop psychiatric symptoms [13], as well as focal neurological deficits, memory deficits, and movement disorders [14].

We present the case of a patient with autoimmune encephalitis secondary to anti-NMDAR. The patient debuted clinically with a headache associated with neuropsychiatric symptoms (i.e., visual and auditory hallucinations, anxiety, aggressiveness) and memory deficits, progressing to autonomic dysfunction (i.e., tachycardia and hypertension), seizures, and stupor with catatonic features. Although large case series reporting on paraneoplastic and autoimmune anti-NMDAR encephalitis have been reported in the literature in recent years, this case is of particular importance due to the stepwise differential diagnosis and treatment management procedure that was used in a regional but not highly specialized hospital setting. This diagnostic management procedure involved initially excluding infectious, metabolic, and toxicological etiologies, followed by the assessment of immunological and paraneoplastic etiologies, yielding positive IgG levels for anti-NMDAR antibodies. The patient was treated successfully with systemic steroid therapy and therapeutic plasmapheresis; moreover, mutism was the only sequela.

Clinical Presentation

A 34-year-old male presented to the Emergency Department complaining of a headache characterized by tightness in the frontoparietal regions that had progressively increased in intensity from 4/10 on the visual analog scale for pain to 7/10 at the time of admission. The headache initially remitted with the use of nonsteroidal anti-inflammatory drugs. The patient developed neuropsychiatric symptoms after a week of the headache onset, which included anxiety, aggressiveness, and visual, as well as auditory hallucinations. A couple of days before the patient was admitted to the hospital, he developed anterograde memory deficits. The patient did not report any symptoms related to an acute infectious process (e.g., fever or malaise), nor alterations in his sleep-wake cycle, movement disorder or seizures. The patient's family history only included two brothers with hypertension and no other relevant aspects of family history. The patient denied the use of controlled substances; he further denied allergies, past blood transfusions, traveling to regions with endemic diseases within the last 3 months, tattoos, and body piercings.

Upon initial physical exploration, we found a recumbent patient with freely chosen body position, a Glasgow coma score of 12 (i.e., eye-opening 4, verbal response 2, motor response 6), without focal neurologic deficits, aware of his environment but with mutism, and without making eye contact. The patient's alert status fluctuated during the day between hypoactivity and somnolence, while at night psychomotor agitation predominated. Tests for meningeal irritation were positive. Pupils were isochoric and with a normal corneal reflex. The patient's integumentary system was hydrated and without alterations. Fundus examination revealed no alterations (e.g., papilledema or hypertensive changes of the retina). The musculoskeletal

exploration revealed normal movements, reflexes, and sensitivity in all extremities. The patient had normal plantar and other deep tendon reflexes. Cerebellar function and muscle strength were not evaluated due to the patient's lack of cooperation. Upon inspection, palpation, auscultation, and percussion, the cardio-respiratory system had no abnormal findings. Abdominal examination yielded no alterations. Upon admission, the patient had the following vital signs: blood pressure of 120/60 mm Hg; a heart rate of 85 bpm; a respiratory rate of 17 rpm; a body temperature of 36.5°C; a body weight of 75 kg; the height of 168 cm; and BMI of 26.6.

Clinical Evolution

The patient was initially evaluated by the Psychiatry Department and was diagnosed with delirium due to unknown or unspecified etiological factors (International Statistical Classification of Diseases and Related Health Problems-11, 6D70.3). Management was initiated with olanzapine 20 mg orally (per os, p.o.) every (quaque, q) 24 h. After being evaluated by the Neurology Department, the presumptive diagnosis of unspecified encephalitis (ICD-11, 1D00.Z) was integrated. Laboratory results on admission are presented in Table 1. A computed tomography (CT) of the brain was performed to assess intra-axial lesions (e.g., hemorrhage, ischemia, and tumors) with normal findings. The CSF analysis reported a cloudy aspect with pleocytosis (i.e., 200 cells per mm^3), normal protein (i.e., 30.8 mg/dL) and glucose (i.e., 59 mg/dL) levels (Table 1). Treatment with acyclovir 800 mg intravenous (i.v.) q8h, as well as ceftriaxone 1 g i.v. q12h and vancomycin 1 g i.v. q12h for 10 days was initiated due to the possibility of an infection of the central nervous system. To exclude systemic viral infection or drug use, the following tests were requested: antibodies for hepatitis B virus, hepatitis C virus, and HIV, as well as urinalysis for benzodiazepines, barbiturates, cannabis, cocaine, methamphetamines, and opiates; all results were reported as negative (Table 2, Table 3). Blood, bronchial secretion, and urine cultures were performed; with all cultures reporting negative results. Procalcitonin serum level was 0.4 ng/mL. A meningoencephalitis PCR assay was performed with no reported bacteria, viral, or yeast infection (Table 2, Table 3) and the culture of the CSF was reported negative. After an infectious etiology was excluded, antiviral and antibiotic therapy were suspended. An electroencephalogram (EEG) was also performed yielding no epileptogenic or abnormal activity.

After 5 days of hospitalization, the patient started to develop asterixis and hyperreflexia in the lower extremities, followed by one generalized tonic-clonic seizure with loss of consciousness. A second EEG was performed after the ictal episode without evidence of epileptogenic or abnormal activity. Management with phenytoin 1 g i.v. was given as an initial dose, followed by 200 mg p.o. q8h, as well as magnesium valproate 600 mg p.o. q12h. Alprazolam 15 mg p.o. q12h was administered to control the psychomotor agitation. The patient developed a urinary tract infection (Table 2, Table 3) but no microorganism was isolated from urine culture; thus ceftriaxone 1 g i.v. q12h for 7 days was administered. The patient developed hypertension (i.e., on average 160/100 mm Hg on several occasions) which was treated with metoprolol 100 mg p.o. q12h and amlodipine 5 mg p.o. q12h with adequate control. The patient continued with lower extremity hyperreflexia, asterixis, nuchal rigidity, and aggressiveness. In search of an autoimmune etiology, the following serum tests were requested: cytoplasmic antineutrophil cytoplasmatic antibodies, perinuclear antineutrophil cytoplasmatic antibodies, anti-double-stranded deoxyribonucleic acid, anti-cardiolipin IgG, anti-cardiolipin

IgM antibody and anti-NMDAR IgG antibody; all were reported as negative, except anti-NDMAR IgG (Table 2, Table 3). Following a positive serum anti-NMDAR, these results were corroborated in CSF. Methylprednisolone 1 g i.v. was administered q24h for 5 days, followed by prednisone 70 mg p.o. q24h and azathioprine 100 mg p.o. q24h. Therapeutic plasmapheresis was administered q72h for a total of 5 sessions; showing notable improvement (i.e., no hyperreflexia, asterixis, nuchal rigidity, and aggressiveness; but continued mutism) after the last session.

The following tumor markers were screened, and all were reported negative: α-fetoprotein, human chorionic gonadotropin, CA125, CA153, CA19.9, and carcinoembryonic antigen (Table 2, Table 3). Screening for a neoplastic process in the brain, simple and contrasted MRI (Fig. 1a–c) were performed, while simple and contrasted thoracic, abdominal, and pelvic CTs were also performed (Fig. 1d–f) to noninvasively assess tumor presence or apparent lymphadenopathy; all imaging modalities reporting normal results. To further search for a primary tumor site, a positron emission tomography was scheduled but the patient refused to undergo this procedure due to clinical improvement and invasiveness nature of the procedure. Regarding the association between germ cell tumors and paraneoplastic encephalitis, testicular ultrasonography was performed with no abnormal findings (Fig. 2a, b). The patient was diagnosed as having paraneoplastic or autoimmune encephalitis (ICD-11, 8E4A.0); furthermore, a stepwise diagnostic and treatment management procedure is depicted in Figure 3. After a month of hospitalization, the patient was released due to clinical improvement. Two months after his discharge, the patient was assessed at the outpatient neurology clinic. The patient remained without movement disorders, memory deficits or neuropsychiatric symptoms. Prednisone 50 mg p.o. q24h, azathioprine 50 mg p.o. q12h, and magnesium valproate 500 mg p.o. q12h were established as the maintenance therapy. Since the patient's language dysfunction persisted, he was referred to the Occupational Therapy and Psychiatry Departments to assist his needs.

Discussion

The case presented here is an example of a stepwise diagnostic and therapeutic approach for patients who develop neuropsychiatric symptoms associated with unspecified encephalitis. This case can assist neurologists, psychiatrists, as well as internal medicine and general practitioners to expediently recognize, diagnose and treat autoimmune encephalitis at a primary and secondary level of contact. Adequate and prompt recognition of the symptoms and clinical evolution is necessary for autoimmune encephalitis to improve the patient's prognosis. The clinician must bear in mind that anti-NMDAR encephalitis has been reported to represent approximately 1% of all the intensive care unit admissions of young patients [9]. Furthermore, after infectious diseases and acute disseminated encephalomyelitis, anti-NMDAR encephalitis is the third leading cause of encephalitis [10, 15]. More than 600 cases around the world had been reported since the first cases were identified in 2005 [14]; however, most of these cases are from retrospective case studies. Considering that most of these reports have been reported employing a retrospective analysis of CFS samples, there is a need for prospective studies relating the diagnostic algorithm needed to ensure that the adequate treatment is provided on a timely fashion. This case report attempts to provide a concise diagnostic

approach (Fig. 3) for clinical settings that do not harbor large populations at risk of encephalitis or concentrate many of these cases.

The case presented above begins with a clinical picture resembling a tension headache (i.e., tension of face and neck muscles); however, as the neurological alterations progressed (i.e., visual and auditory hallucinations, anxiety, and aggressiveness), a diagnosis of delirium was integrated. In anti-NMDAR encephalitis headache often develops alongside fever and pleocytosis, but it is rapidly replaced by psychiatric symptoms [16]. While isolated psychiatric episodes are rare and can occur as initial onset or relapse of anti-NMDAR encephalitis [13], the patient's level of consciousness decreased, and memory deficits and language dysfunction ensued; consequently, encephalitis became the suspected diagnosis. Initially, infectious etiologies were screened, and metabolic and toxicological etiologies were explored. CSF analysis is the gold standard for neurologic infection diagnosis. CSF culture, pathogen-specific polymerase chain reaction, antigen, and antibody tests are among the diagnostic tools for neuroinvasive infections [4]. In 2016, leading experts in the field proposed a diagnostic algorithm based on a syndrome-based diagnostic approach. In this approach, the authors provide criteria for the clinical diagnosis of possible autoimmune encephalitis [3]. These criteria include: (1) subacute onset (i.e., less than 3 months) of memory deficits, altered mental status or psychiatric symptoms; (2) associated with new focal central nervous system findings, seizures, CSF pleocytosis or MRI findings suggestive of encephalitis; and (3) reasonable exclusion of alternative causes [3]. The case presented here on admission fulfilled the first two criteria (i.e., psychiatric symptoms and CSF pleocytosis). As infectious, metabolic and toxicological causes of encephalitis were assessed, the patient's clinical picture progressed. No alterations in the patient's neuroimaging and electrophysiological assessment were identified; however, extreme delta brush in EEG has been associated with anti-NMDAR encephalitis [17]. Furthermore, our patient did not display EEG alterations before or after the seizure episode.

While the patient's clinical picture did not improve with antibiotic or antiviral therapy, movement disorders, other psychiatric manifestations, as well as autonomic instability were established in the clinical picture. After infectious, metabolic, and toxicological etiologies were excluded, autoimmune and paraneoplastic causes were explored. Once the autoimmune etiology was identified in serum and corroborated in CSF, the patient was treated with systemic corticosteroid and plasmapheresis therapy with a positive outcome. Therapeutic plasmapheresis is considered a first-line therapy with a strong recommendation based on observational studies or case series (i.e., grade 1C recommendation) [18]. Our patient responded well to the systemic corticoid steroid and plasmapheresis therapy. After 3 months of continuous therapy, mutism was the only focal neurological deficit that persisted in our patient. In a large multicenter observational study involving anti-NMDAR encephalitis, over half (i.e., 53%) of the patients responded favorably within 4 weeks to first-line therapy or tumor removal, while some patients took up to 18 months to recover [19].

Limitations

After anti-NDMAR encephalitis is identified, a neoplastic process must be excluded [3]. Teratomas have been primarily associated with anti-NMDAR encephalitis in 50% of females between 12 and 45 years [20]. Other tumors associated with anti-NMDAR encephalitis are ovarian teratoma [14, 21], Hodgkin lymphoma [22], ovarian cystadenofibroma [23], and testicular germ-cell tumors [24]. One of the main limitations of this case report is that positron

emission tomography imaging to rule out a tumor was not performed; however, simple and contrasted thoraco-abdominopelvic CT, simple and contrasted brain MRI, and testicular ultrasonography were performed in search of tumors. Another limitation of this study is that antibodies in search of other autoimmune etiologies (e.g., the AMPA receptor, the GABA(B) receptor, and the glycine receptor) were not assessed.

Conclusion

When prodromal headache associated with psychiatric symptoms, memory deficits, decreased levels of consciousness, dyskinesia, autonomic instability, and language dysfunction is present on a patient with a subacute onset, autoimmune encephalitis must be suspected. While an infectious, metabolic, toxicological cause must be assessed and excluded through CSF, serum and imaging modalities (e.g., MRI and CT), high suspicion of an autoimmune etiology must be suspected if the clinical picture progresses in spite of adequate antiviral and antibiotic treatment. Furthermore, appropriate first-line treatment with plasmapheresis and corticosteroid therapy must be initiated once infectious, metabolic or toxicological etiologies are excluded. Once the diagnosis of anti-NMDAR encephalitis is established, a clinical protocol in search of a neoplastic process must be initiated.

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Statement of Ethics

Approval from the ethics committee was not required due to the nature of this case report. Abiding by the Declaration of Helsinki, patient anonymity was guaranteed. Upon hospital admission, the patient signed an informed consent permitting the use of her clinical file information for didactic and research purposes.

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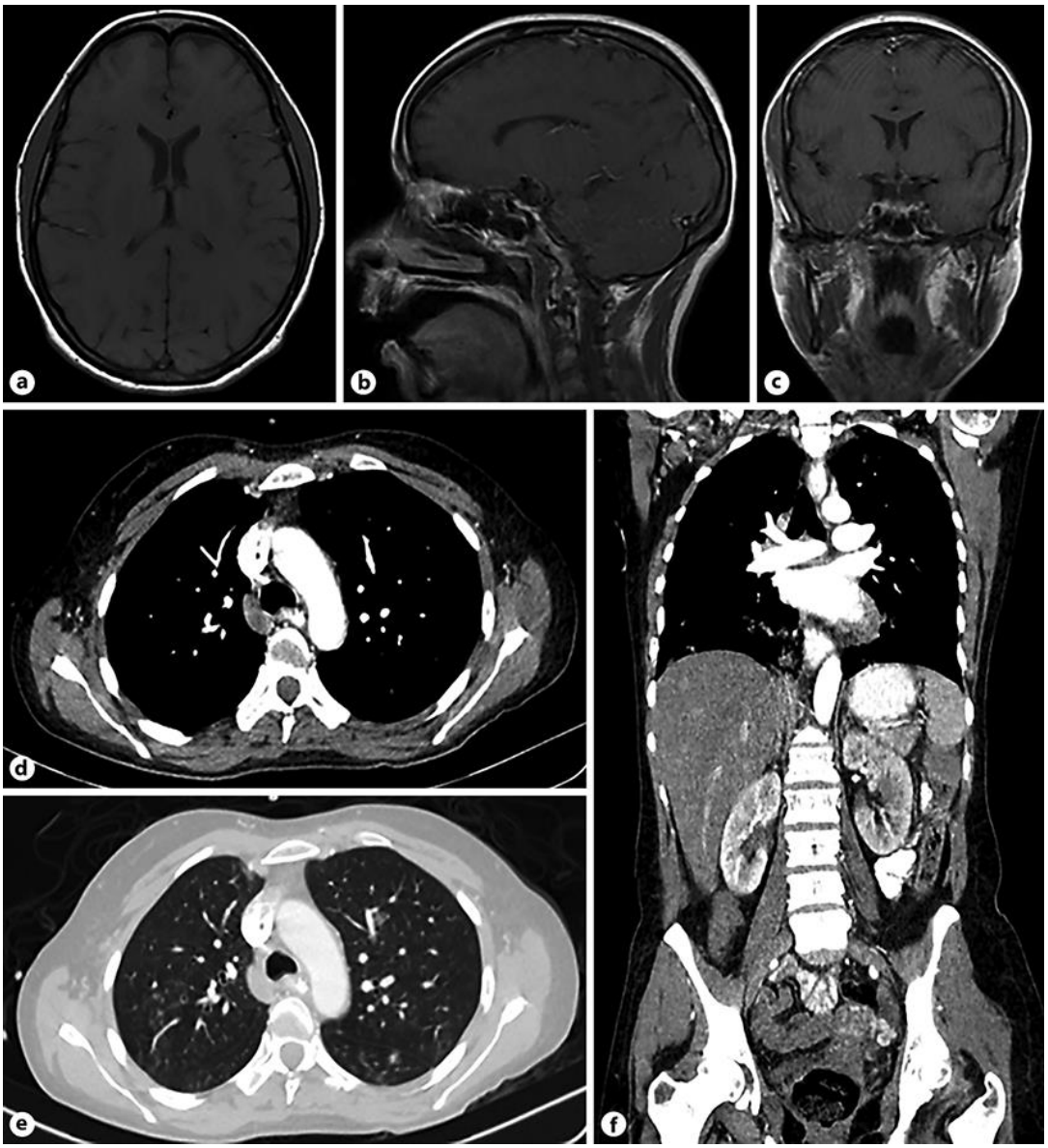

Fig. 1. Brain and thoraco-abdominopelvic imaging. Brain magnetic resonance imaging (MRI) and thoraco-abdominopelvic computed tomography (CT). Normal (**a**) axial, sagittal (**b**), and coronal (**c**) T1-weighted brain MRI scans. **d** Normal CT of the thorax with contrast and mediastinal window. **e** Normal CT of the thorax with contrast and pulmonary window. **f** Normal coronal reconstruction of thoraco-abdominopelvic CT with contrast.

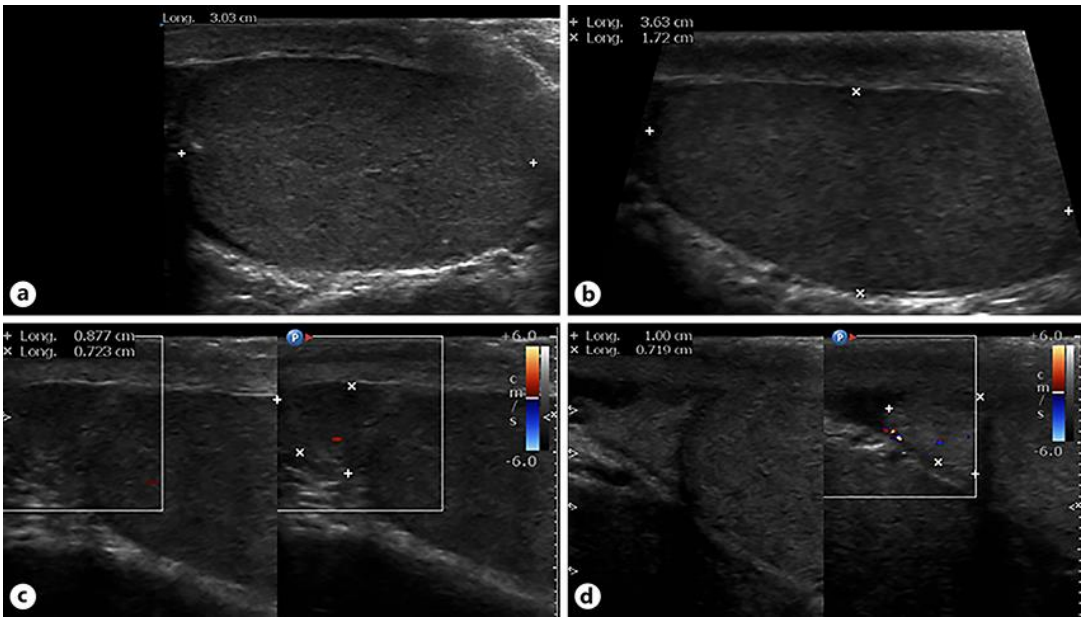

Fig. 2. Testicular ultrasonography. Testicular ultrasonography. **a** Longitudinal view of the right testicle with preserved echogenicity and with no pathological findings. **b** Longitudinal view of the left testicle with preserved echogenicity and with no pathological findings. **c** Longitudinal view of the right epididymis with preserved echogenicity and no pathological findings in gray-scale and Doppler ultrasonography. **d** Longitudinal view of the left epididymis with preserved echogenicity and no pathological findings in gray-scale and Doppler ultrasonography.

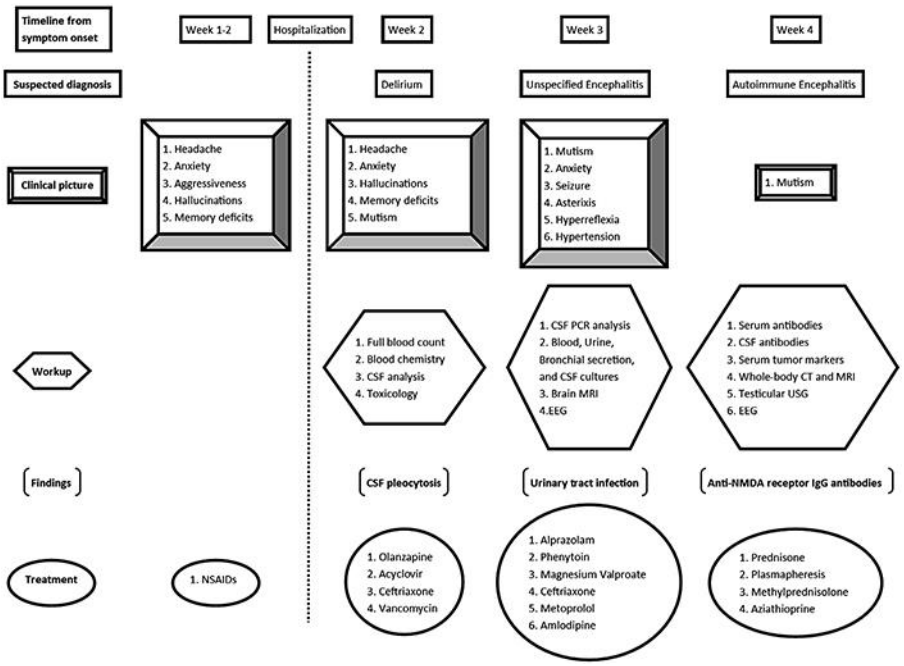

Fig. 3. Multi-step diagnostic and treatment management procedure. NSAIDs, nonsteroidal anti-inflammatory drugs. CSF, Cerebrospinal fluid. PCR, polymerase chain reaction. MRI, magnetic resonance imaging. EEG, electroencephalography. CT, computer tomography. USG, ultrasonography. NDMA, N-methyl-D-aspartate. IgG, Immunoglobulin G.

Table 1. Laboratory test results upon admission

Full blood count		Thyroid function tests	
Hemoglobin	14 g/dL	Serum thyroxine (T4)	8.49 µg/dL
Hematocrit	46%	Free thyroxine (FT4F)	1.08 ng/dL
Erythrocyte count	5,100 µL	Serum triiodothyronine (T3)	88 ng/dL
Platelet count	300,000 µL	T3 resin uptake (T3RU)	2.55 pg/mL
Mean corpuscular volume	90.9 fL	Serum thyrotropin (TSH)	1.23 µU/mL
Mean corpuscular hemoglobin concentration	29.8 g/dL	Blood coagulation	
Leukocyte count	8,500 µL	Prothrombin time	15 s
Lymphocytes	18.1%	Partial thromboplastin time	35 s
Neutrophils	75.5%	International normalized ratio	1.2
Monocytes	5.9 %	Electrolytes	
Eosinophils	0.2%	Sodium	137 mEq/dL
Basophils	0.3%	Potassium	4.1 mE/dL
Blood chemistry		Chlorine	104.1 mEq/dL
Glucose	100 mg/dL	Calcium	9.08 mg/dL
Albumin	3.5 g/dL	Phosphorus	3.5 mg/dL
Urea nitrogen	21.03 mg/dL	Magnesium	2.1 mEq/dL
Blood urea nitrogen	45 mg/dL	Cerebrospinal fluid	
Uric acid	7 mg/dL	Aspect	Cloudy
Cholesterol	130 mg/dL	Leucocytes	200 per mm^3
Triglycerides	110 mg/dL	Erythrocytes	None observed
Liver function enzymes		Protein	30.8 mg/dL
Aspartate transaminase	35 U/L	Glucose	59 mg/dL
Alanine transaminase	30 U/L	Cryptococcal antigen	Negative
Lactate dehydrogenase	240 U/L	Gram staining	No bacteria
Albumin	3.5 mg/dL	Culture	No development
Alkaline phosphatase	60 U/L		
Gamma-glutamyl transpeptidase	30 U/L		

Table 2. Follow-up laboratory test results: cerebrospinal fluid PCR assay

Bacteria	
Escherichia coli K1	Not detected
Haemophilus influenzae	Not detected
Listeria monocytogenes	Not detected
Neisseria meningitides	Not detected
Streptococcus agalactiae	Not detected
Streptococcus pneumoniae	Not detected
Mycobacterium tuberculosis	No detected
Viruses	
Cytomegalovirus	Not detected
Enterovirus	Not detected
Herpes simplex virus 1	Not detected
Herpes simplex virus 2	Not detected
Human herpesvirus 6	Not detected
Human parechovirus	Not detected
Varicella zoster virus	Not detected
Yeast	
Cryptococcus neoformans/gattii	Not detected

Table 3. Follow-up laboratory test results: cerebrospinal fluid PCR assay (continued)

Serum antibodies	
Cytoplasmic antineutrophil cytoplasmatic antibodies (cANCA)	0.1
Perinuclear antineutrophil cytoplasmatic antibodies (pANCA)	0.2
Anti-double-stranded deoxyribonucleic acid	0.6 IU/mL
Anti-cardiolipin IgG antibody	3 IU/mL
Anti-cardiolipin IgM antibody	3.1 IU/mL
Anti-N-methyl-D-aspartate (NMDA) receptor IgG antibody	Positive
Serum viral panel	
Hepatitis B virus	Negative
Hepatitis C virus	Negative
Human immunodeficiency virus	Negative
Serum tumor markers	
Alpha-fetoprotein	4.04 IU/mL
Human chorionic gonadotropin	0.86 mU/mL
CA125	30 IU/mL
CA153	3 IU/mL
CA19.9	7.4 IU/mL
Carcinoembryonic antigen	0.83 ng/mL
Urinalysis	
Appearance	Cloudy
pH	6.0
Specific gravity	1.032
Proteins	30 mg/dL
Ketones, glucose, and nitrite	Negative
Leukocytes	3 per high-power field
Erythrocytes	4 per high-power field
Bacteria	Abundant
Benzodiazepines	Negative
Barbiturates	Negative
Cannabis	Negative
Cocaine	Negative
Methamphetamines	Negative
Opiates	Negative