

# Complex partial status epilepticus revealing anti-NMDA receptor encephalitis

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**ABSTRACT** – Encephalitis with anti-NMDA receptor antibodies is a recently-recognised form of paraneoplastic encephalitis characterized by a prodromal phase of unspecific illness with fever resembling viral disease, followed by memory loss, psychiatric features, seizures, disturbed consciousness, prominent abnormal movements and autonomic imbalance. Association with ovarian teratoma is common. Neurological outcome can be good, especially when surgery is performed at an early stage. Here, we report a case of anti-NMDA receptor encephalitis associated with ovarian teratoma presenting with inaugural complex partial status epilepticus. The nature of abnormal movements at early stages was unclear and abnormal movements were misinterpreted as the recurrence of partial epileptic seizures. Despite its rarity, all clinicians treating epilepsy and movement disorders should be familiar with anti-NMDA receptor encephalitis, that appears to be a very severe but curable disease. *[Published with video sequences]*

**Key words:** complex partial status epilepticus, abnormal movements, encephalitis, NMDA receptor antibodies, ovarian teratoma



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Encephalitis related to ovarian teratoma is a rare form of paraneoplastic encephalitis, first described in 1997 (Nokura *et al.*, 1997; Okamura *et al.*, 1997; Vitaliani *et al.*, 2005). The association with anti-NMDA receptor antibodies was demonstrated only a few years ago (Dalmau *et al.*, 2007) and anti-NMDA receptor encephalitis (ANRE) has since been well characterized in many case reports (Ances *et al.*, 2005; Koide *et al.*, 2007; Sansing *et al.*, 2007; Dalmau *et al.*,

2007; Seki *et al.*, 2008; Novillo-López *et al.*, 2008; Iizuka *et al.*, 2008; Kleinig *et al.*, 2008; Henry *et al.*, 2009). ANRE is often preceded by a prodromal phase of headache, low-grade fever or non-specific viral illness from which patients fully recover. Patients then develop memory loss, psychiatric features like anxiety and hallucinations, disturbed consciousness and seizures. The full-blown clinical picture is characterized by prominent movement disorders

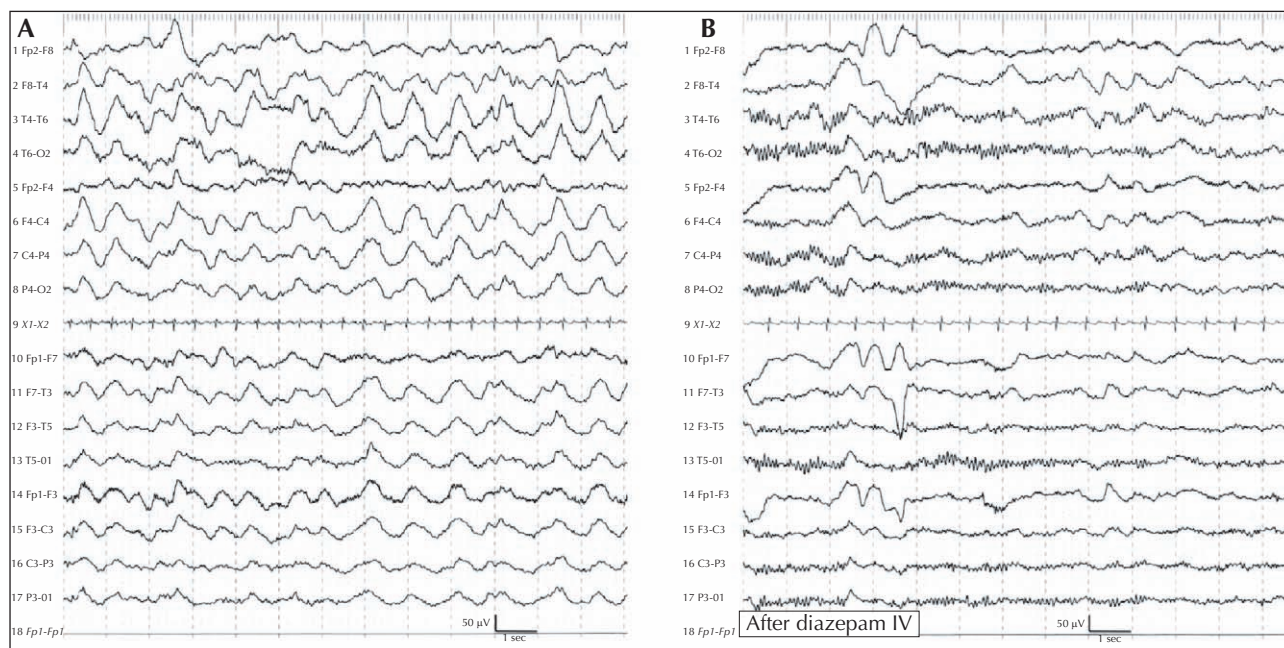
with orofacial and limb dyskinesias accompanied by autonomic imbalance. Association with an ovarian teratoma is common and when the underlying lesion is found and treated early, many patients show full recovery or only mild deficits (Dalmau *et al.*, 2008).

Here, we present a case-report with video sequences of a typical case of ANRE that was characterized by complex partial status epilepticus (CPSE) at onset, followed by abnormal movements that led to diagnostic confusion with seizures.

## Case study

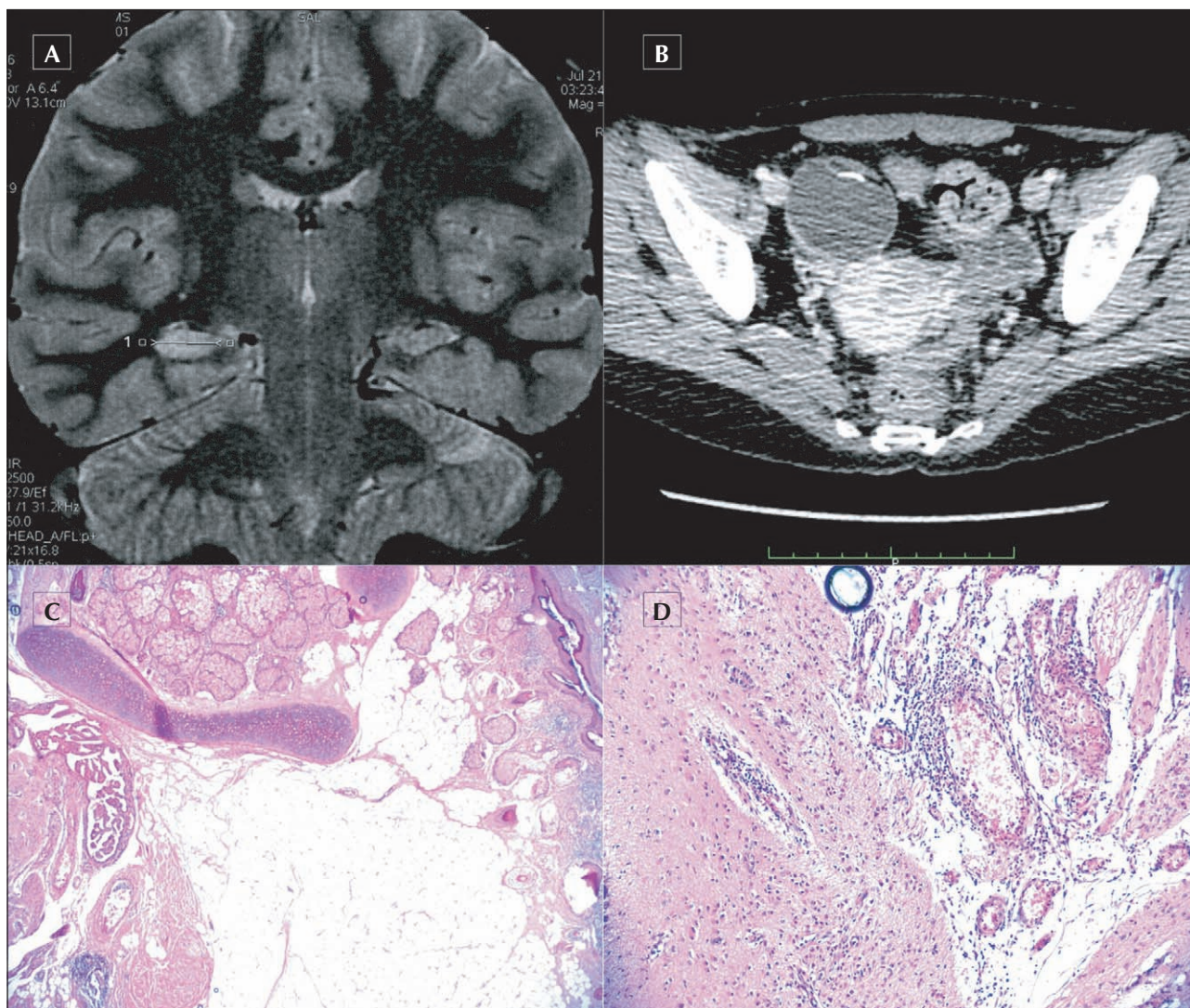
A 25-year-old woman was admitted to a general hospital for unusual headaches. Neurological examination and brain CT scan were normal. Analysis of CSF identified 311 cells, of which 95% were lymphocytes. Following a diagnosis of viral meningitis, the patient clinically improved and was discharged three days later. Two days later she was re-admitted for auditory hallucinations and extreme anxiety, consistent with panic attacks. She was transferred the next day to our neurological department for a state of fluctuating consciousness with temporal and spatial disorientation and recurrent chewing movements (*see video sequence 1A*). EEG confirmed right CPSE, with recurrent seizures characterized by staring, unresponsiveness and oro-alimentary automatisms that co-existed with 1 Hz rhythmic right hemispheric dis-

charges (*figure 1A*). Frank clinical and EEG improvement occurred after intravenous diazepam (10 mg) and fosphenytoin (15 mg/kg) (*see video sequence 1B, figure 1B*). MRI showed a T2-weighted hypersignal of the right hippocampus, extending towards the entorhinal cortex (*figure 2A*). CSF analysis identified four white cells. Treatment with intravenous acyclovir (30 mg/kg/d) was started. The next day, disturbed consciousness and abnormal orofacial movements were considered as a recurrence of CPSE. She was transferred to the intensive care unit (ICU) and treated with intravenous phenobarbital (15 mg/kg). Over a four-week-period she then developed complex abnormal movements, with stereotypic episodes of brief repetitive dystonic posturing of the left hemiface and left upper limb, severe orofacial dyskinesias leading to injury of the lips, bruxism, hypersalivation, oromandibular dystonia with tongue protrusion and episodes of opisthotonus (*video sequence 2*). Several EEG controls showed generalized pseudoperiodic complexes of about 3 Hz. No correlates between EEG activity and the polymorphous dyskinesias were found. She was treated with oral carbamazepine (up to 800 mg/d) and intravenous midazolam (10 mg/h), fentanyl (150 microg/h) and thiopental (2 g/24 h) for four days after orotracheal intubation, followed by tracheotomy three days later. Serological and PCR studies for the following viruses and bacteria were negative: herpes simplex virus I and II, varicella zoster virus, human herpes virus 6, cytomegalovirus, Epstein-Barr virus, HIV, influenza, enterovirus, rotavirus,



**Figure 1.** During the first EEG (A), the patient is confused with oro-alimentary automatisms. EEG shows right hemispheric 1 Hz rhythmic activity. After intravenous diazepam (B), the patient has become responsive and EEG is markedly improved. Note the re-appearance of the alpha rhythm.





**Figure 2.** A) Hypersignal of the right hippocampus on coronal T2-weighted MRI (a control MRI two weeks later showed the disappearance of this lesion). B) Pelvic CT scan reveals a right ovarian mass with cystic and solid components (fat and calcifications), characteristic of teratoma. C, D) Histological findings of the ovarian mass in haematoxylin and eosin staining. At 25 x magnification (C), numerous tissues typical of mature teratoma including adipose, cutaneous, chondral and glial tissue and choroid plexus are identified. At 100 x magnification (D), note the inflammatory reaction around the blood vessels and in the glial tissue.

adenovirus, morbillivirus, rubellavirus, rubulavirus, rabies virus, mycobacteria, *Treponema pallidum*, *Mycoplasma pneumoniae*, *Borrelia burgdorferi*, bartonella, legionella, and *Rickettsia conorii*.

Acyclovir treatment was terminated after six days. Analysis of CSF controls identified 70 and subsequently 170 lymphocytes, and oligoclonal bands were detected. A repeated MRI showed the disappearance of the right temporal hypersignal. High dose intravenous methylprednisolone (1 gm/d for three days) gave no improvement. Polymorphous abnormal movements persisted, and auto-

nomic imbalance with tachycardia, polypnea and blood pressure variations were treated symptomatically. Levetiracetam (up to 1 000 mg/d) treatment was started without immediate benefit. In the following weeks, the patient showed slow spontaneous improvement of the movement disorder and vigilance in the absence of any symptomatic or immunoactive treatments. Seven weeks after onset, she had first visual contact with purposeful movements. Paraneoplastic encephalitis was suspected and high titres of NMDA receptor antibodies in serum and CSF confirmed the diagnosis of ANRE (Prof.

Dalmau, Philadelphia via Prof. Honorat, Lyon). Intravenous immunoglobulin (IVIG) was administered (0.4 gm/kg/d for five days).

Pelvic ultrasound, MRI and CT showed a right ovarian cystic lesion that was surgically removed (*figure 2B*). Histological examination confirmed a mature teratoma with complex architecture containing epidermal, adipose and fibrous tissue with sebaceous and sweat glands, smooth muscle, hair, one bone fragment, cartilage and abundant glial tissue with choroid plexus showing an inflammatory reaction (*figure 2C, D*). The patient continued to improve and showed full recovery after a six-month follow-up period.

## Discussion

This is a report of a characteristic clinical course of ANRE that presented with inaugural CPSE after a non-specific phase of headache associated with lymphocytic pleiocytosis and psychiatric symptoms. Seizures are a common feature of ANRE (Vitaliani *et al.*, 2005; Dalmau *et al.*, 2007; Sansing *et al.*, 2007; Henry *et al.*, 2009), occurring in about two-thirds of patients (76/100) in a recently published large series (Dalmau *et al.*, 2008). Generalized or frontotemporal slow disorganized activity, sometimes with epileptic activity, is usually found on EEGs. Seizures may be part of the initially presenting symptoms (Dalmau *et al.*, 2007). Whereas most patients develop generalized tonico-clonic seizures (46/76), few patients (10/76) show complex partial seizures (Dalmau *et al.*, 2008). Six refractory cases of status epilepticus have been reported, however details were not specified. Thus, inaugural CPSE seems to be an uncommon presentation of ANRE.

For our patient, diagnostic difficulties in the course of the first days following onset were associated with the recrudescence of repetitive dyskinesias of the left hemiface and left hemibody, after treatment of the initial CPSE diagnosis. This led to an increase of intravenous antiepileptic treatments due to a supposed epileptic origin. EEG at this stage showed diffuse pseudoperiodic activity, a non-specific feature found in many types of encephalitis (Brenner and Schaul, 1990), without any correlation with the observed dyskinesias, consistent with a non-epileptic movement disorder. The various types of abnormal movements observed in ANRE, in association with the other clinical features, seem to form a characteristic syndrome that does not conform to existing categories, but is considered by some authors to be a distinctive movement disorder (Kleinig *et al.*, 2008). Semirhythmic repetitive movements of the orofacial region and the limbs are the most prominent symptoms, although abnor-

mal ocular movements, dystonic or choreoathetoid movements of the limbs and abnormal posturing of the trunk can also occur.

Other important clinical clues in our patient were the prodromal presentation of headache, followed by anxiety, auditory hallucinations, disturbed consciousness and the later observed dysautonomia. The association of psychiatric features, together with seizures and abnormal movements, led to the suspected diagnosis of ANRE that was confirmed by successful screening for specific antibodies and identification of ovarian teratoma.

The T2-weighted temporal hypersignal, observed in the first MRI scan, could correspond to the findings described in the case series of Dalmau *et al.* (2008), as MRI showed abnormal findings in the medial temporal lobes and in the cerebral cortex in about half of the patients. Yet, abnormal signal was not present on repeated MRI, acquired after anti-convulsive treatment but before steroids and IVIG, and could thus be a functional consequence of the concomitant CPSE of mesial temporal origin.

CSF analysis in patients with ANRE usually identifies lymphocytic pleiocytosis with frequent oligoclonal banding (Dalmau *et al.*, 2008). For our patient, the white cell count in CSF varied significantly at different times of the disease, including pleiocytosis at the prodromal phase and almost normal results one week later.

Combined tumour resection and immunomodulatory treatment by IVIG led to complete recovery despite the severe course and prolonged stay at the ICU. Favourable outcome has been reported for the majority of patients with successful tumour resection (Dalmau *et al.*, 2008; Iizuka *et al.*, 2008). This is in contrast with other paraneoplastic disorders, such as limbic encephalitis with anti-neuronal antibodies, that usually have poor prognosis (Gultekin *et al.*, 2000).

ANRE is a complex disorder with polymorphous symptoms, including a prodromal phase of unspecific illness, followed by psychiatric symptoms, seizures, decreased consciousness, complex dyskinesias and abnormal movements that do not conform to the categories of known movement disorders associated with autonomic imbalance. Inaugural CPSE is a possible but uncommon presentation. Diagnostic difficulties concern the abnormal movements that can be misinterpreted as ongoing epileptic seizures. Despite its severe spontaneous course, in contrast to other paraneoplastic disorders, ANRE associated with teratoma has a good prognosis when the underlying tumour is removed early. Therefore, all clinicians treating epilepsy and movement disorders should be aware of this well-defined entity. □

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## Disclosures.

None.



## Legends for video sequences

### Video sequence 1

**A)** Patient during initial complex partial status epilepticus showing a state of fluctuating consciousness intermixed with oro-alimentary automatisms.

**B)** Patient is markedly improved and responsive again for two minutes after intravenous diazepam (10 mg).

### Video sequence 2

Sequential videos filmed by the patient's family during a seven week period, illustrating different types of abnormal movements during anti-NMDA receptor encephalitis. First, the patient shows stereotypic repetitive dystonic movements of the left hemiface and the left upper limb. Then several episodes of orofacial dyskinesias can be observed, sometimes accompanied by hypersalivation or by tongue protrusion. Subsequently an episode of opisthotonus is shown, followed by further episodes of polymorphous oromandibular dyskinesias, including bruxism, sustained dystonic mouth-opening movements and repetitive small-amplitude jerks.

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