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Short communication

Anti-NMDA receptor encephalitis presenting with total insomnia — A case report

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ABSTRACT

Fatal insomnia (FI) is the first diagnosis to be considered by most neurologists when approaching a patient presenting with total insomnia followed by personality and cognitive changes, disturbance of alertness, autonomic hyperactivation and movement abnormalities.

We report the case of a 30 year-old male patient who presented with total insomnia followed by episodes of psychomotor restlessness resembling anxiety attacks. Twenty days later, he developed refractory convulsive status epilepticus with admission to Intensive Care Unit. He progressed to a state of reduced alertness and responsiveness, presenting periods of agitation with abnormal dyskinetic movements, periods of autonomic instability and central hypoventilation. Workup revealed antibodies against N-methyl-D-aspartate receptor (NMDAR). Immunotherapy treatment led to a very significant improvement with the patient presenting only slight frontal lobe dysfunction after one year of recovery.

To the best of our knowledge this is the first report of a patient with anti-NMDAR encephalitis first presenting with total insomnia. Our aim is to alert that anti-NMDAR encephalitis must be considered in the differential diagnosis of FI, especially in sporadic cases. Distinguishing the two conditions is very important as, contrarily to the fatal disclosure of FI, anti-NMDAR encephalitis is potentially reversible with adequate treatment even after severe and prolonged disease.

1. Introduction

When approaching a patient presenting with total insomnia followed by personality and cognitive changes, disturbance of alertness, autonomic hyperactivation and motor abnormalities, fatal insomnia (FI) is the first diagnosis to be considered. Although FI is more commonly a hereditary disease, this diagnosis may also be considered in patients without family history as sporadic cases have also been described [1].

In the present article we report the case of a young male patient who presented with total insomnia followed by behavioral changes, seizures and alertness decrease associated with abnormal movements, autonomic hyperactivation and central hypoventilation, which diagnostic workup revealed anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis. A significant clinical improvement occurred after immunotherapy.

1.1. Case report

A 30 year-old male patient with unremarkable personal and familial past medical history presented with total insomnia of sudden onset. Four days later, he developed recurrent episodes of psychomotor restlessness, tachycardia, generalized tremors, diaphoreses and dyspnea with approximately 20 minute duration and was taken to the Emergency Room. Alprazolam was prescribed for anxiety disorder, however total insomnia persisted, the episodes of restlessness increased in frequency, occurring 8 to 10 times per day, and the patient became irritable and aggressive. He was admitted to a Psychiatric Department two days later and medicated with olanzapine, diazepam, haloperidol and valproic acid with no clinical improvement. Twenty days later, he developed hyperthermia (39.7 °C) and refractory generalized tonic–clonic seizures requiring anesthesia with propofol and midazolam. He was transferred to an Intensive Care Unit and empirical treatment with acyclovir, ceftriaxone, dantrolene and bromocriptine was started, considering the hypothesis of central nervous system infection or neuroleptic malignant syndrome. Blood workup including complete blood count, coagulation study, biochemistry and serological testing (Herpes simplex virus type 1 and type 2, Cytomegalovirus, Enterovirus, Echovirus, Adenovirus, Coxsackie virus, *Coxiella burnetii*, *Toxoplasma gondii*, Measles, Mumps, *Treponema pallidum*, *Borrelia burgdorferi* and *Brucella*) was unremarkable, as well as cerebrospinal fluid (CSF) cytochemical analysis, serological testing (Herpes simplex virus type 1 and type 2, Cytomegalovirus, Measles, Adenovirus, Coxsackie virus and Echovirus) and cultures. Brain computed tomography (CT) scan and magnetic resonance imaging (MRI) did not reveal any abnormal findings. Electroencephalogram (EEG) showed slow activity and sparse epileptic activity in the right frontal region. Several attempts to withdraw anesthetic treatment were performed during the following four weeks, but refractory convulsive status epilepticus always recurred.

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One month after status epilepticus onset, the patient was transferred to our hospital in order to perform continuous video-EEG monitoring. At admittance, EEG revealed diffuse slow activity and non-continuous focal seizures, so anesthetic discontinuation was tried once more. Fluctuation of alertness and diminished responsiveness were observed, with periods of total unresponsiveness alternating with periods of dissociative responses to stimuli, characterized by absent response to painful or visual stimuli but resistance to attempts of eyelid opening. Periods of total immobility and generalized hypertonia (Video 1) alternated with periods of agitation with abnormal movements, mainly involving the left upper limb and oromandibular muscles, with variable dyskinetic movements including tremor, choreoathetosis, dystonia and abnormal postures (Videos 2–4). Dyskinetic movements involving the trunk and the remaining limbs were also noticed although less frequently (Video 5). Periods of autonomic instability were identified consisting of tachycardia, arterial hypertension, diaphoresis and hyperthermia. Central hypoventilation was also present, with inability to suspend invasive ventilation after anesthetic withdrawal.

Video-EEG monitoring revealed diffuse asymmetric slowing with right preponderance and frequent rhythmic delta activity in the anterior regions of the right hemisphere (Fig. 1). Sleep patterns were absent. No correlation could be found between abnormal movements and EEG tracing, with most abnormal movements occurring without evidence of ictal patterns (Fig. 2, Video 4). Unequivocal ictal activity was infrequent and was either clinically silent or associated with movements similar to the movements observed in the absence of ictal patterns.

Diagnostic work-up was complemented with systemic autoimmune study (ANAs, anti-dsDNA, anti-SSA, anti-SSB, anti-Sm, anti-RNP, anti-Scl70, anti-Jo-1, p-ANCA, c-ANCA, anti-TPO and anti-tiroglobulin) and search for occult malignancy (tumor markers: CEA, CA19-9, CYFRA 21.1, NSE, β-HCG, PSA, alpha-fetoprotein; anti-neuronal antibodies: anti-Hu, Ri, Yo, amphiphysin, MA2, CV2; thorax X-ray; abdominal and testicular ultrasound), without relevant findings. CSF analysis was repeated revealing normal cytochemistry, negative 14.3.3 protein and positive oligoclonal bands unmatched in serum. Autoimmune encephalitis antibody screening was requested, including antibodies against NMDAR, voltage-gated potassium channel (VGKC) complexes, gamma-aminobutyric acid type B ($GABA_B$) receptor and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor. Considering the clinical suspicion of autoimmune encephalitis, high-dose intravenous (IV) methylprednisolone (MP) was administered for 5 days, followed by MP 1 mg/kg/day. No improvement occurred after 5 days of MP, so IV immunoglobulin (IVIG) was started (25 g/day, for 5 days). As the patient's clinical status continued progressively worsening after IVIG, plasma exchange (PE) on alternate days was tried. An improvement in alertness with short periods of interaction with the environment and brief periods of posterior rhythmic activity in EEG was observed after the third PE session. However, PE had to be discontinued after the fourth session due to hemoptysis secondary to hypofibrinogenemia, associated with severe anemia and hypotension. Nevertheless, 7 days later, after resolution of these medical complications, gradual improvement started with recovery of spontaneous ventilation and progressively longer periods of interaction with the environment.

Brain MRI was repeated and whole body positron emission tomography (PET) scan was performed, without significant findings. Brain ^{18}F-FDG-PET scan revealed hypometabolism in the left hemisphere and relative hypermetabolism in the frontal and temporal regions of the right hemisphere (Fig. 3). Auto-antibody analysis identified anti-NMDAR antibodies in serum and CSF.

Significant progressive clinical improvement occurred in the following months, with stabilization of the autonomic functions and normalization of the sleep–alertness cycle, including the presence of sleep patterns in the EEG, and subsequent recovery of motor skills and language. Behavioral changes, namely psychomotor restlessness and aggressiveness, were initially reported, but gradually resolved during the first four months of convalescence. Immunosuppressive therapy with azathioprine (50 mg/day) was started after immunotherapy withdrawal.

After one year, neuropsychological assessment reveals moderate frontal lobe dysfunction characterized by apathy, impulsivity and dysexecutive syndrome, and EEG shows persistence of slow activity in

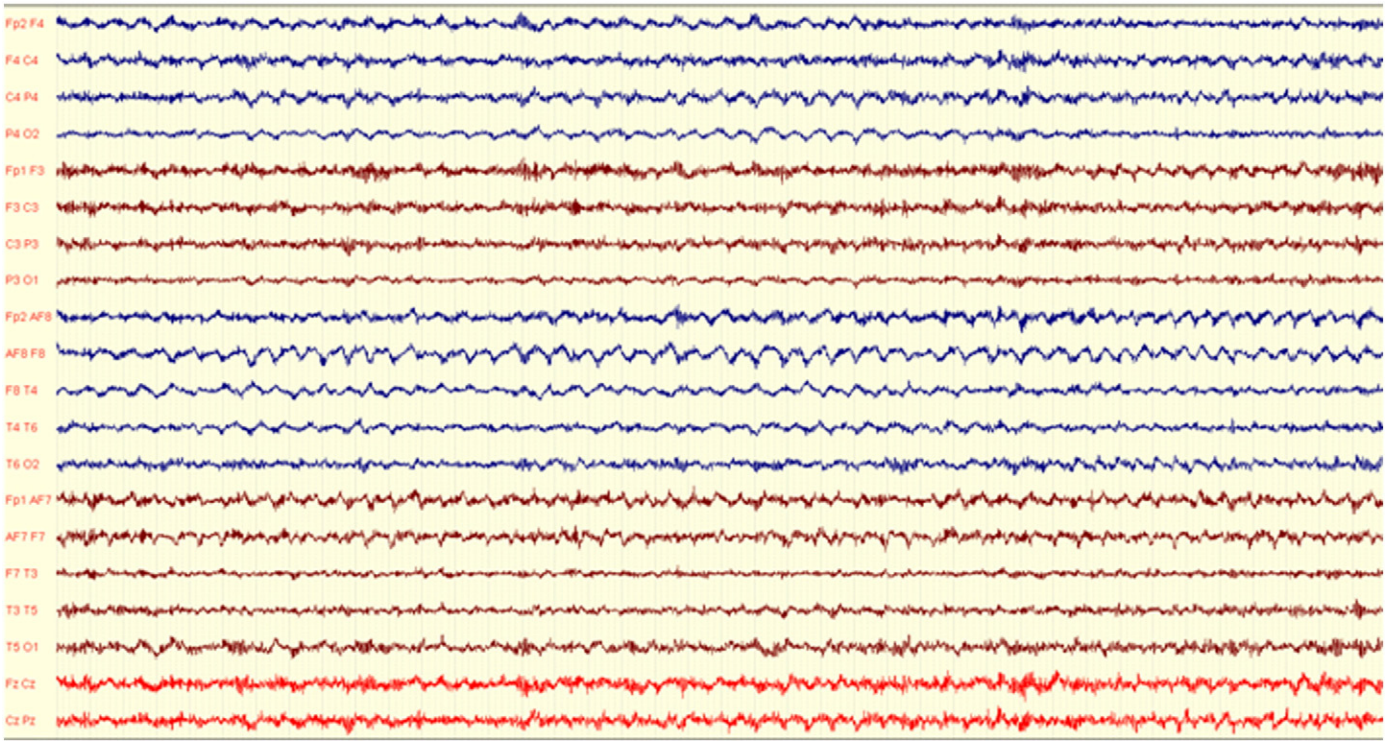

Fig. 1. Electroencephalogram (bipolar montage) showing asymmetric diffuse slow activity with preponderance to the anterior regions of the right hemisphere. Rhythmic delta activity (1.5 Hz) is observed in the right frontal and temporal regions.