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Autonomic instability and asystole: Broadening the differential diagnosis of cardiac arrhythmias

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Anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis is a rare autoimmune disorder associated with ovarian or testicular tumor onconeural antibodies binding to native NMDA receptors (NMDA-R) [1–3]. This results in stereotypic symptoms of a prodromal flu-like symptoms, followed by psychosis, alteration in consciousness and life-threatening autonomic dysfunction. We present a case of recurrent non-ictal asystole in a woman with NMDA-R encephalitis. The potential urgent need for an external temporary pacemaker for asystole underscores the importance of prompt recognition of this potentially reversible disorder.

A 29 year-old-female with a history of a right oophorectomy four years prior presented with 2 days of altered mental status progressing to a florid delusional psychosis. Prior to the onset of these symptoms, the patient had been complaining of nausea, headaches and malaise for 10 days. Two days prior, patient was noted to have labile mood, including yelling, crying, laughing inappropriately, and making unusual religious remarks. This progressed to auditory and visual hallucinations, and the patient was taken to the hospital.

Laboratory tests, including complete blood cell count and chemistry, were all within normal limits. Urine drug screen was positive for cannabinoids. Head computed tomography was negative for any acute changes. She was admitted to an inpatient psychiatry unit and treated with valproate, chlorpromazine, ziprasidone, and large doses of haloperidol. On day 2, the patient developed a malignant catatonia and demonstrated sinus tachycardia up to 150/min; she was subsequently transferred to a telemetry unit. Once on continuous cardiac monitoring, the patient was found to have numerous episodes of sinus arrest and asystole, reported to be as long as 20 s and associated with loss of consciousness. She was thus transferred to a Coronary Intensive Care Unit for further care.

At this point the patient's mental status was quite altered (Glasgow Coma Scale score of 9), with hypersalivation, hypertonia, trismus, and an elevated creatine kinase to 1014 U/L. She was intubated for airway protection. Review of the telemetry strips available showed a sinus arrest with a pause of 12.8 s (Fig. 1). A temporary transvenous pacemaker was placed. Midazolam, diazepam and bromocriptine were started for possible neuroleptic malignant syndrome secondary to use of antipsychotic medications. A lumbar puncture revealed a lymphocytic pleocytosis (WBC 61 cells/mm^3, 97% lymphocytes), with a high opening pressure of 34 cmH_20, and oligoclonal bands at electrophoresis. The electroencephalogram was non-specific and demonstrated no epileptic activity, and a brain magnetic resonance imaging revealed no significant abnormalities. The patient was empirically treated for meningoencephalitis with broad-spectrum antimicrobials.

Considering the acute psychosis in the setting of prior ovarian mass, anti-NMDA-R encephalitis emerged in the differential diagnosis. On day 5, a computed tomography of the pelvis showed complex cystic left adnexal mass. On day 6, the patient underwent left ovarian cystectomy, with pathology revealing a mature cystic teratoma consisting of all three germ layers including neural matter. The NMDA-R antibody in the cerebrospinal fluid and serum returned positive at 1:160 (reference range < 1:1) and 1:640 (reference range < 1:10), respectively. The patient was treated with intravenous immunoglobulin and methylprednisolone. Bradyarrhythmias gradually resolved, and on day 11 the pacemaker was removed. The patient continued to have episodes of tachycardia and hypertension, for which she was started on propranolol and clonidine; these were eventually weaned off before discharge. She underwent an additional four courses of plasmapheresis and four doses of rituximab, ultimately making a full recovery over the course of six months with no new cardiac events.

Anti-NMDA-R encephalitis, first described in 2007 [1], is a rare autoimmune condition associated with an ovarian or testicular teratoma. The immune response against the neural antigen in the teratoma cross-reacts with native NMDA-R. Patients typically present with flu-like symptoms which progress to cognitive and behavioral disturbances, dyskinesias, seizures, loss of consciousness, central hypoventilation and dysautonomia [2,3]. The advanced stage of the anti-NMDA-R syndrome is typically hallmarked by extreme autonomic instability with

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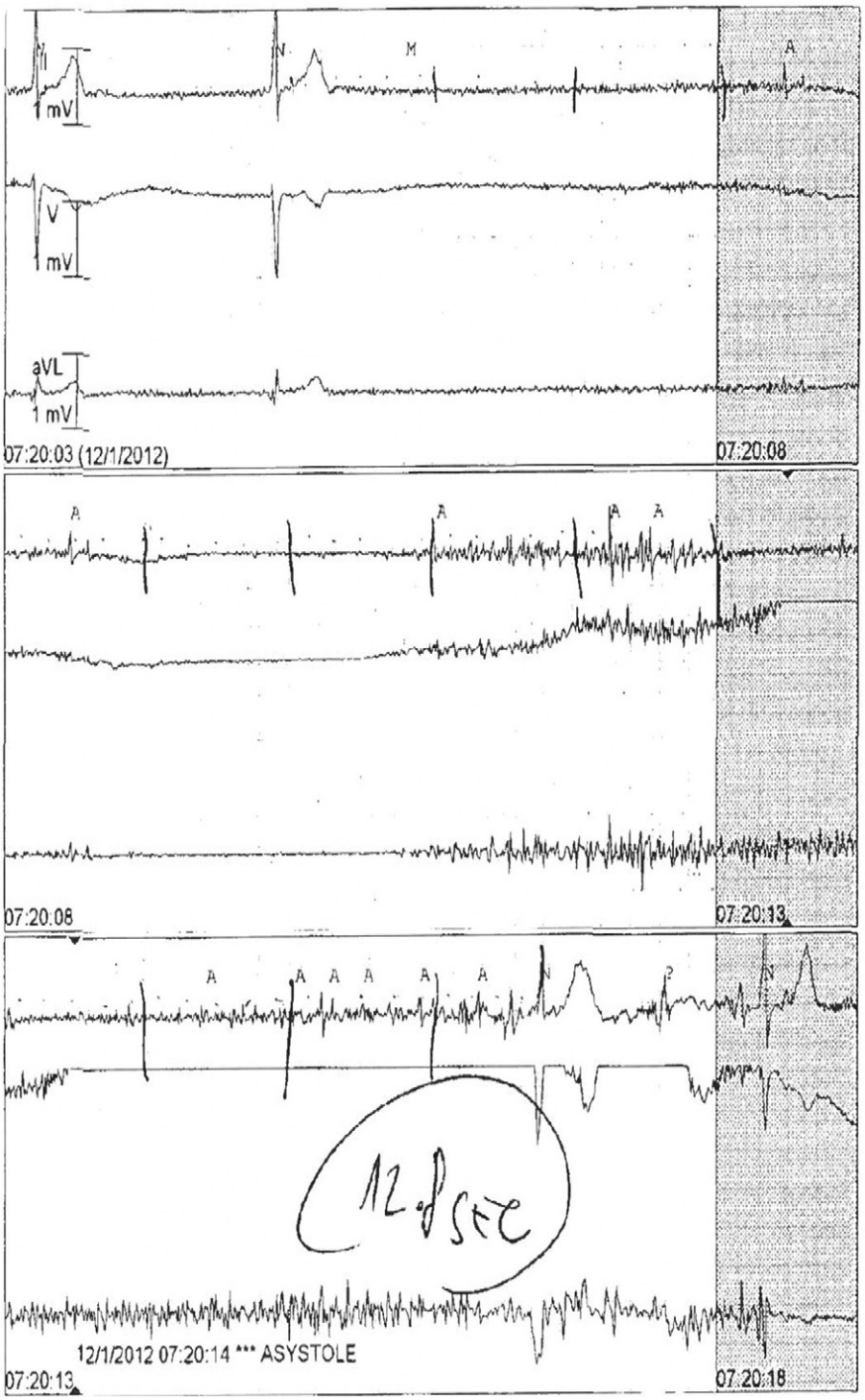

Fig. 1. An example of sinus arrest lasting 12.8 s is shown on ECG telemetry.

hyperthermia alternating with hypothermia, hypoventilation, fluctuating blood pressures, tachycardia and even bradycardia as severe as asystole. Josep Dalmau, who first described the syndrome, reported a case series of 100 patients with anti-NMDA-R encephalitis [2]. Sixty-nine percent of these patients had autonomic instability requiring a mean of 8 weeks of ventilator support, and 37% of these patients had cardiac arrhythmias (four required pacemakers). In a review of 360 affected patients, two patients had sudden cardiac death due to asystole, and one patient died unexpectedly out-of-the-hospital [3]. The dysautonomia, sinus pauses, and asystole are likely caused by a disruption in the centrally driven balance of parasympathetic and sympathetic activity. In fact, the distribution of the NMDA-R is limited to circuitry of autonomic, neuroendocrine, and limbic functions. Within the limbic system network, the insular cortices are reciprocally connected to the anterior cingulate cortex which project to the amygdala [4]. The amygdala serves as an activator in the alarm circuit to the hypothalamus and brainstem, with outflow affecting the preganglionic parasympathetic and sympathetic neurons of the heart [4]. The insular cortex, which lies within the lateral sulcus separating the temporal lobe from the parietal and frontal lobes, has been shown to play a role in controlling cardiac rate and rhythm [5]. Oppenheimer et al. first showed that prolonged stimulation of the left posterior insular cortex in rats can cause complete heart block, bradyarrhythmias and even asystolic death [6]. Stimulation of the right anterior insular cortex in humans

resulted in sympathetic-derived cardiovascular responses such as hypertension and tachycardia, whereas stimulation of left posterior insular cortex resulted in parasympathetic effects such as bradycardia [7].

Treatment for paraneoplastic mediated NMDA-R encephalitis usually includes tumor resection in the cases where a tumor is found, followed by immunotherapy [2,3]. However, an ovarian or testicular teratoma is found only about 38% of cases [8]. Recognition of this syndrome in a timely manner is extremely crucial, given the potential lethal nature of the associated autonomic instability and cardiac arrhythmias, as well as the opportunity for cure with targeted treatment.

Conflict of interest

The authors report no conflict of interest related to this report.

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