Clinical Neurology and Neurosurgery 114 (2012) 1066–1069

Contents lists available at SciVerse ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Case report

Profuse sialorrhea in a case of anti *N*-methyl-D-aspartate receptor (NMDAR) encephalitis

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ARTICLE INFO

Article history:
Received 28 November 2011
Received in revised form 4 February 2012
Accepted 7 February 2012
Available online 4 March 2012

Keywords:
Anti *N*-methyl-D-aspartate receptor encephalitis
Sialorrhea

1. Introduction

In 1997 a syndrome of ovarian teratoma-associated limbic encephalitis (OTLE) was reported in one Japanese girl and one woman, both of whom improved following tumor resection.

Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is a new category of treatment-responsive encephalitis associated with "anti-NMDAR antibodies", which are antibodies to the NR1/NR2 heteromers of NMDAR. Anti-NMDAR encephalitis is associated with tumors (commonly teratomas) in about 60% cases. Despite the severity of the disorder, patients often recovered after tumor removal and immunotherapy, suggesting an immune-mediated pathogenesis.

2. Case report

A 29-year-old female with no medical or psychiatric history presented to the emergency department of a different Hospital with gradually worsening depression and hallucinations. The family reported that she insidiously displayed changes in mood and poor judgment. In a few days, the patient experienced mood-incongruent persecutory delusions, bradyphrenia and unformed visual hallucinations. The patient believed that she was being followed by government organizations because she had been falsely identified as a spy. Her mother reported that she was also reaching out in the air as if to grasp something. She also presented with new onset of generalized tonic clonic seizures, lasting usually less than two minutes and occurring over a week period. However a series of electroencephalograms showed no epileptiform activity.

Later on, the patient was transferred to our institution for further management under the diagnosis of suspected status epilepticus. On admission, the patient was lethargic and confused. However, her neurologic status rapidly deteriorated and she became nonverbal and minimally responsive to pain, eventually requiring mechanical respiratory support and sedation. Furthermore, prominent myoclonus of both upper and lower extremities with choreoathetotic movements and hemiballismus appeared. She subsequently developed jaw opening, upper extremities dystonia and orofacial dyskinesias (see video). The presence of profuse sialorrhea was a striking feature of her clinical presentation as the amount of saliva was up to 2 L per day and required volume replacement and continuous oropharyngeal suctioning. The degree of spasticity, particularly at elbow/shoulder joints, as well as the

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0303-8467/$ – see front matter
doi:10.1016/j.clineuro.2012.02.011

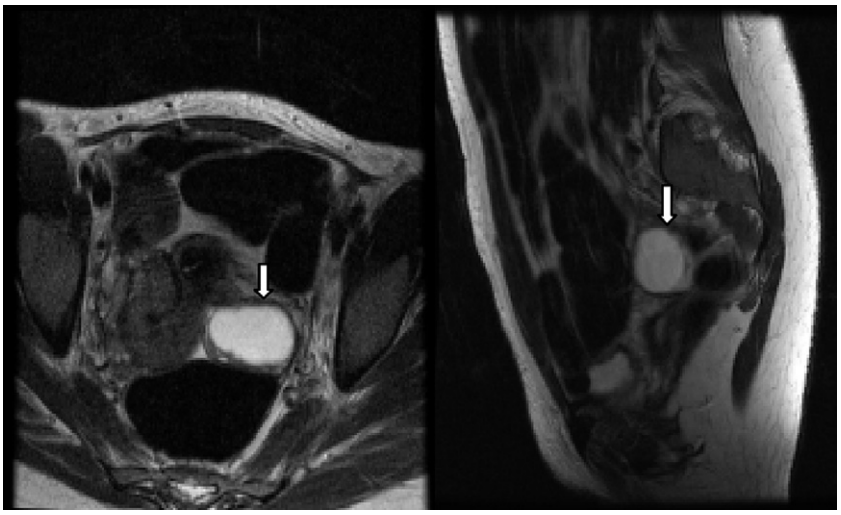

Fig. 1. MRI pelvis axial T2 (A) and sagital T2 (B) obtained during the hospitalization. The arrows point to the ovarian teratoma.

jaw opening dystonia, continued to worsen in spite of daily doses of lorazepam or diazepam up to 18 mg and 60 mg respectively. High doses of other medications, such as diphenhydramine up to 150 mg and bromocriptine up to 22.5 mg daily, were used for a six-week period without significant improvement. Accordingly, the patient received a total of 300 units of Onabotulinum toxin injections in selected bilateral upper extremities muscles. An additional 150 units of Onabotulinum toxin were injected equitably in the masticatory muscles (pterygoid, masseter and temporalis) and salivary glands, with minimal improvement. Neurological examination continued to show prominent orolingual dyskinesias with choreoathetotic movements and hemiballismus refractory to multidrug therapy that included high doses of medications such as haloperidol 15 mg/day, bromocriptine 22.5 mg/day, amantadine 300 mg/day, diazepam 60 mg/day and diphenhydramine 150 mg/day, which were administered over the course of six weeks. Central hypoventilation and autonomic instability also characterized the clinical presentation.

An exhaustive work-up was conducted to rule out possible organic causes (e.g. immunological, infectious, metabolic, iatrogenic and toxic). The brain MRI studies revealed nonspecific scattered T2 hyperintense foci which appeared to be mainly within the bifrontal subcortical white matter. An electroencephalogram demonstrated marked slowing without epileptiform discharges. The examination of the cerebral spinal fluid revealed pleocytosis with lymphocytic predominance and positive oligoclonal bands. Based on suspicion of rabies virus encephalitis (because of profuse sialorrhea and stupor), the patient underwent two skin punch biopsies of the side of neck that were negative. Peripheral blood smear to exclude the diagnosis of neuroacanthocytosis was also negative. Additionally, a complete autoimmune panel, heavy metals, infectious and toxicology screening was conducted. Genetic testing for CAG trinucleotide repeats yielded normal results.

Subsequently, her serum was evaluated for the presence of anti-NMDAR antibodies and the titers were elevated. The anti-NMDAR encephalitis diagnosis was therefore entertained. Later, a MRI of the pelvis revealed an ovarian teratoma (Fig. 1) that was subsequently excised. The histological examination demonstrated a mature cystic ovarian teratoma (Fig. 2). Immunosuppressive treatment with high doses of intravenous methylprednisolone (1 g daily for 5 days) and intravenous immunoglobulin administered at a dose of 0.4 g/kg/day for 5 consecutive days was prescribed. The lack of clinical improvement warranted the use of a second line of therapy which consisted of one dose of cyclophosphamide pulse (23 mg/kg) and four rounds of rituximab 375 mg/m^2 intravenously. During the course of the hospitalization, the patient relentlessly continued to improve (Fig. 3). By the time of her discharge, eleven weeks from admission, she was interactive and ambulating with assistance.

3. Discussion

We report a woman with an atypical presentation of anti-NMDAR encephalitis characterized by the presence of profuse sialorrhea that required volume replacement. This disorder is

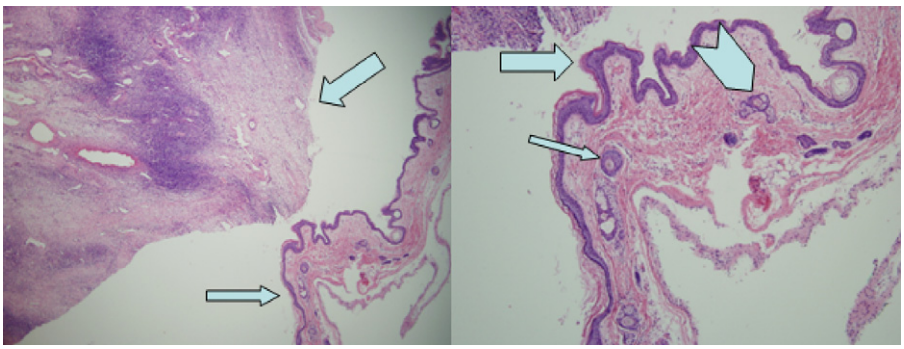

Fig. 2. (A) The thick arrow points to the ovarian tissue whereas the thin arrow points to the skin with its appendages lining the ovarian cyst. (B) Higher power of the well-developed skin lining. The fat arrow shows the keratinized stratified squamous epithelium of skin. The thin arrow points to a hair follicle and the arrowhead points to sebaceous glands.

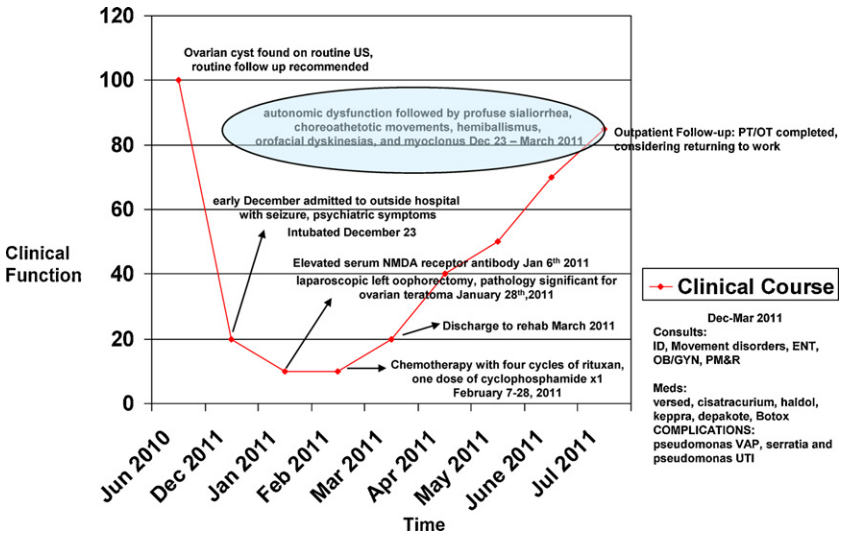

Fig. 3. Clinical course, medical management and short-term outcome of the patient.

associated with antibodies against the NR1/NR2B subunits of the receptor. Typically, it largely affects young people, and its diagnosis is facilitated by the characteristic clinical picture that develops in association with CSF pleocytosis.

Five phases have been recognized: prodromal, psychotic, unresponsive, hyperkinetic, and gradual recovery. During the prodromal phase, patients present with nonspecific viral-like symptoms followed by a psychotic phase. At the unresponsive state, they become mute, akinetic, in a state resembling catatonia. At the hyperkinetic state, patients gradually develop orolingual dyskinesias and athetoid dystonic postures of the fingers. Symptoms evolve to intractable bizarre orofacial-limb dyskinesias such as sustained jaw movements, forceful clenching of the teeth, jaw-opening dystonia, intermittent ocular disconjugation and chorea. This state is followed by hypoventilation and autonomic instability [1].

Among important clinical features of anti-NMDAR encephalitis, central hypoventilation occupies a prominent place and has been reported in 14 of 17 cases (82%) [2]. Interestingly, sialorrhea has been scarcely reported in few case reports [3]. However profound sialorhea, as described in this case, requiring continuous aspiration due to the large volume of saliva, has been rarely documented in the literature [2]. We postulate that sialorrhea could be the result of gabaergic-glutaminergic imbalance of the rostral hypothalamus. This elicits an overexcitation of the hypothalamic control pathways on the preganglionic parasympathetic neurons in the dorsal motor nucleus of the vagus nerve and the nucleus ambiguous, which become overstimulated. Another uncommon feature our case is the presence of hemiballism, which was seen in less than 3% in a review of large number of cases by Dalmau [3].

Most patients have abnormal CSF studies with a lymphocytic pleocytosis. About one third have increased protein, and about 60% have oligoclonal bands. At presentation, about half of the patients have abnormal MRI findings, most commonly increased signal on fluid-attenuated inversion recovery (FLAIR) in the cerebral or cerebellar cortex without significant clinical correlation. The diagnosis of anti-NMDA-receptor encephalitis is confirmed by the detection of antibodies to the NR1 subunit of the NMDA receptor in serum or CSF.

A literature review of possible differential diagnosis for anti-NMDAR encephalitis includes infectious, autoimmune, neurodegenerative etiologies and other paraneoplastic syndromes. Among infectious etiologies, rabies virus cases typically presents with rapid neurologic deterioration and remarkable sialorrhea (as described in this case). Nevertheless, rabies virus cases have rarely demonstrated high CSF protein concentrations or pleocytosis [4]. The spectrum of paraneoplastic syndromes includes a number of antineuronal antibodies, such as the intracellular anti-Hu and anti-Ma, which have been discovered to be associated with neuropsychiatric symptoms. The clinical presentation of CV2 antibodies limbic encephalitis is ample and includes encephalomyelopathy, axonal sensorimotor neuropathy, and more distinctively chorea, uveitis, and optic neuritis. Progressive neurodegenerative disorders, such as choreo-acanthocytosis is characterized by behavioral disturbances, acanthocytes in the blood smear and a distinctive movement phenomenology, including chorea and/or dystonia. Furthermore, few case reports have implicated McLeod syndrome or mitochondrial myopathies as a causative of dementia, parkinsonism and chorea [5]. Among autoimmune diseases, systemic lupus erythematosus and Hashimoto's encephalitis share similar clinical features, especially lupus, which can manifest with neuropsychiatric symptoms, severe encephalitis and/or choreiform movements.

Based on an extensive review, Dalmau and colleagues proposed an algorithmic strategy to guide treatment [1]. The first line of immunotherapy consists of corticosteroids, intravenous immunoglobulins, and plasma exchange (alone or in combination). The second line of immunotherapy (rituximab or cyclophosphamide or both) is usually needed in the case of a delayed diagnosis or in the absence of a tumor [1]. Patients usually start to gradually improve within 2–3 weeks of tumor removal and immunotherapy. The persistence of high CSF antibody titers suggests the need for continuation of treatment.

Relapses of anti-NMDA-receptor encephalitis occur in 20%–25% of patients, with the risk of relapse being associated with the presence or absence of a tumor and the timing of therapy. Patients who underwent tumor resection within 4 months of the onset of neurologic symptoms, often in conjunction with immunotherapy, had fewer neurologic relapses and better overall outcomes [2]. In a series of 100 patients with anti-NMDA-receptor encephalitis, 47 had a full recovery, 28 had mild deficits, 18 had severe deficits, and 7 patients had an illness-related death after a 17-month follow-up [2]. There are only anecdotal case reports of spontaneous recovery without surgical resection of the associated tumor [6].

4. Conclusion

This case underscores the importance of a high index of suspicion for NMDAR encephalitis even in case of atypical features such

as profuse sialorrhea. Thus, clinical practitioners should entertain the diagnosis of anti-NMDAR encephalitis, when a patient exhibits orofacial dyskinesia and profuse sialorrhea.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.clineuro.2012.02.011.

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