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Case report

Management of dyskinesia in anti-NMDAR encephalitis with tramadol

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1. Introduction

Anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a fairly new diagnosis that was discovered in 2005 after four young women developed ovarian teratomas with psychiatric symptoms, seizures, altered mental status, and eventual central hypoventilation [1]. It is an autoimmune encephalitis of variable paraneoplastic origin caused by IgG antibodies against NMDARs [1,2]. Dyskinesia is observed in a majority of patients with anti-NMDAR encephalitis and frequently includes orofacial dyskinesia that is characteristic of the disease [1,2]. Movement disorder often presents within the first month of the disease and may include choreoathetosis, facial and/or limb dyskinesia, and dystonia of variable severity [2]. Although a majority of anti-NMDAR encephalitis patients experience dyskinesia, no specific symptomatic treatment exists for its control. Thus, we present a case of anti-NMDAR encephalitis where tramadol, an NMDAR inhibitor, effectively controlled dyskinesia.

2. Case report

A previously healthy 23-year-old female was transferred to our hospital after being treated for neuropsychiatric symptoms five months prior. Her symptoms began with a reported two weeks of increased anxiety, panic attacks, and aggressive behavior. Upon experiencing generalized seizures, she was admitted to an outside hospital for assumed infectious encephalitis. Serologies were inconsistent with infectious encephalitis, and seizures were poorly controlled on high doses of levetiracetam and phenytoin. A tracheostomy was performed for airway protection and the patient was transferred to the intensive care unit (ICU) on ventilator support. Four months after the primary admission at the outside hospital, a nurse suggested testing for anti-NMDAR encephalitis upon reading the novel *Brain on Fire: My Month of Madness*. Cerebrospinal fluid (CSF) confirmed a positive anti-NMDAR Immunoglobulin G (IgG) antibody test and the patient was transferred to our hospital for further treatment. Upon transfer, our hospital retested the CSF for anti-NMDAR IgG antibody, which returned positive (Euroimmun commercial Biochip cell-based assay).

Upon admission to our hospital, she underwent a course of plasmapheresis (PLEX), five times every other day, followed by intravenous immunoglobulin (IVIG) at 0.4 grams per kilogram (g/kg) of body weight daily for five days, and a dosage of IV rituximab 1000 mg. A right-sided dermoid ovarian tumor was discovered and removed by right salpingoophorectomy. Postoperatively, the patient could not be weaned off the ventilator due to apneic events. Magnetic Resonance Imaging (MRI) showed no hyper-intense lesions and continuous electroencephalogram (EEG) showed diffuse slowing, but no seizure activity.

After right-sided salpingoophorectomy and tapering off sedation, the patient continued to have severe orofacial and limb dyskinesia as shown in Supplementary Video S1 in the online version at DOI: 10.1016/j.clineuro.2016.06.003. We first tried titrating

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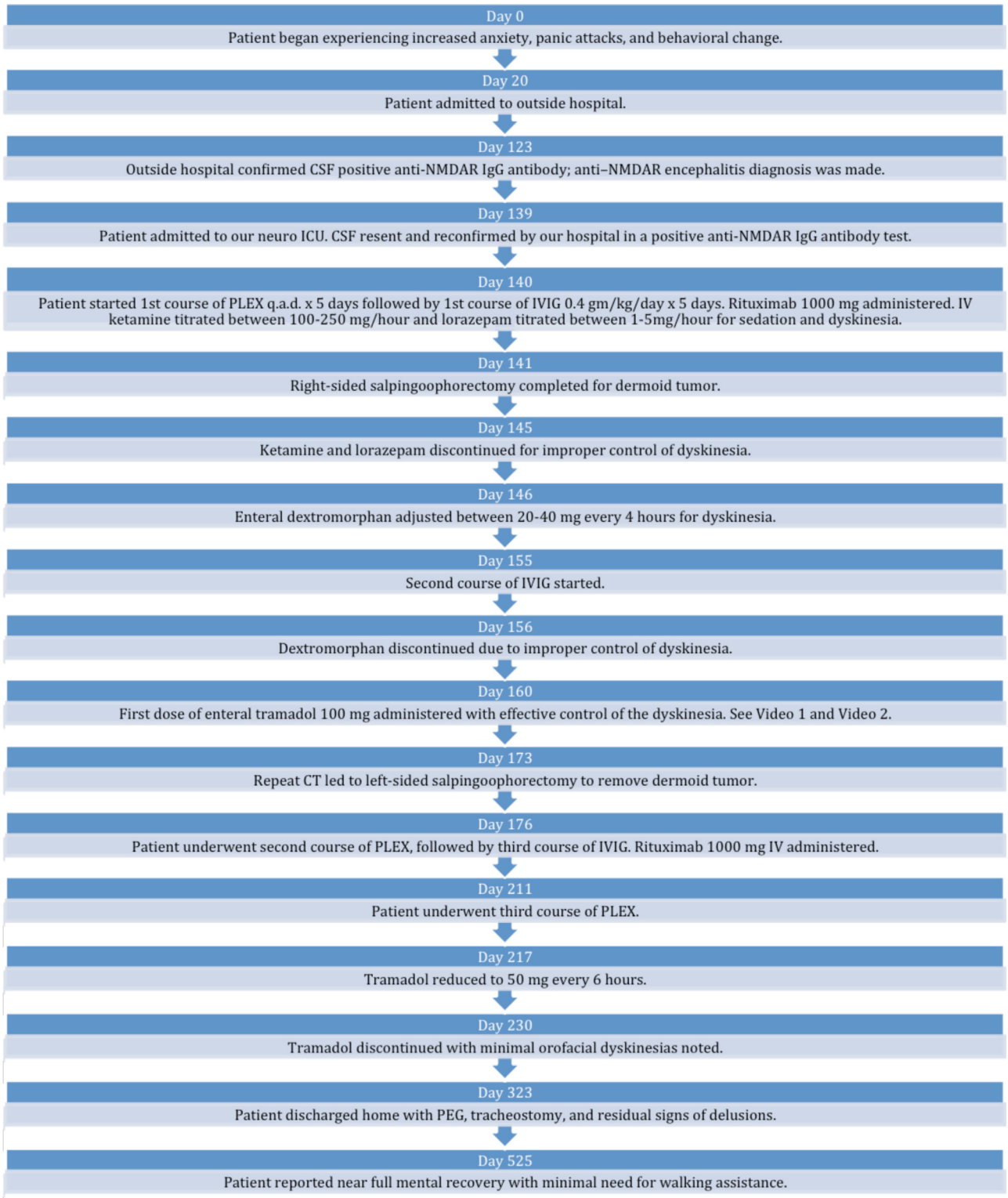

Fig. 1. Timeframe of patient clinical course.

ketamine IV infusion between 100 and 250 mg/h, with concomitant lorazepam infusion at 1–5 mg/h, but discontinued its use due to ineffective control. We also used enteral dextromethorphan, adjusted between 20 and 40 mg every 4 h, which had minimal effect on the dyskinesia. After thinking further on the mechanism of tramadol in attaching to NMDARs, we hypothesized that it could control the dyskinesia. We tried a series of treatments while the patient remained ventilated. She underwent continuous EEG to capture potential seizure activity and all pain medications and sedations were stopped specifically to observe potential effects of the tramadol. The patient was started on enteral tramadol 100 mg, and upon the first dose of tramadol, the patient's orofacial and limb dyskinesia were fully controlled as shown in Supplementary Video S2 in the online version at DOI: 10.1016/j.clineuro.2016.06.003. To ensure this was a reaction to only the tramadol, we waited 8 h for the tramadol to be excreted, the dyskinesia returned, and a second

dosage of enteral tramadol 100 mg again controlled the dyskinesia. We continued tramadol 100 mg every six hours for nearly ten weeks to control the dyskinesia. No side effects from the tramadol were noted. Specifically, continuous EEG was obtained at multiple time points to detect any potential seizure activity as a side effect of tramadol. Two weeks after the start of tramadol, a repeat CT scan led to discovery of a left-sided dermoid tumor removed by left-side salpingoophorectomy. Another round of PLEX, IVIG, and rituximab 1000 mg was administered post surgery. Tramadol was again continued as severe orofacial and limb dyskinesias remained as in Supplementary Video S1 in the online version at DOI: 10.1016/j.clineuro.2016.06.003. On the fifth week of tramadol use, the patient underwent the last course of PLEX. Minimal orofacial dyskinesia remained after discontinuing tramadol upon discharge from the ICU. A timeframe of the patient's clinical course is outlined in Fig. 1. The patient was discharged home nearly seven months after diagnosis, with continued percutaneous endoscopic gastrostomy (PEG) care, a tracheostomy, and residual signs of delusions. Fourteen months after the onset of symptoms, the patient almost fully recovered mentally with minimal need for walking assistance and plans to return to school.

3. Discussion

To our knowledge, this is the first reported case of successful treatment with tramadol for dyskinesia in anti-NMDAR encephalitis (Supplementary Videos S1 and S2 in the online version at DOI: 10.1016/j.clineuro.2016.06.003). In a similar anti-NMDAR encephalitis case report, ketamine infused at 20 mg/hour reversed dyskinesia [3]. However in this case, ketamine titrated between 100 and 250 mg/hour had minimal effect. While data on symptomatic treatment of anti-NMDAR encephalitis is limited in the literature, this topic has been recently addressed in a study conducted in pediatric age patients [4]. In this retrospective series, movement disorder was the third most frequent symptom treated, after agitation and seizures [4]. Five different medications including levodopa-carbidopa, benztropine, baclofen, amantadine and bromocriptine were used in this cohort for movement disorder along with various benzodiapezines and anti-convulsants, though tramadol was not tried [4].

It is hypothesized that the clinical effects of anti-NMDAR encephalitis including dyskinesia may result from inactivation of GABAergic neurons subsequent to depression of NMDARs.[1]This is not surprising when considering GABAergic neurons express higher concentrations of NMDAR than other neuronal subtypes [1]. In *Xenopus* oocytes, tramadol inhibits NMDARs in a concentration-dependent manner, but only inhibits $GABA_a$ receptors at larger concentrations [5]. Thus, we hypothesize an alternative mechanism of tramadol that allows the GABAergic neurons to fire while non-competitively inhibiting NMDARs, forcing the competitive NMDAR antibodies to detach. However, further study is needed on the exact mechanism of tramadol and how it successfully works for treating dyskinesia in anti-NMDAR encephalitis.

4. Conclusion

Severe orofacial and limb dyskinesia is a frequent symptom experienced by anti-NMDAR encephalitis patients, but no treatment specific to symptomatic relief of the dyskinesia in anti-NMDAR encephalitis exists. Current treatment protocols require broad-based immunotherapies that often take several months before recovery from dyskinesia symptoms, but no recommendations exist on how to treat severe dyskinesia before immunotherapy has adequate time to work. In our patient with anti-NMDAR encephalitis, tramadol successfully controlled both orofacial and limb dyskinesia while waiting for immunotherapy to aid in recovery. Future study is needed on the exact mechanism of tramadol in successfully treating symptomatic dyskinesia as it may lead to additional therapies for anti-NMDAR encephalitis.

Author contributions

Dr. Seifi designed, hypothesized, revised, and edited the manuscript and captured all patient video.

Deanna Kitchen drafted and revised the manuscript.

Author disclosures

Ali Seifi and Deanna Kitchen report no disclosures.

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