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Case Report

Tramadol may increase the efficacy of therapeutic plasma exchange in anti-NMDAR encephalitis

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1. Introduction

Anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis was first described in 2005 in females with ovarian teratomas [1]. The disorder is characterized by altered mental status, psychiatric disorders, and seizures with progression to dyskinesias [1]. In many instances the disorder includes a prodrome which includes headaches, hyperthermia, and in some instances nausea, vomiting, and diarrhea [1]. The most common presenting symptom is usually altered short term memory and many patients present first to psychiatrists due to acute psychosis and agitation [1]. Finally, the disease can progress to causing any type of seizures, a comatose state, various movement disorders, or autonomic instability [1,2]. The mainstay of treatment for this disorder is immunotherapy with steroids, intravenous immunoglobulin (IVIG) and/or therapeutic plasma exchange (PLEX) [1]. However, these first-line therapies only improve symptoms in about half of anti-NMDAR encephalitis patients within 4 weeks. As many as 57% of patients in one study went on to require second line therapy including either rituximab, cyclophosphamide or both therapies [1]. These second line immunotherapies significantly improved outcomes in patients and led to less relapses [3]. We propose that tramadol may facilitate the effect of PLEX, thus allowing for a shorter duration of the illness.

2. Case report

We previously reported on a 23 year old (yo) female diagnosed with anti-NMDAR encephalitis who had symptoms of dyskinesia resistant to multiple therapies including PLEX, IVIG, rituximab, ketamine, lorazepam and dextromethorphan [2]. Eventually, we treated her with tramadol in addition to PLEX and IVIG. This treatment regimen led to almost complete resolution of her oral-facial dyskinesias after each dose. She experienced a full recovery and went back to a normal life with no residual symptoms [2]. In this case, we hypothesized that the tramadol helped the dyskinesia by non-competitively inhibiting NMDARs, allowing NMDAR antibodies to detach [2].

Our second case involves a previously healthy 31yo female with newly diagnosed seizures and schizophrenia. The patient's symptoms began with an episode of "psychosis" for which she was diagnosed with schizophrenia. She progressed to having generalized tonic-clonic seizures, and was transferred to our facility for continuous electroencephalographic (EEG) monitoring one month after the start of her symptoms. By the outside hospital report, her EEG showed status epilepticus thereby requiring her intubation and initiation of two more anti-epileptics. At that time, she was started on solumedrol 1 g each day for five days with the last two days of the steroid course being completed at our hospital. She failed to improve any of her symptoms. Her anti-epileptic medications were escalated to include levetiracetam, phenobarbital, and lacosimide. She arrived to our institution intubated approximately one month after initial symptom onset.

Her initial EEG pattern at our institution showed continuous generalized polymorphic delta activity at 2–3 Hz without evidence of epileptiform discharges or seizures. She continued to have oral dyskinesias that mainly consisted of lip smacking and biting motion with her jaw. Her tongue had continuous movement roving throughout her mouth,

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and her eyes continued to open and close constantly. At our facility, she underwent a lumbar puncture, which was positive for anti-NMDAR Immunoglobulin G at a ratio of 1:120 (IgG) (Euroimmun commercial Biochip cell-based assay) analyzed by ARUP Laboratories (Salt Lake City, Utah). The assay used a semi-quantitative indirect immunofluorescence on human embryonic kidney cell cultures expressing recombinant NMDA receptors (transfected HEK 293 cells). The initial protein on the CSF sample was 49 mg/dl with a glucose of 43 mg/dl. There were 179 white blood cells present with a 97% lymphocytic predominance and 2 RBCs. Finally, oligoclonal bands were positive at 8, with negative results for AMPA, GAD, GABA-R antibodies. NMDA receptor anti-bodies were not sent from her serum. Patient had negative CT scans for occult malignancies.

The day after a confirmed positive result for anti-NMDAR antibody, she was subsequently started on a course of PLEX every other day, in fact the PLEX was started 44 days after her first presentation. She underwent three of the five PLEX sessions before we withheld it due to toxic megacolon from *Clostridium difficile* colitis that required a total colectomy. Throughout her three PLEX sessions, she was obtunded and not following commands with only minimal improvement in her facial dyskinesias with ketamine at 20 mcg/kg/min. Six days after her colectomy, we restarted PLEX for another five sessions. Given our experience with the last patient [2], we pre-treated her with tramadol 100 mg enterally three times a day, specifically one hour before each subsequent five PLEX sessions. As compared to the earlier PLEX sessions, the patient rapidly responded to both PLEX and tramadol. Her facial dyskinesias resolved after the first PLEX session and she opened her eyes spontaneously immediately following the first PLEX session. By the end of her third PLEX session in combination with the tramadol, she began to follow commands. By the end of her fifth PLEX session, she was alert and awake enough to interact with her care providers and her facial dyskinesias had completely resolved. She was downgraded from the intensive care unit one week after the last PLEX, at the hospital day 36 (97 days after first symptoms) alert, awake, and following complex commands. At her follow up appointment, nine months after symptoms onset, she continues to do well and is back to work, has not had any recurrent symptoms, and no lasting neurologic effects.

3. Discussion

Tramadol is a weak centrally acting μ-opioid receptor agonist, but additionally acts to inhibit NMDARs at clinically relevant levels [4]. The oral formulation of tramadol has a peak onset of approximately 60 min and is completely absorbed with a higher brain concentration than in plasma [5]. The increased availability in the brain tissue along with its fast peak onset of action makes it an appealing choice for treatment. The most commonly reported side effects of Tramadol include: dizziness, tiredness, drowsiness, fatigue, nausea, vomiting, sweating and dry mouth [5]. In less than 1% of patients, serious side effects of hypotension, circulatory collapse, pruritis, sleep disorders, somnolence, abdominal pain, and tachycardia. [5]

Studies have shown that PLEX for anti-NMDAR encephalitis is effective, but lacks rapid correction of symptoms [4]. The large volume of distribution of NMDAR antibodies and long half life makes PLEX sessions a desirable first-line therapy, but as shown in a large multi-institutional observational study, only 53% of patients who receive first-line immunotherapy or tumor removal experience improvement in symptoms within 4 weeks [1,3]. In anti-NMDAR encephalitis patients treated with first-line immunotherapy, nearly 75% experienced resolved symptoms by 4 months [1,3]. In patients requiring second-line immunotherapy, roughly half of patients recovered by 8 months [1,3]. Additionally, new studies are showing that the earlier and more aggressive treatment leads to better outcomes [3,6]. We hypothesize that PLEX therapy on its own is probably insufficient for quick treatment as it cannot clear the strongly bound NDMAR antibodies from the NMDARs, which is needed for the resolution of symptoms.

On the other hand, when PLEX is administered with a pre-treatment of tramadol, PLEX successfully controlled the dyskinesia and allowed the patient to become alert and oriented as seen in this case and in our prior case study. Tramadol non-competitively inhibits NMDARs in a concentration dependent manner [2,4]. Therefore, we cautiously hypothesize that PLEX administered with a pre-treatment of tramadol more likely works quickly and improves dyskinesia because tramadol has a higher affinity for the NMDAR. The affinity of tramadol to the NMDAR forces the detachment of the NMDAR antibody from the receptor long enough to allow PLEX to work in removing the NMDAR antibodies. We are currently not aware of any studies that directly compare the binding affinity between Tramadol and the NMDA antibody. The patients' redevelopment of facial dyskinesia as tramadol wore off further supports this theory that tramadol has a higher affinity for the NMDAR [2]. Additionally, the resolved symptoms after a full cycle of PLEX therapy with tramadol administration also support this theory as multiple sessions are required to fully clear the NMDAR antibodies. Future studies are needed to confirm this effect, but we believe tramadol is a safe and effective treatment for anti-NMDAR encephalitis. If our theories are correct, tramadol could lead to a faster effect of PLEX and shorter duration of symptoms in anti-NMDAR encephalitis.

4. Conclusion

In patients with anti-NMDAR encephalitis, PLEX therapy is a mainstay for treatment, but is slow in effectively treating a majority of patients with anti-NMDAR encephalitis. In this case study of a patient with anti-NMDAR encephalitis, PLEX therapy alone was insufficient in quickly treating the debilitating symptoms. However, when PLEX therapy was administered after pre-treating with tramadol, the patient achieved a rapid and observable recovery. Although the exact mechanism of tramadol when administered with PLEX therapy in anti-NMDAR encephalitis is not fully understood, the potential for a shorter duration of the illness is evident with this treatment, which has the potential for many therapeutic and financial benefits.

Author disclosures

None.

Author contributions

Dr. Dengler drafted and revised the manuscript.
Deanna Kitchen revised the manuscript.
Dr. Seifi designed, hypothesized, and revised the manuscript.

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