Case Report

Use of dexmedetomidine as adjunctive therapy for anti-N-methyl-D-aspartate receptor encephalitis

Christopher J. Babbitt*, Jean Lake and Glenn K. Levine
Pediatric Critical Care, Miller's Children Hospital, Long California, CA, USA

Received 2 May 2013

Revised 7 June 2013

Accepted 8 June 2013

Abstract. Anti-N-methyl-D-aspartate receptor encephalitis is a recently discovered disease that is more commonly being diagnosed in children. Patients often require intensive care and assisted ventilation due to agitation, abnormal movements, hypoventilation, seizures and autonomic instability. There is no consensus on which medicines are best suited to acutely treat this constellation of central nervous system symptoms. We present the first case report of using dexmedetomidine to treat this condition.

Keywords: Dexmedetomidine, encephalitis, seizures, anti-N-methyl-D-aspartate receptor

1. Introduction

Anti-N-methyl-D-aspartate (NMDAR) receptor encephalitis is a recently discovered disease that is more commonly being diagnosed in children. Patients with this disease can develop episodes of agitation, seizures and abnormal movements that are often difficult to control pharmacologically [1]. We present the first case report of using dexmedetomidine to treat the central nervous system symptoms of this disease.

2. Case report

A previously well 7-year-old female was admitted to the pediatric intensive care unit (PICU) for seizures and altered mental status. Three weeks earlier, she had

headaches, fever and an upper respiratory infection. She was taken to an outside emergency department twice over the previous week for concerns of blank stares and not acting right. Laboratory studies and computer tomography of the brain were normal at that time. At the second visit, she was started on levetiracetam for possible seizures. She then became anxious, was unable to sleep more than a few hours at a time and complained of nightmares. On the day of admission, the family stated that she “went crazy,” was very anxious, and started screaming, “I need help, I need help.” There was no fever, diarrhea, upper respiratory infection symptoms at the time of the PICU admission, but was having daily headaches treated with ibuprofen.

The patient was afebrile on initial presentation with a mild tachycardia with heart rate of 130 beats per minute. Neurologic examination showed that she was only intermittently oriented to person and not to place or date. She did not recognize her parents and appeared to be having both visual and auditory

*Corresponding author: Christopher J. Babbitt, Pediatric Critical Care, Miller's Children Hospital, Long California, CA 90808, USA. Tel.: +1 562 933 8743; Fax: +1 562 933 8744; E-mail: cbabbitt@memorialcare.org.

hallucinations. At times, she became agitated, screamed loudly, arched her back and had movements of both upper and lower extremities. These episodes were treated with 0.05 mg/kg of lorazepam. Cerebrospinal fluid showed four white blood cells/mm³, protein 13 mg/dL and glucose 57 mg/dL. Vancomycin, ceftriaxone and acyclovir were initiated. Infectious disease work up was negative, but cerebral spinal fluid came back positive for NMDAR antibodies (1:10 dilution). She was treated with intravenous immunoglobulin (IVIG) for anti-NMDAR encephalitis two days after admission and received 400 mg/kg over five days.

Initially in the PICU, the patient continued with episodes of agitation, followed with abnormal movements. She would become stiff, arch and have what appeared to be dyskinesia of her extremities. It was difficult to tell whether these were complex partial seizures or just abnormal movements. Lorazepam was administered fourteen times during the first three days in the PICU. Initial electroencephalography was slow, but without seizures. Risperidone was added on hospital day two, as anti-NMDAR encephalitis was felt to be the most likely diagnosis at that time. Initially she was started on 0.25 mg three times a day, but ultimately increased to 1.5 mg three times a day. She continued to receive lorazepam (0.05–0.1 mg/kg) for agitation and possible, complex partial seizures. Overall, her baseline mental status continued to deteriorate and she began to have sinus tachycardia into the 200 beats per minute and hypertension with the episodes. The episodes occurred 3–4 times a shift and at this time, she was generally comatose except for episodes of agitation. Telemetry showed extreme delta brushes and a few seizure episodes. The seizures did not correlate with the abnormal movements, but were seen when she would turn her head to the left and stare blankly. At this time, on hospital day four, she was started on valproic acid for the seizures. Risperidone was stopped and a dexmedetomidine infusion was initiated at 0.4 µg/kg/h. Within a few hours of receiving dexmedetomidine, the episodes became much less frequent and resolved after three days. The infusion was weaned to 0.1 µg/kg/h over four days, but there was recurrence of brief episodes of agitation and dyskinesia without autonomic changes. At this point, the infusion was increased to 0.2 µg/kg/h and she was placed on oral clonidine. Dexmedetomidine was then weaned off over 48 hours and she remained on clonidine for eight more days.

She left the PICU after 15 days and was discharged from the hospital after 20 days. She was successfully

weaned off clonidine and valproate before discharge. She was able to ambulate independently with some rare problems with balance and word finding. Work up for malignancy was negative while in the hospital and outpatient follow up will be continued with rehabilitation and neurology.

3. Discussion

In 2007, specific autoantibodies to NMDAR were detected in a group of patients with a syndrome of memory deficits, psychiatric symptoms, decreased consciousness, hypoventilation and ovarian teratomas [2]. This disorder has become a leading cause of autoimmune encephalitis in children and adolescents, with 40% of patients being younger than 18 years of age [3]. Patients are often referred to psychiatric facilities due to agitation and bizarre behavior, but can subsequently develop seizures and progressive decline in consciousness [1]. Our patient had classic features of anti-NMDAR encephalitis, including altered sensorium, abnormal movements, agitation and autonomic instability. She also had extreme delta brushes on telemetry and this has been described in children and adults that have NMDAR encephalitis [4,5].

Most of the literature has focused on the diagnosis, antibodies, association with malignancy and immunotherapy treatment of the disease. Recently, psychiatric literature has discussed treatment options for symptom control [6]. Patients often receive benzodiazepines, as they have become the first line therapy for acute management of seizures. However, it is not clear that benzodiazepines are the best medications to treat the constellation of central nervous system symptoms.

NMDAR are excitatory, tetrameric receptors with two classes of subunits: NR1 and NR2 that bind glycine or glutamate. In anti-NMDAR encephalitis, NR1 NMDAR antibodies decrease NMDAR surface density and synaptic localization via selective antibody-mediated capping and internalization of surface NMDA receptors [7]. The NMDAR hypoactivity results in the inactivation of gamma-aminobutyric acid-ergic neurons, resulting in disinhibition of excitatory pathways and a frontostriatal syndrome [2]. Due to this mechanism, some have suggested the drugs that work via the NMDAR, such as ketamine, methadone, and nitrous oxide not be used for patients with NMDAR encephalitis [8]. Risperidone is a second-generation neuroleptic that has been used to treat encephalitis and was recommended in a recent proposed algorithm to

treat pediatric delirium [9]. Unfortunately, our patient continued to have episodes of extreme agitation and worsening autonomic instability despite reaching doses of risperidone generally not used on young children.

Clonidine, an alpha-2 agonist, has previously been shown to block the neuropathic and hyperactive side effects of NMDAR antagonists [10]. Dexmedetomidine is a newer intravenous alpha-2 agonist that has become the drug of choice for post-operative sedation for pediatric patients undergoing congenital heart repair [11]. It is helpful in achieving sedation while also allowing stable hemodynamics in the immediate post op period [12]. Furthermore, it has been advocated for use in transport of combative pediatric patients because it does not cause respiratory depression [13]. This was of critical importance to us because one of the hallmarks of NMDAR encephalitis is hypoventilation syndrome. From our experience with congenital heart patients, we hypothesized that this patient would be an excellent candidate for dexmedetomidine.

The same day that it was started, we were able to achieve a state where she was calm and interactive and ceased to have episodes of autonomic instability. The first attempt to wean off dexmedetomidine resulted in another episode of agitation. However, the addition of clonidine allowed it to be successfully weaned off. It is clear that during that same period she had a tremendous response to the IVIG, which led to dramatic improvement in her neurologic condition. We believe that the adjunctive therapy of dexmedetomidine allowed her to rest, stop pulling out intravenous lines, receive nasogastric feeds and eliminated the autonomic instability while finishing IVIG therapy. It is possible that initiating clonidine earlier could have had the same effect, but we chose to start with an intravenous agent that would allow us to titrate the dose based on the response.

In conclusion, anti-NMDAR encephalitis is being recognized increasingly in children. Controlling delirium, dystonia, agitation and autonomic instability while preventing hypoventilation can be challenging. Dexmedetomidine should be considered as the primary medication to treat this constellation of central nervous system symptoms. It has effects on both the central nervous and cardiovascular system that are desirable for patients

with anti-NMDAR encephalitis. As it has no anticonvulsant properties, seizures must be excluded or treated simultaneously with an anti-epileptic medication.

References

- [1] Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol* 2008;7(12):1091–8.
- [2] Dalmau J, Tüzün E, Wu HY, Masjuan J, Rossi JE, Voloschin A, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol* 2007;61(1):25–36.
- [3] Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol* 2011;10(1):63–74.
- [4] Schmitt SE, Pargeon K, Frechette ES, Hirsch LJ, Dalmau J, Friedman D. Extreme delta brush: a unique EEG pattern in adults with anti-NMDA receptor encephalitis. *Neurology* 2012;79(11):1094–100.
- [5] Armangue T, Titulaer MJ, Málaga I, Bataller L, Gabilondo I, Graus F, et al; Spanish Anti-N-methyl-D-Aspartate Receptor (NMDAR) Encephalitis Work Group. Pediatric anti-N-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. *J Pediatr* 2013;162(4):850–6.e2.
- [6] Kayser MS, Dalmau J. Anti-NMDA receptor encephalitis in psychiatry. *Clin Psych Rev* 2011;7(3):189–93.
- [7] Hughes EG, Peng X, Gleichman AJ, Lai M, Zhou L, Tsou R, et al. Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. *J Neurosci* 2010;30(17):5866–75.
- [8] Prybylowski PG, Dunkman WJ, Liu R, Chen L. Case report: Anti-N-methyl-D-aspartate receptor encephalitis and its anesthetic implications. *Anesth Analg* 2011;113(5):1188–91.
- [9] Karnik NS, Joshi SV, Paterno C, Shaw R. Subtypes of pediatric delirium: a treatment algorithm. *Psychosomatics* 2007;48(3):253–7.
- [10] Jevtovic-Todorovic V, Wozniak DF, Powell S, Nardi A, Olney JW. Clonidine potentiates the neuropathic pain-relieving action of MK-801 while preventing its neurotoxic and hyperactivity side effects. *Brain Res* 1998;781(1–2):202–11.
- [11] Chrysostomou C. Dexmedetomidine: should it be standard after pediatric cardiac surgery?*. *Pediatr Crit Care Med* 2012;13(6):696–7.
- [12] Gupta P, Whiteside W, Sabati A, Tesoro TM, Gossett JM, Tobias JD, et al. Safety and efficacy of prolonged dexmedetomidine use in critically ill children with heart disease*. *Pediatr Crit Care Med* 2012;13(6):660–6.
- [13] Watt KM, Walgos J, Cheifetz IM, Turner DA. Dexmedetomidine for transport of a spontaneously breathing combative child. *Pediatrics* 2012;130(3):e690–4.