Remission From Behavioral Dysregulation in a Child With PTSD After Receiving Procedural Ketamine

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abstract

Ketamine, an N-methyl-D-aspartate-type glutamate receptor antagonist, has long been used for anesthesia and has recently been investigated for its rapid antidepressant effects in adults with treatment-resistant depression and posttraumatic stress disorder (PTSD). We report a case of a child with PTSD and episodes of severe aggression and emotional dysregulation that were refractory to multiple medical and behavioral interventions. This child demonstrated sustained (8–13 days) remission from these symptoms when exposed to ketamine in the context of 2 procedures. We review the sparse literature on the uses of ketamine for behavioral purposes in children. This case suggests that ketamine should be further explored as a potential treatment option for children with severe refractory behavioral aggression.

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Dr Donoghue participated in the initial interview of the patients' parents and gathered information from his medical records and providers, performed a comprehensive literature search, and drafted the initial case report; Dr Roback reviewed and revised the case report; Dr Cullen carried out the initial interview of the subject's parents and reviewed and revised the case report; and all authors approved the final case report as submitted.

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Ketamine, a N-methyl-D-aspartate-type glutamate receptor antagonist, has long been used for anesthesia and has recently been investigated for its rapid antidepressant effects in adults with treatment-resistant depression^{1,2} and posttraumatic stress disorder (PTSD).³ This case describes a child with PTSD and episodes of significant aggression and emotional dysregulation that were refractory to multiple medical and behavioral interventions, who demonstrated sustained (8–13 days) remission from these symptoms when exposed to ketamine on 2 occasions.

CASE REPORT

This patient is a 7-year-old-boy with a psychiatric history significant for PTSD, reactive attachment disorder, and disruptive behavior disorder who displayed frequent (multiple times per day) episodes of severe emotional and behavioral outbursts involving destruction of property. The severe level of physical aggression often required physical restraints. History is

notable for traumatic experiences including severe abuse during early childhood at age 5. Past medication trials* to address these problems included antidepressants, stimulants, α -2 agonist medications, histamine modulators, and mood stabilizers. None of these medication trials led to any substantial improvement. In the past 2 years, he required many hospitalizations for behavioral outbursts and inability to be safe at home. He currently resides in a long-term residential care facility.

At age 7, the patient underwent surgery for a tonsillectomy and received 10 mg intravenous ketamine along with nitrous oxide, propofol 50 mg, rocuronium 10 mg, decadron 12 mg (divided), ondansetron 4 mg (divided), neostigmine 2 mg, and glycopyrrolate 0.4 mg. In the ensuing days, the patient's care providers at the residential treatment center observed

*Specific past prescribed medications include sertraline, mirtazapine, lorazepam, trazodone, amphetamine aspartate, atomoxetine, guanfacine, clonidine, valproic acid, and hydroxyzine.

that the intensity and frequency of his aggressive behaviors dramatically lessened and that he exhibited a newfound ability to control his emotions and behavior. They documented that he had no physical restraints during that week, which was a major change. When he did occasionally become upset during this time period, his emotions and behaviors did not escalate in his typical fashion. His adoptive parents noted that he was more affectionate to them. Strikingly, during this time, the therapist noted that the child spoke openly during therapy about his past trauma and abuse, something he had never done in the past. It was felt by his therapist that he was able to make substantial gains in the therapeutic goals during that postoperative time. After 13 days, he returned to his baseline behaviors with respect to behavioral and emotional dysregulation.

Three months later, the child underwent a sedated magnetic resonance imaging and again received intravenous ketamine 10 mg. Once more, for several days after the procedure, the patient's care providers at the residential treatment center documented that he displayed less aggressive behavior and an improved ability to regulate his emotions. He again made progress in his psychotherapy, similar to his response after the first surgery. This time, the remission lasted 8 days before the baseline symptoms returned.

DISCUSSION

Severe behavioral dysregulation in children and adolescents is often difficult to treat, especially in the setting of a history of traumatic early experiences such as child abuse.⁴ When children's behavioral disorders are most severe, they often require treatment in a residential setting.⁵ This is not ideal in patients like the boy presented here who have disrupted attachment relationships with their caregivers, for whom

treatment focuses on fostering the caregiver-child attachment relationship⁶; out-of-home placement inhibits the progress of this treatment goal. Given this situation, novel treatments are urgently needed for children with trauma histories who have severe and treatment-resistant behavioral problems.

There is a growing literature supporting ketamine for treatment-resistant depression in adults^{1,2} and, more recently, PTSD.³ The literature on ketamine in children for psychiatric indications is limited to just 1 report, however. Papolos reported using intranasal ketamine to treat children with what he described as the "fear-of-harm phenotype" of pediatric bipolar disorder. The description of this phenotype has similar features to those seen in children with PTSD, including reactive aggression in response to perceived threats (thought to be developed through recurrent nightmares). Papolos reported a rapid, marked improvement in many symptomatic dimensions, including aggression, with intranasal ketamine treatment in his clinical practice.⁷ Two previous reports in young adults suggest that ketamine may be useful for behavioral disturbances outside the context of bipolar disorder, depression, or PTSD. Intranasal ketamine was used to treat refractory intermittent explosive disorder in a 20-year-old man and was successful in aborting explosive episodes refractory to other interventions.⁸ Similarly, another case report described a 29-year-old woman with autism spectrum disorder for whom repeated doses of intranasal ketamine led to decreased depressive symptoms, as well as increased cognitive flexibility, tolerance of routine change, and ease in interacting with others.⁹ The case presented here is the first report documenting a significant improvement in disruptive behavior in a child outside of the context of a bipolar diagnosis. As noted earlier,

ketamine has been shown to be helpful for adults with PTSD; although pre- and post-PTSD symptoms were not directly assessed, the therapist's notes that the patient was more willing to discuss his past traumas in therapy was suggestive that this medication might be useful for PTSD in children.

The mechanism behind our patient's rapid and sustained clinical improvement after exposure to ketamine on 2 separate occasions is unclear. Studies have shown that N-methyl-D-aspartate antagonists activate a molecular signaling cascade that ultimately results in more new spine synapses in the prefrontal cortex of animal models.^{10,11} In treatment-resistant depression, a proposed mechanism for its antidepressant effects is that ketamine increase brain-derived neurotrophic factor (a key supporter of neuronal health and synapse formation¹²) in the prefrontal cortex¹³ and can rescue and restore the losses in neurogenesis and synaptic plasticity that are seen with severe depression.¹⁴ Speculatively, for our patient, this increased neuroplasticity could play a role in unlocking neural pathways damaged from early trauma, opening the door for the possibility of recovery through engagement in therapy. This case report suggests the need for future study using ketamine as a treatment option for children with a history of trauma and severe behavioral dysregulation who have not responded to first-line medication and behavioral therapy approaches.

ABBREVIATION

PTSD: posttraumatic stress disorder

REFERENCES

1. Murrough JW, Iosifescu DV, Chang LC, et al. Antidepressant efficacy of ketamine in treatment-resistant major depression: a

- two-site randomized controlled trial. *Am J Psychiatry*. 2013;170(10):1134–1142 doi:10.1176/appi.ajp.2013.13030392
2. Fond G, Loundou A, Rabu C, et al. Ketamine administration in depressive disorders: a systematic review and meta-analysis. *Psychopharmacology (Berl)*. 2014;231(18):3663–3676 doi: 10.1007/s00213-014-3664-5
3. Feder A, Parides MK, Murrough JW, et al. Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: a randomized clinical trial. *JAMA Psychiatry*. 2014;71(6): 681–688 doi:10.1001/jamapsychiatry.2014.62
4. Shenk CE, Dorn LD, Kolko DJ, Rausch JR, Insana SP. Prior exposure to interpersonal violence and long-term treatment response for boys with a disruptive behavior disorder. *J Trauma Stress*. 2014;27(5):585–592 doi:10.1002/jts.21962
5. Hazell PL, Tarren-Sweeney M, Vimpani GV, Keatinge D, Callan K. Children with disruptive behaviours II: clinical and community service needs. *J Paediatr Child Health*. 2002;38(1):32–40 www.ncbi.nlm.nih.gov/pubmed/11869398. Accessed November 25, 2014
6. Boris NW, Zeanah CH; Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with reactive attachment disorder of infancy and early childhood. *J Am Acad Child Adolesc Psychiatry*. 2005;44(11):1206–1219. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16239871>. Accessed November 25, 2014
7. Papolos DF, Teicher MH, Faedda GL, Murphy P, Mattis S. Clinical experience using intranasal ketamine in the treatment of pediatric bipolar disorder/fear of harm phenotype. *J Affect Disord*. 2013;147(1–3):431–436 doi:10.1016/j.jad.2012.08.040
8. Berner JE. Intranasal ketamine for intermittent explosive disorder: a case report. *J Clin Psychiatry*. 2007;68(8):1305. Available at: www.ncbi.nlm.nih.gov/pubmed/17854260. Accessed October 1, 2014
9. Wink LK, O'Melia AM, Shaffer RC, et al. Intranasal ketamine treatment in an adult with autism spectrum disorder. *J Clin Psychiatry*. 2014;75(8):835–836 doi: 10.4088/JCP.13cr08917
10. Li N, Liu R-J, Dwyer JM, et al. Glutamate N-methyl-D-aspartate receptor antagonists rapidly reverse behavioral and synaptic deficits caused by chronic stress exposure. *Biol Psychiatry*. 2011; 69(8):754–761 doi:10.1016/j.biopsych.2010.12.015
11. Li N, Lee B, Liu R-J, et al. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science*. 2010; 329(5994):959–964 doi:10.1126/science.1190287
12. Huang EJ, Reichardt LF. Neurotrophins: roles in neuronal development and function. *Annu Rev Neurosci*. 2001;24: 677–736 doi:10.1146/annurev.neuro.24.1.677
13. Zhou W, Wang N, Yang C, Li X-M, Zhou Z-Q, Yang J-J. Ketamine-induced antidepressant effects are associated with AMPA receptors-mediated upregulation of mTOR and BDNF in rat hippocampus and prefrontal cortex. *Eur Psychiatry*. 2014;29(7):419–423 doi: 10.1016/j.eurpsy.2013.10.005
14. Browne CA, Lucki I. Antidepressant effects of ketamine: mechanisms underlying fast-acting novel antidepressants. *Front Pharmacol*. 2013; 4(December):161 doi:10.3389/fphar.2013.00161