Clinical/Scientific Notes

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ADMINISTRATION OF ISOFLURANE-CONTROLLED DYSKINETIC MOVEMENTS CAUSED BY ANTI-NMDAR ENCEPHALITIS

Common clinical features of anti-NMDAR encephalitis are psychiatric symptoms, decreased level of consciousness, seizures, autonomic dysfunction, orofacial dyskinesias, and several types of abnormal movements. The present case report addresses the challenging management of these movement abnormalities with a volatile anesthetic in the prolonged period of intensive care treatment.[1,2]

Level of evidence. This is a single observational study without controls, which provides Class IV evidence.

Case report. A 38-year-old woman developed flu-like symptoms, reversal of circadian rhythm, hallucinations, and acute psychosis and was admitted after a first generalized seizure. During the following days, she developed recurrent generalized seizures and eventually complex partial status epilepticus, became unresponsive, and required mechanical ventilation on the intensive care unit (ICU). At this time, she displayed only subtle involuntary dyskinetic movements restricted to the orofacial region.

Cranial CT and MRI showed no abnormalities. CSF analysis revealed 66 leukocytes/μL (mainly lymphocytes), slightly elevated total protein (0.580 g/L), normal glucose and lactate, and local synthesis of immunoglobulin (Ig)G, IgA, and IgM. Consequently, the tentative diagnosis was meningoencephalitis of suspected viral origin. However, microbiologic workup and most antibody testing proved negative. Instead, CSF and serum analysis for NMDAR antibodies was positive (CSF 1:320, serum 1:3,200). Since pelvic CT revealed a cyst of the right ovary, which was histopathologically classified as a fully differentiated teratoma (ovariectomy was performed 38 days after admission), the patient was diagnosed with paraneoplastic anti-NMDAR encephalitis.

While the epileptic status was aborted by anticonvulsants at this stage, the initial dyskinetic movements exacerbated into prolonged and massive dyskinetic attacks, affecting all parts of the body including the diaphragm. Attempts to control the dyskinesia with tiapride or biperiden failed. Despite eventual sedation with simultaneous IV ketamine, midazolam, and propofol at very high doses, the movement disorder became intolerable because of severe tongue-biting and ventilator incompatibility with multiple life-threatening desaturations.

Finally, with the initial intention of achieving deeper sedation, the volatile anesthetic isoflurane was administered (via the miniature vaporizer AnaConDa, Sedana Medical, Uppsala, Sweden). This resulted in sustainable control of the movement disorder, even after discontinuation of the above-mentioned IV sedatives. Starting at a minimal alveolar concentration (MAC) of 1.90, we reduced gas administration stepwise to a MAC of <0.3, a very low concentration in terms of sedative potency. Characteristic dyskinesia-like episodes, tongue and teeth injuries, and fighting against the ventilator almost completely ceased, allowing nursing, and basic mobilization, as well as spontaneous, assisted ventilation. The treatment was well-tolerated except for a transient slight elevation in liver enzymes without clinically relevant sequelae. When isoflurane was suspended to perform neurologic examination, dyskinetic attacks reappeared within minutes. Volatile sedation was continued for more than 4 months and gradually tapered off after clinical improvement. The control of dyskinesia enabled proper placement of central venous lines facilitating multimodal immunomodulatory therapy after high-dose methylprednisolone (which was the first immunomodulatory therapy 31 days after admission) and IV immunoglobulins including immunoadsorption, plasmapheresis, rituximab, and finally cyclophosphamide. Under this treatment, the antibodies started to decline not before 6 months later (at 1 year follow-up: serum IgG 1:100, no IgM, no IgA; at discharge: CSF IgG 1:32). The patient improved slowly and was transferred to rehabilitation after 13 months in-hospital treatment. On follow-up examination 12 months after discharge, she had nearly fully recovered.

Discussion. Orofacial dyskinesias and abnormal movements are present in more than 85% of patients with anti-NMDAR encephalitis and are frequently difficult to control, resulting in lip and tongue injuries or broken teeth and compromising medical treatment including ventilation.[2] Choreatic movements of the extremities and postural abnormalities are other

common features.[3] Almost invariably, dyskinesia has to be controlled by relaxation or deep sedation with a combination of drugs.[1]

Potential mechanisms of action of isoflurane on dyskinetic movements in NMDAR encephalitis are speculative. Isoflurane may depress spinal motor neurons via glycine receptor potentiation.[4] Moreover, isoflurane specifically increases the NMDA receptor activity.[5] Vice versa, in experimental studies, intrathecally administered NMDAR antagonists led to a MAC reduction of isoflurane.[6] Taken together, a putative specific effect of isoflurane on the NMDAR may have accounted for the very low isoflurane concentrations sufficient to stop the patient's dyskinetic attacks.

The use of volatile anesthetics is still off-label for long-term ICU sedation, even if it was recommended as an alternative sedation in the recent German guideline.[7] To our knowledge, this is the longest application of isoflurane in the ICU ever reported. Although we observed no major obvious side effects, this treatment should only be administered by experienced ICU staff under close multimodal monitoring.

Long-term administration of isoflurane may offer an effective way of controlling dyskinetic movements caused by anti-NMDAR encephalitis.

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