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CORRESPONDENCE

Chronic Diseases and Translational Medicine

A case of ischemic–hypoxic encephalopathy due to oral succinylcholine ingestion

Dear Editor,

Cases of succinylcholine poisoning are rarely seen in clinic, and severe brain damage due to ingestion of succinylcholine is even rarer. Here, we report on a patient who poisoned herself via oral ingestion of succinylcholine, discuss the clinical characteristics, pathogenesis, and treatment of the succinylcholine-related ischemic–hypoxic encephalopathy that this patient suffered, and review the relevant literature. This study aimed to improve clinicians' understanding of ischemic–hypoxic encephalopathy due to succinylcholine chloride toxicity.

Ischemic–hypoxic encephalopathy due to succinylcholine chloride toxicity is extremely rare, with only several (about 3) reports of this condition (ischemic-hypoxic encephalopaty) due to illegal use of succinycholine chloride in China. All of these reports describe poisoning via injection. No previous reports of ischemic–hypoxic encephalopathy due to oral succinylcholine chloride intake have been reported in the literature.

A 31-year-old woman was admitted to a local hospital on January 8, 2019. The patient had experienced a disturbance of consciousness for 8 h. On admission, her blood pressure was measured to be 103/67 mmHg, heart rate 84 beats/min, body temperature 36.8°C, and SPO_2 94%. Physical examination on admission revealed decreased mentation, decreased responsiveness to questions, and poor temporal and spatial orientation. Left and right pupil diameters were 4.5 and 3.0 mm, respectively. Photophobia and decreased vertical eye movements were also noted. The tongue was deviated to the right, dentition was normal, and swallowing and gag reflex were normal. Her limbs were observed to be elevated slightly, but the patient was not cooperative enough for formal muscle testing and the toes were downgoing bilaterally. The rest of the central nervous system exam and cardiopulmonary examination were unremarkable. The patient was physically fit and her medical history was unremarkable; no apparent history of cardiovascular illness, epilepsy, or diabetes was noted. Emergency head CT was unremarkable. Sinus rhythm was noted on electrocardiogram and routine bloods, liver, and kidney function tests and cholinesterase levels were within normal limits. The initial differential diagnoses were suggested as toxic encephalopathy, cerebral infarction, and cerebral sinus thrombosis.

After inpatient admission, lumbar puncture, cerebrovascular imaging, echocardiography, and electroencephalography were all unremarkable. Bilateral lesions in the basal nucleus were revealed on T1- and T2-weighted magnetic resonance imaging (MRI), while fluid-attenuated inversion recovery (FIAIR) sequencing also showed high-intensity signals in the basal nucleus (Figure 1A). On January 13, 2019, the patient's cognitive function declined further and she became less cooperative with cognitive evaluation. She also suffered a seizure and complained of blurred vision postictally. On further examination, she was found to have right gaze deviation, and the adduction was impaired in the left eye. These symptoms gradually improved after 2 days, but blurred vision persisted. The subsequent carotid artery CTA showed no vascular abnormalities. Repeat lumbar puncture and electroencephalography were unremarkable and visual evoked potentials were delayed bilaterally (Figure 1E). Repeat MRI of the brain showed similar bilateral basal ganglion lesions on February 1, 2019.

Findings of the aforementioned examinations effectively ruled out cerebrovascular disease and the diagnosis of toxic encephalopathy was strongly considered. The patient was then administered supplements of vitamin Bs, Mouse Nerve Growth Factor to promote nerve growth, and medication to improve brain circulation and brain metabolism. Meanwhile, other symptomatic supportive treatments were provided and bedside rehabilitation exercises were also conducted. Her symptoms gradually improved. She was discharged two weeks later. Long-term follow-up as an outpatient revealed gradual improvements in cognitive function (Table 1) and self-reported vision. The following three times of repeat MRI of the brain revealed a gradual decrease in the sizes of intracranial lesions (Figure 1B–D, the imaging were taken on April 10, 2019,

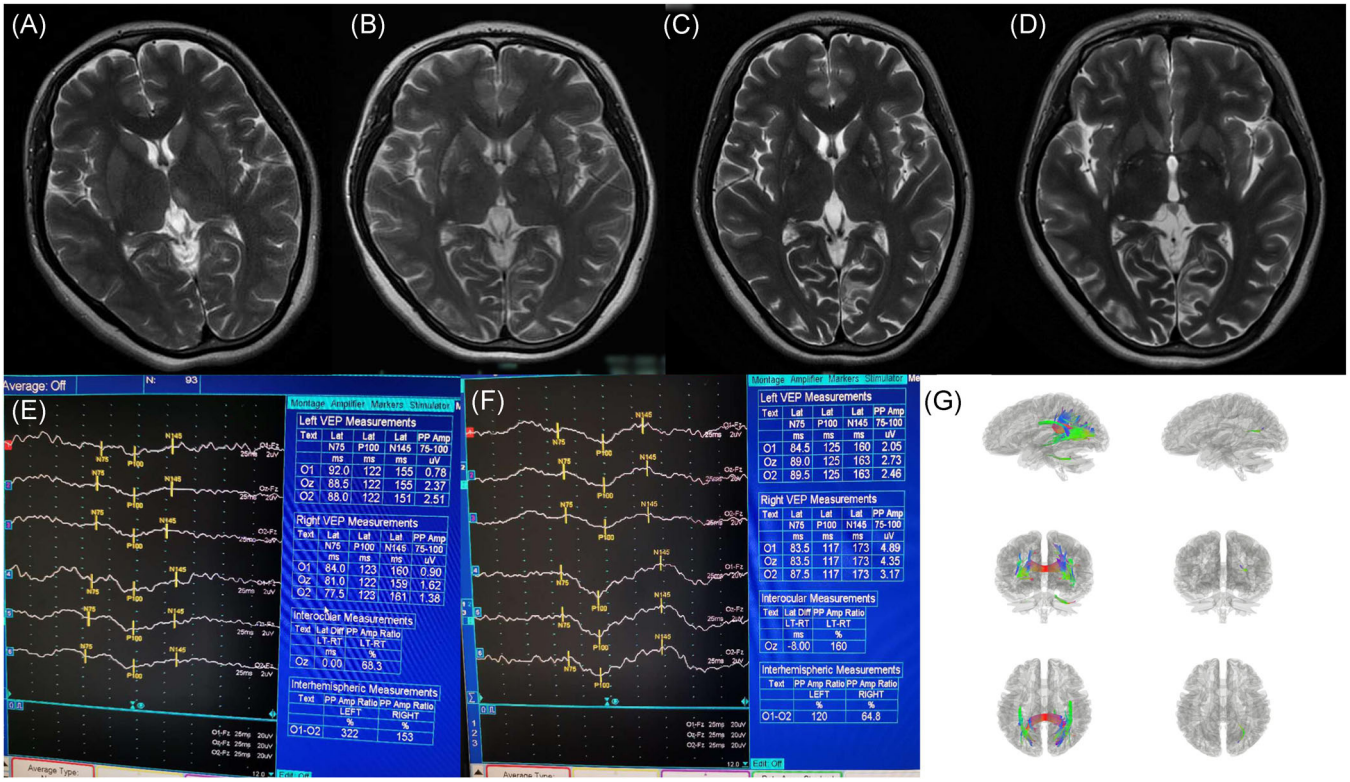

FIGURE 1 Cranial MRI, lesions DTI fiber bundle tracking imaging, and VEP examination of the patient in the hospital and during outpatient follow-up. (A–D) The imaging showed that the lesion signal in the bilateral basal ganglion region gradually decreased and the lesion gradually shrank from January 10, 2019 to April 18, 2020. (E, F) The results of primary VEP showed that the amplitude of the main wave decreased on both sides and the latency period was prolonged on the right side. The repeat EMG showed that the amplitude of the bilateral main wave had decreased a little, and the function of the visual pathway had improved compared with the initial examination. (G) DTI fiber bundle tracking imaging indicated that the increased fiber bundles were mainly located in the corpus callosum and the right cingulate, on comparing the second DTI imaging with the first DTI imaging. The left side showed an increase in white matter bundles of over 5%, and the right side showed an increase in white matter bundles of over 10%. DTI, diffusion tensor imaging; EMG, electromyogram; VEP, visual evoked potential

TABLE 1 Scores of neuropsychiatric tests during the follow-up period

Time	HAMD	HAMA	MMSE	MoCA	Boston-30
2019.03.18	59	41	13	17	NT
2019.05.09	40	24	27	24	NT
2019.11.19	17	13	28	28	26
2020.04.18	4	3	30	30	27

Abbreviations: HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; MMSE, Mini-mental State Examination; MoCA, Montreal Cognitive Assessment; NT, not tested.

August 5, 2019 and April 18, 2020). Secondary brain diffusion tensor imaging (DTI) revealed significantly increased left frontal lobe and corpus callosum fiber bundle connectivity compared with earlier in her disease course (the first DTI was performed 6 months ago, Figure 1G). Meanwhile, the repeat visual evoked potentials revealed improved but still prolonged latency (Figure 1F).

During the outpatient follow-up period, the patient's family members accidentally discovered that she had been purchasing succinylcholine chloride online before initial hospital admission. On inquiry, the patient admitted that she had orally ingested the substance. She was discovered to have had intermittent bouts of depression since the birth of her child as well as having an inharmonious relationship with her husband, quarreling often. Before initial hospital admission, she suffered an episode of extreme depression and ingested the substance on impulse. At this point, the diagnosis of ischemic–hypoxic encephalopathy due to succinylcholine chloride toxicity became definitive.

Succinylcholine chloride is a short-acting, depolarizing skeletal muscle relaxant commonly used as an adjunct to general anesthesia, to facilitate endotracheal intubation and to relax the skeletal musculature during surgery.[1] After absorption into the body, succinylcholine is partially hydrolyzed into succinylmonocholine by pseudocholinesterase in the blood and liver. Succinylcholine chloride is a highly potent nicotinic acetylcholine receptor agonist at the neuromuscular junction and is resistant to acetylcholinesterase. Thus, it cannot be metabolized effectively and results in continuous muscle fiber depolarization that eventually

leads to paralysis.[2] Paralysis typically occurs about 1 min after administration and lasts approximately 7–12 min.[3] If the paralysis persists, it may further inhibit respiration, leading to ischemia and hypoxia of the brain. Hypoxic–ischemic encephalopathy caused by accidentally ingested succinylcholine has also been reported.[4] Also, oral intake of large doses of succinylcholine chloride in animals has been reported to result in severe trembling, paralysis, bowel and bladder incontinence, and death.[5]

The muscle relaxation effect starts from the neck muscles, and gradually spreads to the scapular abdomen and extremities. The muscles of the neck and extremities are the most obvious, followed by the muscles of the face, tongue, and throat and mastication. Respiratory paralysis is not obvious on ingestion of general doses, but high doses result in paralysis of the respiratory muscles.[6] Here, we hypothesize that the patient orally ingested a large amount of succinylcholine chloride and suffered ventilatory dysfunction, decreased oxygenation, and hypoxemia. Central nervous system function was subsequently impaired, and she suffered the aforementioned clinical manifestations. In addition, neuromuscular blocking agents induce the release of histamine, which in turn leads to hypotension, blushing, and tachycardia.[7] Lowered blood pressure also causes cerebral ischemia and hypoxia, which may lead to alterations in consciousness. Organs such as the heart, liver, and kidneys, however, are more tolerant to hypoxia and their function remains relatively unimpaired. This may also explain what happened to the patient. In addition, one of the adverse reactions of succinylcholine is an increase in intraocular pressure; it is known that succinylcholine can cause contraction of the extraocular muscle, resulting in an increase in intraocular pressure,[8] which is thought to be associated with the decreased vision of the patient.

The central nervous system mainly derives energy from aerobic metabolism of glucose and has almost no energy reserves. The brain is therefore very sensitive to hypoxia. Pathomorphological changes of cerebral vessels during acute brain hypoxia induce degradation of separate neurons, gliacytes, and fibers of white matter and often lead to infarctions of different sizes and localizations in the central nervous system. Severe hypoxia and delayed treatment cause irreversible damage to brain tissue, causing localized necrosis, liquefaction, brain atrophy, and other organic changes. In acute ischemia and hypoxic injury, certain tissues in the brain are more likely to be injured and are injured earlier than others. Gray matter is more sensitive than white matter to ischemia and hypoxia; cortical and hippocampal neurons are affected the most, as are the striatum and the cerebellum.[9] The brain stem motor nucleus, however, is more tolerant of hypoxemic conditions.[9] Several previous studies have reported that acute ischemia and hypoxia easily damage the basal ganglia, the periventricular gray matter, the thalamus, and the cortex.[10–14] Demyelinative changes clinically manifest as alterations in consciousness, cognitive impairment, and extrapyramidal symptoms. Diffusion-weighted MR images and T2-weighted images become positive in early stages of a hypoxic–ischemic event.[15] On early brain T1- and T2-weighted MRI, focal lesions can be found, and DWI revealed high signal intensity in the basal ganglia in this patient. Thus, this patient's image display is confirmed to the reported description. In this case, the patient presented with acute alterations of consciousness due to cortical damage and damage to the reticular activating system. Cortical damage likewise resulted in cognitive impairment, and damage to the optic nerve and oculomotor nerve pathways resulted in decreased vision and extraocular movements. Cerebral imaging and clinical examination findings ultimately localized the lesion to the deep gray matter of the bilateral basal ganglia.

This patient's medical history, mode of symptom onset, and initial imaging led to cerebrovascular disease being strongly considered as an etiology, although the patient had no associated risk factors. However, the neuroimaging studies did not suggest intracranial or extracranial vascular pathology. A detailed physical examination and comprehensive workup definitively excluded vascular and metabolic impairments, and toxic encephalopathy was considered as the most likely diagnosis. The evolution of lesions on repeat imaging and a confirmed history of oral succinylcholine chloride ingestion definitively established the diagnosis of ischemic–hypoxic encephalopathy due to succinylcholine chloride toxicity. After symptomatic therapy, the clinic signs of this patient improved gradually, and DTI imaging also showed partial recovery of white matter fiber connections later in the follow-up.

This case suggests that precise diagnosis is a dynamic process that requires continuous collection of supplementary data to establish a basis for diagnostic confirmation. For patients suspected of suffering succinylcholine chloride poisoning, as in this case, eliciting a history of substance intake as well as a detailed diagnostic workup are essential for timely diagnosis and effective treatment. One drawback in this case is that we could not determine from the patient the precise dose of succinylcholine that had been ingested because she had cognitive impairment.

DECLARATION OF PATIENT CONSENT

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest. Professor Guoping Peng is a member of Chronic Diseases and Translational Medicine editorial board and is not involved in the peer review process of this article.

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REFERENCES

1. Foldes FF, McNall PG, Borrego-Hinojosa JM. Succinylcholine: a new approach to muscular relaxation in anesthesiology. *N Engl J Med*. 1952;247(16):596-600.
2. Ahmad M, Khan NA, Furqan A. Comparing the functional outcome of different dose regimes ff succinylcholine when used for rapid induction and intubation. *J Ayub Med Coll Abbottabad*. 2018;30(3):401-404.
3. Ehrenfeld JM, Cassedy EA, Forbes VE, Mercaldo ND, Sandberg WS. Modified rapid sequence induction and intubation: a survey of United States current practice. *Anesth Analg*. 2012;115(1):95-101.
4. Qiu B, Hu ZX, Dong J, Liu YX. Identification of poisoning injury degree of succinylcholine chloride: a case report. *Chin J Forensic Med*. 2014;29(06):600-601 (in Chinese).
5. Ju WB, Geng YY, Gao S, Zhao GY, Gao ZG. The oral toxicological tests of suxamethonium chloride in mice and minks. *Heilongjiang Anim Sci Vet Med*. 2013;5(3):112-113.
6. Abdullah B. Rocuronium versus succinylcholine for rapid sequence intubation. *Acad Emerg Med*. 2020;27(1):66-68.
7. Huang L, Sang CN, Desai MS. A chronology for the identification and disclosure of adverse effects of Succinylcholine. *J Anesth Hist*. 2019;5(3):65-84.
8. Chinese Pharmacopoeia Commission. *Pharmacopoeia of the People's Republic of China*. China Medical Science and Technology Press; 2010:1015-1016.
9. Vannucci RC. Hypoxic-ischemic encephalopathy. *Am J Perinatol*. 2000;17(3):113-120.
10. Kim DM, Lee IH, Park JY, Hwang SB, Yoo DS, Song CJ. Acute carbon monoxide poisoning: MR imaging findings with clinical correlation. *Diagn Inc Interv Imaging*. 2017;98(4):299-306.
11. Fugate JE. Anoxic-ischemic brain injury. *Neurol Clin*. 2017;35(4):601-611.
12. Rowland MJ, Ezra M, Winkler A, et al. Calcium channel blockade with nimodipine reverses MRI evidence of cerebral oedema following acute hypoxia. *J Cereb Blood Flow Metab*. 2019;39(2):285-301.
13. Harteman JC, Nikkels PG, Benders MJ, Kwee A, Groenendaal F, de Vries LS. Placental pathology in full-term infants with hypoxic-ischemic neonatal encephalopathy and association with magnetic resonance imaging pattern of brain injury. *J Pediatr*. 2013;163(4):968-995.
14. Bekiesinska-Figatowska M, Mierzewska H, Jurkiewicz E. Basal ganglia lesions in children and adults. *Eur J Radiol*. 2013;82(5):837-849.
15. Huang BY, Castillo M. Hypoxic-ischemic brain injury: imaging findings from birth to adulthood. *Radiographics*. 2008;28(2):417-617.