Huntington's Disease: Review and Anesthetic Case Management

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Huntington's disease is a dominantly inherited progressive autosomal disease that affects the basal ganglia. Symptoms appear later in life and manifest as progressive mental deterioration and involuntary choreiform movements. Patients with Huntington's disease develop a progressive but variable dementia. Dysphagia, the most significant related motor symptom, hinders nutrition intake and places the patient at risk for aspiration. The combination of involuntary choreoathetoid movements, depression, and apathy leads to cachexia. Factors of considerable concern to the anesthesiologist who treats patients with Huntington's disease may include how to treat frail elderly people incapable of cooperation, how to treat patients suffering from malnourishment, and how to treat patients with an increased risk for aspiration or exaggerated responses to sodium thiopental and succinylcholine. The successful anesthetic management of a 65-yr-old woman with Huntington's disease who presented for full-mouth extractions is described.

Key Words: Huntington's disease; Basal ganglia; Involuntary choreiform movements; Dementia; Autosomal; Personality change; Milkmaid sign; GABA.

Most cases of Huntington's disease in the USA can be traced back to three settlers who came to North America from England in 1630.[1] The families of these men had been persecuted in England for witchcraft. Unfortunately, their problems continued, and several family members were tried and executed for witchcraft in the colonies as well. One of the original three men settled in East Hampton, Long Island, NY. His descendants, the Mulford family, were locally known to be afflicted with a "strange and frightening disease."[1]

As a child, George Huntington was fascinated by the condition affecting the Mulfords. He would visit patients with his father and grandfather, both of whom were family physicians in East Hampton. He graduated from the University of Columbia in 1871 and in 1872 wrote his first and only paper, "On Chorea," that describes the hereditary illness that bears his name.[2] The condition was a keen family interest, having been first recognized by his grandfather, classified by his father, and finally formally described in the literature by George himself.

The incidence of Huntington's disease in the USA and in most western countries is 4–10 per 100,000.[3] In Britain, there are 6000 people with the disease and 20,000 at risk for developing it.[4] Since it is an autosomally transmitted disease, men and women are equally affected. Huntington's disease has the lowest spontaneous mutation rate of any known genetic disorder.[5] It is virtually impossible for someone without an affected parent to develop the illness. The abnormal gene responsible is located in chromosome 4.[6] There is complete penetrance and variable expression—all individuals with an affected parent will eventually manifest some symptoms, provided that they live long enough. Onset is typically between 30–50 yr of age, with great variability.[7] Juvenile onset of the disease (symptoms beginning before age 20) occurs in 10% of affected persons.[8] Death typically occurs 10–30 yr after onset.

Huntington's disease is characterized by a triad of symptoms: personality changes, dementia, and chorei-

Received October 22, 1998; accepted for publication December 22, 1998.

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Anesth Prog 45:150–153 1999

ISSN 0003-3006/99/$9.50
SSDI 0003-3006(99)

form movements.[9] Again, the pattern is variable and does not appear to be familial. Behavioral changes may occur 10 yr before movement disorders begin. Initially, subtle personality changes may be noticed. Affected individuals may display problems with impulsive behavior, substance abuse, criminal activity, and sexual promiscuity.[10] Depression is common early in the illness.[11] Irritability and apathy are extremely common.[12] Choreoathetoid movements (extreme range of motion and jerky involuntary movements, with muscle tone that varies from hypotonia to hypertonia) develop in 95% of people with Huntington's disease.[8] A common early sign of Huntington's disease is the "milk maid sign," in which the hand grip of the affected individual rhythmically tightens and relaxes.[8] People with Huntington's disease develop a wide, swaying gait, and falls are common. Dysarthria is also very common. As the dementia and choreiform movements progress, patients eventually require total care. The constant involuntary movements lead to weight loss and cachexia. The most ominous motor symptom, dysphagia, greatly increases the risk of aspiration. The cachexia, in conjunction with aspiration complications, is the most common cause of death.[7]

Many patients who are at risk for developing Huntington's disease are extremely fearful of their possible affliction and monitor their own motor coordination excessively. However, the intellectual decline and degradation of personality are feared even more than the motor symptoms.[13] The reported incidence of suicide in this group is 7–200 times that of the general population.[14] In a study by Wexler,[13] 50% of people at risk reported that they would seriously consider suicide if they did develop symptoms of the disease. Many of these patients at risk seek out alternative therapies such as herbs and psychic healers. Some become obsessed with the possibility of developing the affliction and become desperate enough to try almost any unproven therapy in the hopes of prevention. The paranoia and delusions that develop can contribute to impulsiveness in their treatment decisions.

The mechanism of the disease is premature destruction of neurons in the basal ganglia. Dementia is related to basal ganglia dysfunction, not disturbances in the cortex. The degeneration of neurons begins in the striatum and progresses outward from there, with the earliest and most severe atrophy occurring in the tail of the caudate nucleus.[15] (The striatum includes the caudate nucleus and putamen, and the basal ganglia includes the caudate nucleus, putamen, globus pallidus, substantia nigra, subthalamic nucleus, and red nucleus.)

To understand the mechanism of the disease process, an understanding of the function of the basal ganglia is necessary. This region functions in the initiation and control of motor movement. Almost all areas of the cortex project to the striatum, with these inputs being excitatory and mediated by glutamate. Output from the basal ganglia is through inhibitory neurons mediated by gamma-aminobutyric acid (GABA); these neurons extend from the internal segment of the globus pallidus to the thalamus. The processing of signals from the cortex involves two major pathways. The direct pathway projects from the striatum to the internal segment of the globus pallidus, and activation results in disinhibition of the thalamic relay neurons that facilitate motor movement. The indirect pathway involves a subset of striatal neurons that project to the external segment of the globus pallidus and restrict the inhibitory projection to the subthalamic nucleus; the net effect is suppression of thalamic relay neuron activity and inhibition of movement. The activity of the two pathways is modulated by a dopamine and GABA loop between the striatum and the substantia nigra with the assistance of cholinergic interneurons in the striatum. Since the basal ganglia is so intimately involved with motor control, it is easy to see how control can be lost with its dysfunction. The early stages of Huntington's disease are associated with destruction of small-sized to medium-sized spiny interneurons that contain GABA; this destruction causes diminishment of GABA and of concentrations of glutamic acid decarboxylase (the synthesizing enzyme for GABA).[15] The result is a net increase in dopaminergic function and a loss of the inhibitory effects from GABA-secreting neurons, with subsequent involuntary choreiform movements.

There is no particularly efficacious treatment for Huntington's disease at the present time. A common agent used is haloperidol, a nonselective antagonist of dopamine receptors. The rationale for its use is to relieve choreoathetoid movements by antagonizing dopamine receptors with dopamine-blocking agents. Fluphenazine has also been used to this effect, and both can attenuate the chorea as well as some of the irritability, hallucinations, and delusions. Unfortunately, these agents are not effective for controlling movements that occur later in the disease process. Attempts have been made, with poor success, to increase available GABA and to increase the effect of GABA at its receptors.[15] To date, there is no effective long-term treatment for the disorder. A promising therapeutic approach involves the use of fetal cell grafts to promote functional recovery from the disorder. Animal models have shown that striatal grafts transplanted to a lesioned caudate nucleus can survive and grow into morphologically mature tissue, with GABA release being partially restored in the globus pallidus and substantia nigra.[16]

CASE REPORT

A 65-yr-old white woman weighing approximately 55 kg presented for full-mouth extractions under general

anesthesia. The patient presented to the operating room in restraints and exhibited spontaneous vigorous choreoathetoid movements and advanced dementia.

The patient's medical history included Huntington's disease and breast cancer. Her surgical history included a left mastectomy in 1996, a gastrostomy tube placement in 1995, and an appendectomy in 1991. Her laboratory values were all within normal limits. The patient's chest radiograph was also noncontributory. The patient had no history of cardiovascular, pulmonary, hepatic, renal, endocrine, or gastrointestinal tract disease. Current medications prescribed to the patient included benztropine (Cogentin), paroxetine (Paxil), aspirin, buspirone (Buspar), hydrocodone–acetaminophen, and promethazine (on an as-needed basis only).

The patient was brought directly into the operating room. She tried to escape out of the bed and to break free from her restraints. Intravenous access was virtually impossible. It was clear that some modifications in the anesthetic technique would be required to successfully complete this case.

The patient was preoxygenated and monitors were placed. A mixture of oxygen and 3% sevoflurane was administered. As the patient became sedated, intravenous access was obtained. To complete the induction, 3 mg morphine, 100 mg lidocaine, and 100 mg propofol were administered. Cricoid pressure was maintained at all times during induction. No muscle paralysis agents were employed, and the patient was nasally intubated without difficulty using a no. 6 nasal Rae endotracheal tube. After induction, anesthesia was maintained with a mixture of oxygen, nitrous oxide, and desflurane supplemented by morphine. The case proceeded uneventfully, and the patient, intubated and spontaneously breathing, was taken postoperatively to the postanesthesia care unit. She was extubated 2 min after entry to the recovery room without difficulty, and her course was uncomplicated.

DISCUSSION

There are numerous anesthetic considerations for the patient with Huntington's disease. Premedication with metaclopramide was not done because of reports of an exacerbation of the choreiform movements.[17] Stewart[8] feels that anticholinergics should also be avoided with this group, since there is a relative balance between dopamine and acetylcholine in the striatum, and anticholinergics may further increase the choreiform movements. If an anticholinergic must be given, glycopyrrolate, a quaternary ammonium that cannot cross the blood–brain barrier, is preferred over atropine, a tertiary amine that can cross the blood–brain barrier. Since meperidine is unique among the narcotics in that it has narcotic, local anesthetic, and anticholinergic properties similar to atropine, its use is also relatively contraindicated.

There are reports that sodium thiopental (STP) can cause prolonged apnea in this population. Davies[18] reported that a man with Huntingtin's disease suffered prolonged apnea for a period of 1 hr following induction with STP. Similarly, Blanloeil reported that a 40 kg, 41-yr-old man induced with STP remained apneic for a period of 1 hr after induction. Although the induction doses of STP in these reports are considered excessive (all were greater than 5 mg/kg), we chose to avoid STP and instead employed propofol, an agent that has not been implicated in the literature for prolonged apnea in this group. Kaufman and Erb[19] reported a case in which a 42-yr-old woman was induced to a state of general anesthesia with 120 mg of propofol and then maintained under anesthesia with a propofol infusion supplemented with fentanyl. The patient reportedly opened her eyes 7 min after the infusion was stopped.

Gualandi and Bonfanti[20] reported a case of prolonged apnea of 2 hr following administration of 50 mg succinylcholine to a woman by intubation. Conversely, Brown and Cross[21] administered succinylcholine without incident to two brothers afflicted with the disease who had normal dibucaine numbers. Similarly, Costarino and Gross[22] administered succinylcholine at a dose of 0.6 mg/kg without prolonged apnea to an afflicted patient in a rapid-sequence induction technique. It appears, therefore, that succinylcholine can be used without incident for patients in this group. Since we did not require muscle relaxants for acceptable intubating conditions, we chose to eliminate their use in this case.

Another anesthetic consideration in this patient population centers around the dysphagia that is so common to this group. Dysphagia is probably the most significant motor symptom because it hinders the nutritional intake of those with Huntington's disease and places them at risk for aspiration. Therefore, at the termination of the anesthetic, airway reflexes must be assurred to minimize the risk of postoperative aspiration. We chose to use sevoflurane for induction (since desflurane is a modest airway irritant) and then switched to desflurane for the remainder of the procedure. This allowed for a more rapid recovery and faster return of airway reflexes, thus minimizing the risk of aspiration.

SUMMARY

An in-depth review of Huntington's disease and a description of the successful anesthetic management of a patient in the advanced stages of this disease is pre-

sented. After gaining initial control and intravenous access with sevoflurane sedation, we chose to use the sedative–hypnotic propofol to complete the induction and minimize the risk of prolonged apnea, however slight that may be. The authors believe, however, that sodium thiopental in the induction range of 3–5 mg/kg (as recommended by Stoelting and Miller[23] in their textbook, *Basics of Anesthesia*) is acceptable for use, since all cases of prolonged apnea reviewed occurred at doses of approximately twice the recommended range. Similarly, we avoided the use of succinylcholine and all other muscle relaxants because we were able to establish acceptable intubating conditions without them, again adding to the simplicity and safety of the anesthetic. Desflurane and a minimal amount of morphine allowed a rapid recovery and an uneventful postoperative course. A thorough knowledge of the disease process and the anesthetic implications allowed us to safely manage the anesthesia in a patient in the advanced stages of Huntington's disease.

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