Case Report

Sudden unexpected nocturnal death in Chiari type 1 malformation and potential role of opioid analgesics

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Abstract

Background: Chiari malformation type 1 (CM1) is a common congenital anomaly of the craniocervical junction. CM1 is reported to run a usually benign course and patients typically experience no symptoms or chronic, slowly progressive symptoms. However, recent reports indicate that a subset of patients with CM1 may present with acute deterioration and sudden unexpected death (SUD). We report a case of SUD during sleep in a young man with CM1, which we believe was related to the administration of common and therapeutic doses of narcotic analgesics for the management of pain. We will clarify the pathophysiology of acute deterioration and SUD in CM1 and the possibility that the adverse effects of opiate analgesics likely were the leading cause of death in our patient.

Case Description: In this review, we present a 29-year-old male with worsening headache secondary to previously diagnosed CM1. The patient died suddenly and unexpectedly after administration of common and therapeutic doses of narcotic analgesics for the management of pain.

Conclusion: The mechanism(s) of acute neurological deterioration and sudden death in patients with CM1 remains poorly understood. We believe the rapid fatal deterioration in our patient following administration of opioids suggests that this category of medication may cause sudden unexpected "neurogenic" cardiac death in CM1 patients by inducing sleep-related breathing difficulties and associated hypercapnia. Hypercapnia by further increasing intracranial pressure can result in a sudden pressure-induced decompensation of the cardiopulmonary control centers in the brain stem and cause instantaneous cardiorespiratory arrest.

Key Words: Chiari malformation, hydrocephalus, isolation of fourth ventricle, opioid analgesics, sudden unexpected death

INTRODUCTION

The adult type Chiari malformation or Chiari malformation type 1 (CM1) is a common congenital anomaly of the craniocervical junction, often defined as descent of the cerebellar tonsils ≥5 mm below the foramen magnum.[6,25] A majority of patients with CM1 are asymptomatic.[25] However, depending on the the degree and severity of malformation symptoms may develop during late childhood or adulthoo.[25] Those who

become symptomatic commonly present with headache and sub-acute or chronic symptoms related to slowly evolving compression of the neural tissues within the region of the craniocervical junction.[2] Nonetheless, a subset of patients with CM1 may present with acute neurological deficit or sudden unexpected death (SUD).[1,15,23,25,27,29,31-33] The aim of this report is to describe a case of sudden unexpected nocturnal death (SUND) in a young man with CM1 associated with the administration of common and therapeutic doses of narcotic analgesics for the management of headache, and to elucidate the etiopathology of SUND in the setting of narcotic analgesics and CM1. We also emphasize basic strategies that may prevent SUND in people with CM1.

CASE REPORT

A 29-year-old African-American male was admitted to our hospital because of headache associated with nausea, vomiting, and blurred vision. Intermittent headaches over the preceding 4 years were ascribed to CM1. In the month prior to admission, the patient's headaches had increased in frequency and in severity. He described the headaches as pounding and rated the intensity of the pain as 10 on a scale of 0 to 10, where 10 is the most severe. The pain began in the occipital region and extended to the forehead unrelated to coughing or straining. A few days before admission, nausea, vomiting, and blurred vision accompanied some of the episodes of headache. As the patient's headaches continued to worsen, he was admitted to an outside hospital. Magnetic resonance imaging (MRI) of the brain showed an 18 mm cerebellar tonsillar herniation and a disproportionately large communicating fourth ventricle with dilated but stable ventricular system, and no change from previous studies [Figure 1]. Cervical spine MRI was normal. In light of the patient's worsening symptoms, he was transferred to the University Hospital of Brooklyn for surgical intervention. The patient did not report limb weakness, paresthesia, or breathing difficulty, nor a history of cardiac arrhythmia, hypoglycemia,
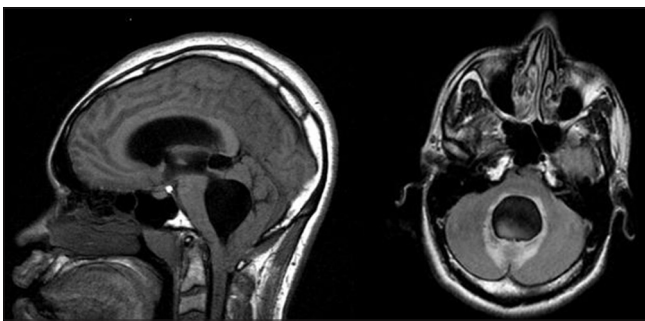

Figure 1: T1-weighted sagittal MRI of the brain (left) reveals inferior displacement of the cerebellar tonsils 18 millimetrs below the level of C1 consistent with a Chiari I malformation and and a pear-shaped disproportionately large communicating fourth ventricle. Axial T1-weighted MRI (right), note enlarged fourth ventricle

alcohol abuse, or epilepsy. The patient had no family history of neurologic or cardiac disease. Preadmission medications included variable amounts of acetaminophen, hydrocodone, and ibuprofen for headache control.

On evaluation, the patient's vital signs were normal, the lungs were clear and no bradycardia or cardiac pauses were observed. He was alert and oriented. There was no nuchal rigidity to passive flexion of the neck. The pupils were equal and reactive to light. The optic disc margins were sharp and the visual fields were normal. The remainders of the physical and neurological examinations were normal except for mild bilateral horizontal gaze-evoked nystagmus and a slightly unsteady gait. Laboratory studies, including complete blood count, serum electrolytes, blood glucose, urine specimen, and the results of the blood pressure and heart rate monitoring were normal. The patient was considered in stable condition because of a stable ventricular size with stable vital signs, relative preservation of motor and sensory pathways, and no respiratory stress during alertness. In light of his presumed stable condition, medical management of the patient's acute cephalodynia rather than urgent surgery became the priority. He was disconnected from the vital signs monitor and admitted to the neurosurgical ward for surgery to be scheduled after presurgical risk assessment testing, including routine laboratory studies, chest X-ray, and electrocardiogram. Medical management of the patient's pain during the first 24 hours of admission, starting in the emergency room and continuing in the neurosurgical ward, included 60 mg of codeine by mouth, 650 mg of acetaminophen by mouth, 10 mg of intravenous (IV) morphine sulfate (2, 4, and 4 mg at 4-hour intervals), 4 mg of IV hydromorphone, and 10 mg of IV metoclopramide. At 4:10 am on the second day of hospitalization, about 26 hours after admission, the patient complained of severe headache. Upon rising from bed, he became incontinent of urine. After the patient was placed in bed, hydromorphone 4 mg and metoclopramide 10 mg were given IV. At 8:00 am, the patient was found cold and pulseless in bed with no recordable blood pressure or cardiac activity on electrocardiogram and was pronounced dead. A complete postmortem examination revealed a CM1 with mild hydrocephalus without uncal herniation or syringomyelia. Toxicological screening was negative. The cause of death was not identified, but myocardial infarction, cardiac conduction defect, and suffocation due to vomiting or choking were convincingly excluded.

DISCUSSION

SUD has no agreed universal definition. Furthermore, the classic descriptions of the SUD do not account for recent advances in science and technology and are mainly clinical. The World Health Organization generally defines

SUD or its synonyms as natural and unexpected death within 24 hours of the onset of an illness symptom irrespective of the underlying pathology. In addition, death occurring unwitnessed within 24 hours of a person being seen alive and functioning normal with no diagnosis after postmortem examination is regarded as SUD.[27] Sudden and unexpected death of adolescents or adults during sleep is defined as sudden unexpected nocturnal death syndrome (SUNDS) or dead-in-bed syndrome.[2]

The SUNDS long puzzled those interested in its prevention and management. The detection of gene mutations causing long QT syndrome established that cardiac arrhythmia may cause sudden unexpected nocturnal death (SUND) in young individuals.[2] Therefore, cardiac arrhythmias are mainly discussed in the context of SUNDS in young adults. The other well-known etiologies of adults SUNDS include coronary artery disease, ischemic and nonischemic heart disease, pulmonary embolism, intracerebral bleed, hypoglycemia, and epilepsy.[7,12,27] The patient's death occurred unexpectedly before clinical workup could be completed, but the history, clinical data, imaging studies, postmortem, and the laboratory findings provided sufficient evidence to justify exclusion of all these possibilities.

Recently chronic hydrocephalus, CM1 and other disorders of the craniocervical junction have been implicated in the pathogenesis of SUD (neurogenic SUD).[1,15-17,23,27,29,31,33] The postmortem studies in patients with SUD attributed to the craniocervical junction disorders have identified a variety of medullary lesions as the only apparent cause of death.[16,17] The most notable finding shared by the majority of these cases has been gross preservation of motor and sensory pathways, suggesting that a defect in the brainstem autonomic cardiorespiratory centers and inability of these centers to respond to typical homeostatic stress plays an important role in the etiopathology of sudden death associated with craniocervical junction disorders.[14,15] Automatic respiration control, predominantly during sleep, depends on the activity of chemoreceptive neurons that respond to hypoxia, hypercapnia, and pH in the blood and cerebrospinal fluid (CSF) and is chemically regulated by both peripheral chemoreceptors and chemosensitive centers within the medulla.[3] With a partial impairment of the medullary chemosensitive centers, the stimulating action of carbon dioxide upon the brainstem respiratory center and ventilatory responses to hypercapnia and hypoxia-due to a greater hypercapnic ventilatory response during wakefulness as compared with sleep-remains preserved during alertness.[3,8,21] Thus, the victims of neurogenic SUD and neurogenic SUND, due to the preservation of motor and sensory pathways and relatively normal ventilatory response, are generally considered healthy with no or minimal neurological signs prior to their event.[3,8,16,21] Nevertheless, ongoing compromises of autonomic centers in the brainstem related to the nonspecific structural lesions of the craniocervical junction can lead to a wide variety of autonomic disturbances including emesis, cardiorespiratory problems, sleep apnea, sudden death, and death during sleep.[4,8,14,16,21] Short and long-term opioid use is also associated with several potential adverse effects and toxicities, including respiratory depression and sleep-related breathing disorders, predominantly central sleep apnea.[24,35] There is evidence that even addition of a small dose of opiates at night can precipitate central sleep apnea in patients who were receiving chronic opiate therapy without history of sleep apnea.[24] Nocturnal hypoxia and hypercapnia associated with sleep-related breathing disorders can cause elevation of intracranial pressure (ICP).[26] Increased ICP in patients with CM1 can give rise to further downward displacement of the brain into the spinal canal and additional compression of vital brainstem structures and the upper spinal cord. These effects, by further destabilizing the cardiopulmonary control centers in the brainstem during sleep, may result in lethal brainstem compression and neurogenic SUND.[24,26,27] These data support our view that the immediate cause of sudden death in this patient, with CM1, chronic hydrocephalus, and a long history of taking opioids, was the exacerbation of sleep-related breathing deficiencies as a consequence of additional opioid administration.[24] The final result was increased $PaCO_2$, which elevated the patient's cerebral blood flow during sleep, further expanded intracerebral volume, and resulted in a pressure-induced decompensation of cerebral neuronal pathways, resulting in disturbances of the cardiopulmonary control centers in the brainstem, and neurogenic SUND.[24,26,27]

Consensus on the effective management of patients with CM1 is still evolving. Since many patients with CM1 are identified after MRI imaging for an unrelated disorder, the determination of which patients with CM1 require treatment can be challenging.[23] Furthermore, the management of patients with CM1 who present with hydrocephalus and headaches alone is not well defined. Nonetheless, surgical intervention is indicated when it is certain that the patient is symptomatic and CM1 is the cause of the symptoms. Sleep apnea, hydrocephalus, acute neurological deficits, and headaches respond to proper surgical intervention.[4,9,13] Posterior fossa decompression by suboccipital craniectomy combined with laminectomy of the upper cervical segments in patients without ventricular dilatation and ventriculoperitoneal shunting for management of hydrocephalus associated with CM1 are advocated as the treatment of choice.[4,9,13] Similarly, there are reports that minimally invasive endoscopic third ventriculostomy is an effective and durable method of treatment for CM1 associated with hydrocephalus and a subgroup of patients

without evidence of hydrocephalus.[11,18,19] Therefore, we believe that timely endoscopic third ventriculostomy or standard ventriculoperitoneal shunting, coupled with judicious use of pain medications and more closely monitored respiratory function, would have averted death of the patient in this report.

The identification of a pear-shaped enlarged fourth ventricle in our patient raised the possibility of isolation of fourth ventricle or disproportionately large communicating fourth ventricle (DLCFV). Isolation of fourth ventricle develops when the occlusion of inlet and outlet of the fourth ventricle isolate the fourth ventricle from the rest of the ventricular system and subarachnoid spaces. Continuation of CSF production by the fourth ventricle choroid plexus in a closed ventricular space results in cystic dilatation of the fourth ventricle, which requires appropriate medical and surgical attention.[28] When CT or MRI examinations show a communicating hydrocephalus with an excessively enlarged fourth ventricle, which is not "isolated" from the remaining ventricular system, the term DLCFV is used.[10] In patients with CM1 anatomical variations at the level of the foramen of Magendie, obstruction of the foramen of Magendie by an arachnoid veil (may not be evident on imaging studies), congenital atresia or idiopathic stenosis of the foramina of Magendie and Luschka are considered usual etiologies of chronic hydrocephalus with DLCFV.[22,30,34] We were unable to confirm occlusion of the aqueduct or the foramina of Magendie and Luschka by imaging or postmortem examination. However, these conditions are considered rare and their diagnosis may be difficult. Moreover, studies conducted to date have shown endoscopic third ventriculostomy is an effective treatment for Chiari malformation associated with hydrocephalus with or without DLCFV.[11,18-20]

CONCLUSION

We believe basic patient care and medical management of patients with CM1 should include prudent long-term monitoring of newly identified patients with CM1 because of the potential risks for developing syringomyelia, sleep apnea, or other new symptoms. Timely surgical intervention is indicated when the patient becomes symptomatic and CM1 is the cause of the symptoms. Minimally invasive endoscopic third ventriculostomy should be considered for hydrocephalus associated with CM1. Nonopioid analgesics, including acetaminophen and nonsteroidal antiinflammatory drugs, should be the first-line agents in the management of pain in patients with CM1. Opioids may add to the alteration of the central respiratory rhythm generators and produce changes that can be sufficient to cause death. If pain is severe and requires treatment with opioids, adjunctive nonopioids may be used and the physician should be alert to possible side effects. There are substantial adverse events and harm to patients from inappropriate medical management, and many are deadly.[5] Therefore, more attention should be focused on the safe and appropriate use of all medications and particularly opioids for the treatment of pain to minimize the risks associated with medical care.

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Commentary

At the center of this paper is the question about what exactly is Chiari malformation.

It was first described by a pathologist who observed the descent of the cerebellar tonsils in cadavers of individuals with myelomeningocele. Hence, Chiari malformation was for long associated with spina bifida. In the 1938 Penfield[1] described the case of a young woman who could not wink whom he operated under the presumptive diagnosis of CP angle tumor. Penfield observed that the tonsils were descended; as the patient had a thoracic meningocele Penfield linked both conditions. In the following years, other papers[2] described the descent of the cerebellar tonsils in individuals without any form of spina bifida. For many, the etiology is a disproportion between the cerebellar volume and that of the posterior fossa, nonetheless along the years other alternatives have been presented. I recommend reading Milrohat.[3]

Nowadays it is fair to say that we are in a position to defend our opinion about what we believe is the etiology of the descended tonsils, but we are not remotely near of understanding the pathophysiology of the gamut of symptoms that we, correctly or not, have attributed to the descend of the cerebellar tonsils.

The question raised by any clinical paper on Chiari is: are descended cerebellar tonsils sufficient for diagnosing Chiari or we need some symptoms associated to the finding?

How shall we weight the symptoms and the imaging? This question posed in the real world of our daily practice, not on the ideal world of the bureaucrats.

Nowadays we order brain MRI for a simple headache. So when the patient comes with headaches, not necessarily provoked by a Valsalva, but has evidence of Chiari malformation, do we proceed and decompress?

Do we act to preempt the possibility of more severe consequences? Are headaches just the beginning of a process such as we believe colon polyps are? Or, headaches do not "progress" into something more ominous as described in this paper.

How can we define the many subsets of Chiari patients that while having identical MRI have a different clinical picture?

The answer to this question will come through a thorough epistemological inquiry about causality.

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