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Sudden Unexpected Death Caused by Neuroepithelial (Colloid) Cyst of the Third Ventricle

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ABSTRACT: Sudden unexpected death caused by a colloid cyst of the third ventricle in young apparently healthy persons is an uncommon phenomenon that nevertheless occurs regularly in medical examiner's cases and may occur in general hospital pathology practice. This entity has not received proper attention in the general or forensic pathology literature in spite of the fact that sudden death has been appreciated in the clinical literature for many years. We report four cases of sudden unexpected death in young persons whose only major previous complaint was that of chronic relapsing headaches. Because of the sudden and unexpected nature of their deaths, these cases came to the attention of the medical examiner and the colloid cysts were discovered at autopsy. The history of this lesion, its histogenesis, its pathological physiology, and the experiences of others are reviewed.

KEYWORDS: pathology and biology, brain, death, colloid cysts

The occurrence of sudden and unexpected death caused by neuroepithelial (colloid) cysts of the third and fourth ventricles has been appreciated since the thesis of Grossiord [*1*] in 1941, in which he reported that 14 of his 72 reviewed cases died in this manner. Other reviews and reports cite instances of acute fatal outcome with this lesion [*2–5*] but with less frequency. This catastrophic complication from colloid cysts, however, is only infrequently highlighted in the general pathology or forensic pathology literature [*6, 7*] and is mentioned in only one textbook, in a now out-of-print but still authoritative text on forensic medicine [*7*]. We have unexpectedly encountered this lesion four times in the past three years in the case material of the Office of the Medical Examiner of Cook County, Illinois, and we report our experience for the benefit of others.

Case Reports

Case 1

A 30-year-old white female presented at the emergency room of a local hospital at about 6:55 p.m. complaining of headache, nausea, and a feeling of malaise persisting for three days. Upon admission her temperature was 37.8°C (100°F) and she appeared to be suffering from a cold. She had been vomiting for the past 24 h and was quite fatigued. The patient re-

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ported that she had had "tension" headaches for many years for which she had taken a variety of medications (Equagesic® and Sudafed®) but had never been extensively studied for her headaches. She was admitted, given Tylenol®, Valium®, and Dalmane® for her headache, put to bed, and informed that more tests would be done in the morning. At about 6:30 a.m. the next morning the patient was found dead in her bed. The body was taken to the Office of the Medical Examiner, Cook County, Illinois, where an autopsy was performed.

The autopsy revealed only minimal pulmonary congestion and no obvious anatomical cause for the death. The brain was removed and fixed in 10% formalin (no brain weight was recorded). Toxicologic studies showed trace amounts of morphine and codeine as well as 1.6 mg/100 mL of meprobamate in the blood. The brain appeared swollen with flattened gyri, narrowed sulci, and the floor of the third ventricle bulging downward. Coronal sections of the brain revealed severe symmetrical dilation of the lateral ventricles, fenestration of the septum pellucidum, and a 1.5-cm colloid cyst occluding the foramina of Monro.

Case 2

A 33-year-old white female who had been suffering from headaches for two years had had two or three episodes of severe headache associated with nausea and vomiting leading to sudden collapse at home. She was brought to the emergency room of a local hospital by ambulance. Upon arrival at the hospital the patient was comatose, experiencing difficulty with breathing, and had fixed and dilated pupils. She was thought to have suffered an acute intracranial hemorrhage. She was placed on a respirator because of coma and respiratory incompetence. Because of a deteriorating and eventually isoelectric electroencephalogram, the respirator was turned off after a few hours, and death was declared. The body was taken to the Office of the Medical Examiner, Cook County, Illinois, where an autopsy was performed.

The general autopsy revealed no anatomic cause of death. The heart was not enlarged and coronary vessels were normal. The brain was removed and fixed in formalin. Toxicologic studies gave negative results. The brain revealed no subarachnoid hemorrhage but was swollen, with the gyri flattened and the sulci narrowed. Coronal sections showed grossly dilated ventricles, a fenestrated septum pellucidum, and a 1.5-cm colloid cyst obstructing the foramina of Monro.

Case 3

A 30-year-old black male was found unresponsive at 8:00 a.m. in the bathroom by his wife. He had been unable to sleep the night before because of a severe headache and had apparently been vomiting. An ambulance was summoned but the patient was dead on arrival at the emergency room of a local hospital. The patient was said to have suffered from migraine headaches since the age of 13 years and had been treated with Cafergot® and Sinequan® in the past. The body was taken to the Office of the Medical Examiner, Cook County, Illinois, where an autopsy was performed.

An autopsy revealed mild coronary atherosclerosis with 30 to 40% narrowing of the left anterior descending coronary artery. There were superficial bruises above one eye. The brain was removed and fixed in formalin. A blood sample was taken for toxicologic examination and the results were negative. The brain was swollen, the gyri flattened, and the sulci narrowed. Coronal sections revealed greatly dilated lateral ventricles and a colloid cyst about 2 cm in diameter obstructing the foramina of Monro (Fig. 1).

Case 4

A 17-year-old black female had been having severe headaches that were intermittent on 22 Dec. 1979, and she went to an emergency room where she was given Tylenol #3 and sent

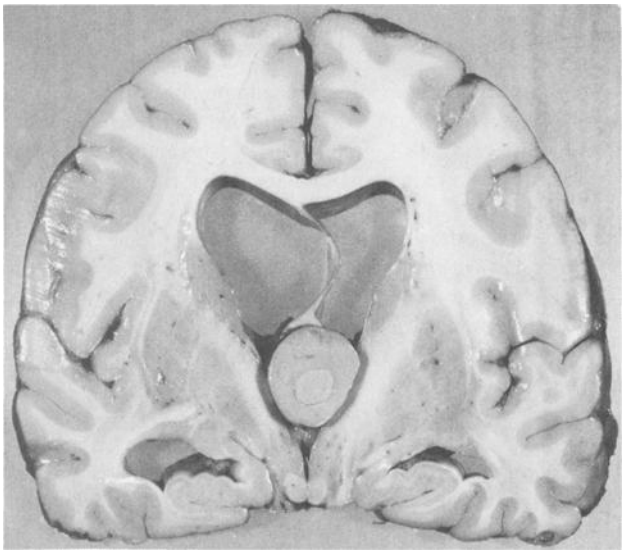

FIG. 1—*This photograph illustrates the typical features of the lesions seen in each of the cases. In this case, Case 3, the colloid cyst is about 2 cm in diameter, occupies the entire space of the foramina of Monro, and is intimately associated with the choroid plexus and tela choroidea.*

home. The next morning the patient experienced nausea and vomiting and was unable to stand. The patient was again brought to the emergency room of a local hospital where she was found to be stuporous and to have a dilated, nonreactive left pupil. Her breathing was irregular, and she was admitted with a diagnosis of probable intracranial hemorrhage or brain tumor. About 8 h after admission the patient had a cardiorespiratory arrest, after which she could not breathe on her own. She was placed on a respirator. Carotid angiography showed no cerebral circulation. The respirator was turned off about an hour later and death declared. After a general autopsy that showed no significant findings had been performed in another hospital, the body and organs were brought to the Office of the Medical Examiner, Cook County, Illinois.

The brain was cut after fixation in formalin and revealed dilated lateral ventricles and a 1.8-cm-diameter colloid cyst obstructing the foramina of Monro. Toxicologic analysis gave negative results.

Discussion

Colloid cysts of the third ventricle should probably be considered as one of a variety of possible neuroepithelial cysts within the nervous system [*8, 9*]. The precise origin of these lesions is controversial; it has been said they are remnants of the paraphysis, an organ of uncertain function that appears at peak development by the tenth week of gestation but is totally degenerated by the fourth month in utero in man and probably also in other higher animals. In reptiles and amphibians it is observed as an epithelial organ in the roof of the third ventricle even in adult animals [*10–13*].

Cysts of the region of the third ventricle, fornix, and foramen of Monro have been reported since 1858, when Wallmann [*14*] noted their occurrence apparently for the first time. Colloid cysts, as they have appropriately been called, vary in size from a few millimetres to several centimetres in diameter and usually contain a gelatinous mucoid substance that becomes coagulated after formalin fixation to a rubbery consistency. The protein concentration of the cyst has only rarely been analyzed, but in one instance it was reported to have

been 72 mg/100 mL [*15*]. The cysts are lined by low cuboidal cells that may be ciliated, squamous, or columnar, or may contain mucus [*8,9,12,13*]. Ultrastructurally the lining cells contain cilia or basal bodies or both [*8,9,11,13*], microvilli [*8,9,11*], intercytoplasmic dense specialization, and junctional complexes [*8,9*]. A relationship to so-called arachnoidal cysts has been proposed, but those lesions generally are more laterally placed and do not possess the typical epithelial lining nor the intimate relationship with the foramina of Monro of most colloid cysts [*8,9,13*]. The very close anatomic association of these cysts with the choroid plexus and its tela chorioidea implies origin from that structure. This argument is bolstered by the reported association of a colloid cyst of otherwise classical appearance with the choroid plexus of the fourth ventricle [*16*]. Nevertheless much of this controversy is avoided by the use of the nonspecific term neuroepithelial (colloid) cyst, regardless of location.

Colloid cysts have been reported in patients of a wide range of ages, from 1 to 69 years, but peak incidence is between 20 and 40 years [*2,3,5,6*]. Males seem to be affected at least three times more frequently than females [*10*]. Symptoms usually include headache, which may may be intermittent or positional, may be unassociated with any other sign or symptom, or may include any or all of the following: disturbance of gait or of mentation, nausea, and vomiting, sometimes projectile. Also reported, though less commonly, are blurring of vision, dizziness, tinnitus, hypothalamic dysfunction, siezures, and incontinence [*2–5,17*]. In children, head-bobbing tremors originally referred to as "the bobble-head doll" sign have been reported [*15,18*].

Neurological examination, when performed, may reveal papilledema, cerebellar signs and nystagmus, Babinski signs and hyperreflexia or hyporeflexia, and sixth nerve palsy [*2,3*]. Plain skull films or angiograms rarely demonstrate the lesion, but ventriculograms, pneumoencephalograms, and most recently, computerized axial tomograms (CAT scans), with and without contrast infusion, may clearly demonstrate the lesion as a mass of lower or greater density than surrounding brain [*2,19–21*], usually in the region of the foramen of Monro in the center of the brain.

Treatment of colloid cyst is surgical removal with or without associated shunting of the hydrocephalic ventricles, caused, no doubt, by the tendency of the cyst to occlude the foramina of Monro. Several surgical approaches to the lesion have been reported, the earliest of which is the operation of Dandy [*2,17,21*].

In medicolegal practice, the phenomenon of sudden and unexpected death is a constantly recurring problem that challenges the forensic pathologist. In most instances the cause of death is demonstrated in or ascribed to the cardiovascular, respiratory, or gastrointestinal system. In most series, lesions of the central nervous system that cause sudden unexpected death are much less common than cardiorespiratory or gastrointestinal causes but include rupture of an aneurysm, hypertensive hemorrhage, meningitis, or massive infarction. Sudden death caused by brain tumor comprises only a small number of cases [*22,23*].

Colloid cyst of the third ventricle as a cause of sudden death has not received proper emphasis in the forensic or general pathology literature if the frequency of this lesion in our experience is any indication of its commonnness. The most recent review of this lesion is the report of DiMaio and DiMaio [*6*] in 1974, who describe sudden and unexpected deaths in three patients: a 14-year-old male, a 23-year-old male, and a 19-year-old female. The histories of these individuals are very similar to our own cases and illustrate the chronic, unsuspected, and fatal nature of the lesion.

A similar report is that of Nelson and Haymaker [*24*], who describe the sudden and unexpected deaths of two military aircraft pilots and one passenger on a commercial aircraft who had had headaches for years but who had their final exacerbation of their colloid cysts while in flight in the pressurized compartment of an aircraft. The true nature of their condition was not appreciated until an autopsy was done.

As to the incidence of colloid cyst in a medical examiner's or coroner's case load, it is difficult to assess. The DiMaios report [*6*] only three cases among 17 404 forensic autopsies

over a ten-year period. In our experience the incidence is much greater, four cases in less than three years, during which time some 8000 autopsies were done. We have no reliable figures concerning the number of brain tumors that cause unexpected death, but the reported incidence of colloid cyst is very low, since no cases were found in a series of 109 brain tumor cases [*25*] and only three were found in 58 brain tumor cases in another medical examiner's series [*6*]. Nevertheless, there is every reason to suspect that this lesion occurs regularly but has been frequently overlooked, probably because of the lack of awareness of its existence as an entity capable of causing sudden death and the relative obscurity of the tumor.

The mechanism by which colloid cysts cause sudden unexpected death is probably based on an acute decompensated obstructive hydrocephalus. Given the location of the lesion, as others have suggested [*2,5,6,17*] it may act as a "ball valve" within the foramina of Monro, intermittently blocking the flow of cerebrospinal fluid (CSF) from the lateral ventricles until the mass becomes firmly lodged in the foramen, totally preventing egress of fluid. When outflow of CSF is prevented it continues to accumulate at the rate of about 0.3 to 0.4 mL/min [*26*] and to be partially reabsorbed along the ependymal surface at a rate difficult to determine in these cases.

An equilibrium of sorts is established; it eventually shifts in favor of CSF accumulation and expansion of the ventricles with stretching and then tearing of the septum pellucidum. This equilibrium may further shift as a result of the tumor pressing on the venous drainage of the choroid plexus, which may enhance CSF production, thus worsening an already bad situaton [*5*]. The increased internal pressure of the ventricles is exerted on the CSF, which is external to the surface of the brain and which can be reabsorbed by the arachnoid villi and spinal roots. This removal of CSF allows the brain to expand and accommodate itself to the rising pressure and mass effect of the obstructed ventricles. This effort at homeostasis, in time, is exhausted; then no more CSF can be absorbed and pressure rises in the brain stem as a result of the diminishing column of spinal CSF and progressive herniation. Progressive expansion and alterations in respiration and function of the third cranial nerve are noted, and eventually coma and respiratory failure and death occur [*2*].

It is difficult to determine the interval of time between blockage of CSF flow and death, but the first phase of compensation following blockage must last many hours. However, once signs of severely increased intracranial pressure are noted, there is probably little time remaining when intervention will be possible. Furthermore, it is not known what factors initiate or allow the decompensated phase of this tumor. It is noted that, in most cases, once symptoms begin from a colloid cyst exacerbations of headache and other neurological symptoms recur with increasing regularity and severity.

As seen above, most of the symptoms of colloid cyst are not diagnostic for this condition and may be misinterpreted as migraine headaches, transient ischemic attacks or small strokes, a brain tumor of another sort, chronic sinusitis, dementia, or behavioral abnormality such as hysterical reaction. The clinical diagnosis rests on awareness of the possibility of this lesion and the use of computerized axial tomography and its associated noninvasive techniques. For the pathologist a complete autopsy with examination of the central nervous system in cases of sudden unexpected death associated with headache should be performed and will usually demonstrate the lesion and immediately suggest the diagnosis.

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