Intracranial causes of death and their mechanisms

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Abstract

Intracranial causes of death trail in incidence behind cardiovascular and respiratory system pathologies in most deaths occurring in hospitals. When intracranial pathology becomes more important is in the forensic arena, where it is often supposed that in troublesome cases such as sudden and unexpected deaths or where there appears to be no anatomic cause of death revealed in the general autopsy, the cause must be in the brain. This hope is often dashed after a careful neuropathological examination. Intracranial causes of death are discussed here mostly within the context of the forensic exercise where complex processes may be involved such as: electrophysiological dysfunctions; disorders of respiratory control; dysfunction of the intracranial pressure/volume equilibrium.

Keywords brain death; SIDS-SUID; sudden death; SUDEP; unexpected death

Introduction

In the course of the forensic exercise demands are often made of the pathologist that the hospital pathologist is almost never called upon to deal with. These demands are often listed as: what?; how?; when?; where?; why?; and who?. Another difference is that the forensic pathologist usually must state the medical cause(s) of death when an autopsy is done as well as the manner of death (homicide, suicide, accident, natural or undetermined). The most challenging is the determination of ageing and dating of processes, causal mechanisms of the processes and their functional significance. Such information may have great significance when the case goes to litigation in civil or criminal courts. These tasks may call for a much deeper understanding of basic processes and the ability to communicate the scientific bases for his or her opinions. This may require discussions that make use of physiology, pathophysiology, biochemistry, anatomy, histology, biomechanics, radiology, and many other fields that are not usually required on a day-to-day basis of the hospital pathologist. The hospital pathologist is generally not "examined" or cross-examined under oath by anyone. The forensic pathologist, on the other hand, is commonly called upon to explain and justify the opinions reached on the record. He/she may have to "educate" the trier of fact (jury or judge) when called upon to give evidence, so that the evidence presented can be understood and taken into account in rendering judgements. This must occur within the context of the methods and procedures of science.

Most in-hospital deaths occur because of "natural" disease processes which are typically revealed at autopsy. In forensic cases, "natural" manners of death predominate with heart diseases accounting for >50% of cases followed by respiratory diseases (>14%). Intracranial causes account for >15%, with the remainder divided amongst digestive-urogenital and other causes.[1]

Intracranial causes of death

These types of deaths are usually sought as a last resort when the general autopsy fails to fix the cause of death. Mostly this search is fruitless. A basic understanding is needed to appreciate what sorts of processes can produce death directly, rapidly or not. These processes-mechanisms bring about death mostly by one or more of the following: conditions that produce increased intracranial pressure resulting in herniation; global or widespread damage/necrosis of substantial portions of the brain, as in the respirator brain phenomenon; physical destruction of the brain stem or large portions of the brain; "functional" disruptions of vital functions such as sudden deaths in epilepsy and sudden infant death syndrome. Most individuals dying from the neurodegenerative diseases do so because the neurological deficits caused by these diseases lead to the victim being bedfast, contracting pneumonia, urinary tract infections, decubitae, sepsis, or inanition. A theme that runs through these mechanisms is the rapidity at which death occurs. A special category which often poses a challenge is those deaths that occur suddenly and unexpectedly. These types of death may constitute up to 10% of deaths on a forensic service.

Stroke

Haemorrhagic stroke was and is a major cause of death from an intracranial process[2] though "hypertensive" haemorrhage is diminishing in incidence due to widespread recognition and effective treatment of arterial hypertension. These haemorrhages most commonly involve the external capsule-basal ganglia with rupture into the ventricle being the fatal event. Less common are haemorrhages into the cerebellum or pons. The mechanisms of death for haemorrhagic strokes are said to be due to mass effects of the haemorrhage and intraventricular haemorrhage.

Ruptured aneurysms or vascular anomalies may account for about 10% of intracranially caused deaths. This category is diminishing also due to improved cranial imaging technologies and new modes of treatment that include endovascular interventions, antithrombotic drugs, and stereotactic radiosurgery. When an intracranial haemorrhage occurs the victim is usually able to be taken to hospital. There is usually an imaging study that reveals the pathology, and a neuropathological autopsy examination will also usually reveal the pathological process responsible.

Cerebral venous thrombosis is an often missed condition that can lead to subarachnoid haemorrhage, haemorrhagic infarctions, and sometimes subdural haemorrhages.[3]

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Epilepsy-related deaths

Unexpected and often sudden deaths in epileptic persons unrelated to status epilepticus have been known for more than 100 years.[4,5] Such deaths are not particularly uncommon and have been reported widely. The incidence of sudden unexpected death in epilepsy (SUDEP) across the epileptic population which represents about 1.2% of the general population has been reported to be 1.2 to 3.5 per 1000 patient years[6] but may be much more common in individuals who have intracranial traumatic lesions or other structural lesions as a basis for their seizure disorder. While neuropathological examinations in epileptic persons who did not die in the circumstances of SUDEP commonly show no obvious pathology (10% or fewer), in one population of SUDEP victims 70% had structural brain lesions.[7] Such lesions were: old traumatic contusions (26.1%); prior surgical site (10%); cortical malformations (5.9%); Ammon's horn sclerosis (10%); cerebellar atrophy (6%); old subdural haematomas (7.6%); hydrocephalus (8.4%).

In another study of 124 SUDEP victims their characteristics were: males to females (3:1); mean age of 31.4 years; males' hearts were significantly heavier than the norm[8] but females' hearts were not. Easily 50% of SUDEP victims had no anticonvulsant in the blood at autopsy, and a significant percentage had subtherapeutic levels of an anticonvulsant. In the same population 25% of deaths occurred while in the presence of another individual. It appears that resuscitation efforts only rarely were successful. In other studies[9] anticonvulsant compliance was higher. In a study from Allegheny County, Pennsylvania[10] heart weights in both men and women were both higher than the norm, the mean age was about 45 years and many of the other characteristics were similar. In most studies SUDEP victims are usually found dead in bed or in circumstances typical of normal activities. Autopsy findings are usually not definitive for cause of death.

Proposed mechanisms for SUDEP cases include: spill-over of intracranial electrical events during a seizure into nerves reaching the heart (both sympathetic and parasympathetic) which either stop the heart or induce tachyarrhythmias (usually ventricular fibrillation). In animal seizure models it has been demonstrated that simultaneous "lock step" sympathetic and parasympathetic neural discharges can reach the heart and induce arrhythmias.[11] The role of sympathetic overload and stress have also been suggested and studied in animal models.[12] Possibly associated with this mechanism may be alterations in distribution of β adrenergic receptors in the heart in SUDEP victims. Seizure-related dysfunctions in respiratory control possibly involving serotonin acting on the brain stem may be responsible for fatal seizure-related apnoea. Neurogenic pulmonary oedema possibly involving acute right heart failure has also been postulated to cause seizure deaths.[13] In recent years the role of ion gated receptor channelopathies in the heart associated with Brugada syndrome, the "long Q-T" syndrome[14] and other variants may explain some epilepsy-related sudden deaths. Abnormalities of the cardiac conducting system or the myocardium itself may contribute to epilepsy-related deaths. Some of the above conditions can be dealt with by a careful examination of the heart by an expert in cardiac pathology, but many will require the newer technologies of genetic analysis.

Sudden infant death syndrome

This complex phenomenon variously referred to as "crib death", sudden infant death syndrome (SIDS) or sudden unexplained death in infancy (SUID) has been an enigma for many years. It is appropriate to think of this condition as more of a label than a diagnosis for those cases that involve the unexpected death of apparently healthy infants (usually under the age of 6 months) most commonly in their beds. The autopsies of such victims are usually not definitively revealing as to cause, for if there were demonstrable anatomic or physiological causes the deaths would not be a mystery.[15,16]

There are a number of circumstantial issues which are commonly raised in SIDS deaths, the most common of which is the sleep environment of the infant. Prone sleeping and side sleeping positions appear as a risk factor in many series[17] in which the infant may also be found with the bed covers or pillows over his/her head. Programs that encourage supine sleeping position have resulted in marked reduction of SIDS. Some dysfunction in the respiratory control mechanisms of the brain stem due to subtle birth injury/hypoxia or other causes including genetic mutations have been suggested as at least part of the causal chain in SIDS cases.[18] Some cases that might yield answers to the SIDS puzzle might come from very careful neuropathological study of the lower pons, and medulla where the main anatomical components of respiratory control reside[19] where gliosis may be found.

Other causative issues with SIDS cases involve suffocation by co-sleeping, pillows or bedding that impair breathing, positional asphyxia and entrapment[20] recent immunizations,[21] parents who smoke and tobacco smoke in the sleep environment maternal, alcohol and caffeine use during pregnancy.[22]

It is not at all uncommon that some cases which have the characteristics of SIDS may represent some form inflicted injury that can include manual asphyxia by a caregiver.[23] Such cases may be completely missed by the autopsy pathologist and only come to light when a caregiver later confesses to smothering. It is not uncommon when the circumstances of SIDS occur, that attempts at resuscitation and vigorous efforts at intubation, and ventilation by emergency response personnel or others can result in injuries that may be misinterpreted as homicidal inflicted trauma rather than being iatrogenic in nature. In such a case a caregiver may incorrectly be charged with homicidal child abuse. Such cases require critical evaluation including developing a time line for events such as the success or lack thereof of intubation and ventilation, and cardiac resuscitation, careful interpretation of radiographs and the autopsy. It should be remembered that cardiac arrest and poor brain perfusion during the arrest and resuscitation attempts may result in reperfusion vascular injury when circulation is restored[24] or if the resuscitation is prolonged. The punctate and perivascular haemorrhages in vulnerable areas of the brain have been confused with lesions due to trauma, inflicted or accidental. In this context it should be remembered that young infants whose cranial bones have not yet ossified, probably are not capable of showing brain contusions (coup or contrecoup) with head impacts.

The effects of increased intracranial pressure

There are many circumstances in which increased intracranial pressure can cause unexpected and even rapid deaths. This is

