SUDDEN NATURAL DEATH

Contents

Cardiovascular

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Introduction

Incidence

Sudden cardiac death occurs in 300 000–400 000 individuals annually in the USA, with an incidence of 100–200/100 000 per year. In adults 40 years of age or younger, the incidence is far lower. For example, in Olmsted County, Minnesota, the incidence of sudden death in young adults has been estimated to be 5–10/100 000 population per year.

Definition

Sudden cardiac death is natural, nonviolent, unexpected, and occurs within a short time of the onset of acute symptoms (usually 1 h, for purposes of definition). When the definition of death is less than 2 h after onset of symptoms, 12% of deaths are sudden and 88% are due to cardiac causes. When applying a symptom duration of less than 24 h, 32% of deaths are sudden and cardiac causes of death decline to 75%.

Epidemiology

The ages at which sudden death is most prevalent are birth to 6 months (sudden infant death syndrome) and between 45 and 75 years. Only 19% of sudden natural deaths in children between 1 and 13 years of age are cardiac in origin, whereas in the 14–21-year-old age range 30% are cardiac. In the adult population, the most common cause of sudden death is coronary heart disease, with various forms of cardiomyopathies the second most common cause. The proportion of deaths from heart disease that are sudden declines with advancing age. In the Framingham study, 62% of all coronary heart disease deaths were sudden in men aged 45–54 years, whereas in the 55–64-year and 65–74-year age groups, the percentage of sudden death declined to 58% and 42%, respectively. There was a 3.8-fold higher incidence of sudden cardiac death in men than in women. The excess relative risk in men peaked at 55–64 years, reflected in a male-to-female ratio of 6.75:1; this ratio decreased to 2.17:1 in the 65–74-year age group. Racial differences in the incidence of sudden cardiac death have also been noted: blacks have an increased risk compared to whites. Hereditary factors are important in a variety of causes of sudden cardiac death, including atherosclerosis, cardiomyopathies, and channel diseases.

Causes of Sudden Cardiac Death

Virtually any pathologic process that involves the heart may result in sudden death by virtue of the wide variety of mechanisms that may result in terminal arrhythmias. Acute ischemia, infiltrative diseases (primarily scars or inflammation), cardiac hypertrophy, and cardiac failure are the most common anatomic substrates of ventricular arrhythmias and may have a variety of interrelated causes (Table 1).

In developed countries, coronary atherosclerosis is by far the most common finding in cases of sudden cardiac death in patients older than 30–35 years. Coronary atherosclerosis may result in sudden death by acute ischemia, arrhythmias secondary to healed infarcts, cardiac rupture, and acute heart failure. The second most common cause of sudden death is intrinsic myocardial diseases, which may be classified as hypertrophic cardiomyopathy, dilated cardiomyopathy, hypertensive cardiomyopathy, and idiopathic left ventricular hypertrophy. The third most common cause of death is valvular disease, especially mitral valve prolapse and aortic stenosis. Congenital heart diseases that may result in sudden death include coronary artery anomalies, forms of hypertrophic cardiomyopathy, and forms of aortic stenosis; these are an especially important cause of death in men and women younger than 35 years of age.

In adolescents and young adults, myocarditis, cardiomyopathies (right ventricular dysplasia and hypertrophic and idiopathic left ventricular hypertrophy),

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Table 1 Causes and mechanisms of sudden cardiac death

Immediate cause	*Underlying causes*	*Mechanisms*
Acute ischemia	Coronary atherosclerosis	Ventricular fibrillation
	Nonatherosclerotic coronary diseases	Bradycardia
	Aortic stenosis	Electromechanical dissociation (usually end-stage or postresuscitation)
Infiltrative diseases	Inflammatory (myocarditis)	Ventricular fibrillation
	Scars (healed infarcts, cardiomyopathy)	Bradyarrhythmias (uncommon[a])
Cardiac hypertrophy	Hypertrophic cardiomyopathy	Ventricular fibrillation
	Systemic hypertension	Bradyarrhythmias (uncommon)
	Idiopathic concentric left ventricular hypertrophy	
	Aortic stenosis	
Cardiac dilatation (congestive failure)	Dilated cardiomyopathy	Ventricular fibrillation
	Chronic ischemia	Bradyarrhythmias (uncommon)
	Systemic hypertension	
	Aortic insufficiency	
	Mitral insufficiency	
Tamponade	Ruptured myocardial infarct	Pulseless electrical activity
	Aortic rupture	
Disruption of blood flow	Pulmonary embolism	Pulseless electrical activity
	Mitral stenosis	Ventricular fibrillation
	Left atrial myxoma	
Global myocardial hypoxia	Severe ischemic heart disease	Baroreflex stimulation with bradyarrhythmias
	Aortic stenosis	Ventricular tachyarrhythmias
	Pulmonary embolism	
Acute heart failure	Massive myocardial infarct	Pulseless electrical activity
	Ruptured papillary muscle	Ventricular fibrillation
	Chordal or leaflet rupture	
Systemic hypoxia	Pulmonary stenosis	Bradyarrhythmias
	Pulmonary hypertension	
Vasovagal	Neuromuscular diseases	Baroreflex stimulation with bradycardia
Preexcitation	Accessory pathways	Atrial fibrillation → ventricular fibrillation
Long QT	Congenital and acquired states	Ventricular fibrillation (torsade de pointes)
Heart block	Atrioventricular nodal scarring, inflammation, tumor	Bradycardia → ventricular fibrillation

[a]Especially in the presence of infiltrative processes involving the conduction system.
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and coronary artery anomalies are the most common causes of sudden cardiac death in individuals with structural heart disease (Tables 2–4).

The most common identifiable causes of sudden death in young children are myocarditis and congenital heart disease, including coronary artery anomalies and hypertrophic cardiomyopathy. Up to 50% of cardiac causes in children who die during exercise are idiopathic arrhythmias with apparently normal heart at autopsy. For children and young adults, in cases of apparent sudden cardiac death with no morphologic cardiac abnormalities at autopsy, genetic abnormalities of ion channels or calcium signaling should be considered.

Table 2 Causes of sudden cardiac death in infants and children

Anatomic findings	*0–1 years (n = 20)*	*1–21 years (n = 50)*
Coronary artery anomalies	10 (50%)	12 (24%)
Myocarditis	0	14 (28%)
No finding	7 (35%)	10 (20%)
Other findings	2 (10%)	8 (16%)
Hypertrophic cardiomyopathy	1 (5%)	6 (12%)

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Degrees of Certainty and Causes of Death

The underlying substrates for ventricular arrhythmias may be chronic or subacute conditions, leading to difficulties in assessing a precise cause of death. Occasionally, there may be more than one anatomic abnormality that may lead to a lethal arrhythmia, and the exact cause of the terminal event may be difficult

Table 3 Causes of death, ages 21–30

Cause of death	
Atherosclerosis	64 (28%)
No finding[a]	49 (21%)
Idiopathic left ventricular hypertrophy	27 (12%)
Hypertrophic cardiomyopathy	16 (7%)
Myocarditis	14 (6%)
Anomalous coronary artery	9 (4%)
Dilated cardiomyopathy	7 (3%)
Tunnel coronary artery	7 (3%)
Aortic dissection	7 (3%)
Rheumatic mitral stenosis	6 (3%)
Complex congenital heart disease	5 (2%)
Hypertensive left ventricular hypertrophy	4 (2%)
Endocarditis	4 (2%)
Sarcoidosis	3 (1%)
Aortic stenosis	3 (1%)
Floppy mitral valve	2 (1%)
Right ventricular cardiomyopathy	2 (1%)
Coronary aneurysm (congenital)	1 (0.4%)
Amyloid	1 (0.4%)
Pericarditis	1 (0.4%)
Total	229

[a]The proportion of these cases caused by channel disorders is unknown.

Due to rounding totals are more than 100%.

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Table 4 Causes of death, ages 31–40

Cause of death	*n (%)*
Atherosclerosis	258 (60%)
No finding	38 (9%)
Hypertensive left ventricular hypertrophy	26 (6%)
Idiopathic left ventricular hypertrophy	18 (4%)
Dilated cardiomyopathy	16 (4%)
Hypertrophic cardiomyopathy	13 (3%)
Myocarditis	12 (3%)
Sarcoidosis	10 (2%)
Aortic stenosis	9 (2%)
Aortic dissection	8 (2%)
Endocarditis	6 (1%)
Floppy mitral valve	6 (1%)
Tunnel coronary artery	3 (1%)
Right ventricular dysplasia	3 (1%)
Rheumatic mitral stenosis	3 (1%)
Anomalous coronary artery	2 (0.5%)
Coronary artery dissection	2 (0.4%)
Congenital heart disease	1 (0.2%)
Lipomatous hypertrophy, atrial septum	1 (0.2%)
Total	432

Due to rounding totals are more than 100%.

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to determine. Definite causes of death are those that result in cardiac tamponade, cardiac rupture, and acute coronary thrombi. Other causes, such as stable atherosclerotic plaque, left ventricular hypertrophy, ventricular scars, focal myocarditis, and cardiomyopathy, should be only considered when other potential conditions have been excluded.

Coronary Atherosclerosis

Coronary Morphology in Sudden Cardiac Death due to Atherosclerosis

Based on autopsy studies comparing the degree of luminal narrowing of coronary arteries between patients dying suddenly with those dying of other causes, it has been determined that 75–80% of cross-sectional luminal narrowing is a useful figure for separating critical stenosis that may result in acute myocardial ischemia from noncritical stenosis. However, any decision that death is due to coronary atherosclerosis, especially in the presence of a stable plaque, must be supported by rigorous exclusion of other noncardiac causes of death.

The frequency of coronary thrombosis in sudden coronary death varies from 20% to 70%. The time interval between onset of symptoms and death, the presence of concurrent conditions that may cause arrhythmias (scars and ventricular hypertrophy), and the type of prodromal symptom (stable angina, unstable angina, or no apparent symptoms) all affect the incidence of thrombi in coronary sudden cardiac death. Coronary thrombosis may occur over two major substrates: rupture of thin-cap fibroatheroma (Figure 1) and plaque erosion (Figure 2). Plaque erosion occurs in men and women younger than age 50 and is less common, whereas plaque rupture is more common, occurs at all ages in adults, and is associated with hypercholesterolemia.

Myocardial Findings in Sudden Coronary Death

The likelihood of discovering an acute infarction in autopsied cases of sudden coronary death is more than 50% in hospital-based studies of sudden death. In out-of-hospital deaths, and cases of instantaneous sudden death with no symptoms, or symptoms lasting less than 1 h, acute infarcts are unusual, and are found in less than 25% of cases.

The incidence of healed infarcts in out-of-hospital sudden coronary deaths is greater than that of acute infarcts. The rate of healed infarcts is greater in the elderly and patients with diabetes mellitus.

Postinfarction cardiac rupture, when it involves the free wall, is almost uniformly fatal. The incidence of rupture is highest in the elderly, women, patients

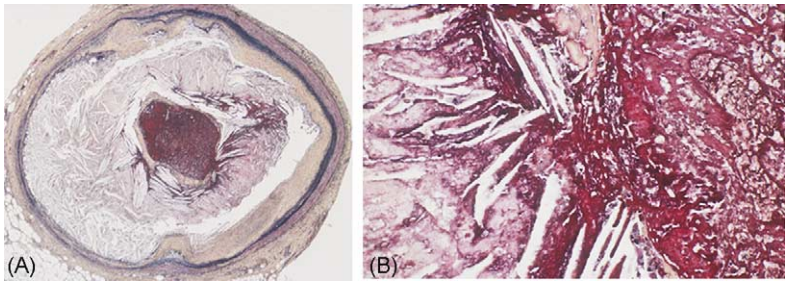

Figure 1 Coronary artery thrombosis secondary to plaque rupture. (A) A cross-section of the left anterior descending coronary artery severely narrowed by lipid-rich atherosclerotic plaque. The lumen (center) is filled with thrombus. (B) A higher magnification of plaque rupture with cholesterol clefts at the site of rupture of the fibrous cap. Movat pentachrome stain.

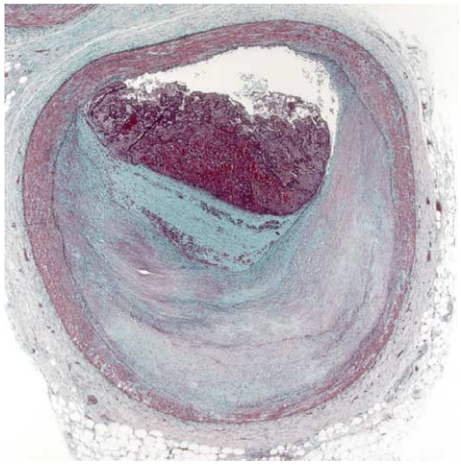

Figure 2 Coronary artery thrombosis secondary to plaque erosion. The left anterior descending coronary artery demonstrates moderately severe narrowing by fibrous plaque with luminal thrombus that is nearly occlusive. The cap is rich in proteoglycans (green staining with alcian blue, Movat pentachrome stain) and there is no cap rupture, as in plaque rupture.

without previous infarction, and in patients with hypertension. The underlying acute infarct is generally transmural, involving at least 20% of the left ventricle. The time interval between infarct and rupture is usually 1–4 days after infarction but can range between 1 day and 3 weeks.

Mechanisms and Underlying Conditions

The mechanism of sudden death in most cases of ischemic heart disease is ventricular fibrillation; 20–30% of patients die with bradyarrhythmias, and a minority of patients have diffuse myocardial damage resulting in acute heart failure or pulseless electrical activity. The mechanisms of ischemia-induced ventricular arrhythmias are most likely related to reentry phenomena. The incidence of ventricular fibrillation during the first 30 days after acute myocardial infarction is increased in patients with anterior-wall infarctions and bundle-branch block.

Congenital Coronary Artery Anomalies

Anomalous Left Main Coronary Artery

The most common coronary anomaly resulting in sudden death is an aberrant left main arising in the right coronary sinus of Valsalva. There is a male-to-female ratio of 4:1 to 9:1. Sudden death occurs in up to two-thirds of individuals with this anomaly, 75% of which occur during exercise. Most patients are adolescents or young adults, although death may occur as young as 1 month of age. There are often premonitory symptoms of syncope or chest pain, but stress electrocardiograms and stress echocardiograms are often negative.

Pathologically, there are several variants to this anomaly. The common feature is the presence of the left main ostium within the right sinus (Figure 3). This ostium is typically near the commissure, and in some cases it actually lies above the commissure between the right and left sinuses. Often, the ostium is somewhat malformed and slitlike, and an ostial ridge is present. The proximal artery lies within the aortic media and traverses between the aorta and pulmonary trunk.

The pathophysiology of sudden death in patients with aberrant left main coronary artery may be related to compression of the left main by the pulmonary trunk and aorta, diastolic compression of the vessel lying within the aortic media, and poor filling during diastole because of ostial ridges or slitlike ostia.

Anomalous Right Coronary Artery

In contrast to anomalous left main coronary artery, anomalous right from the left sinus is usually an incidental finding, although up to one-third of patients may die suddenly. Approximately 50% of these deaths are exercise-related, and most deaths occur in young and middle-aged adults younger than age 35.

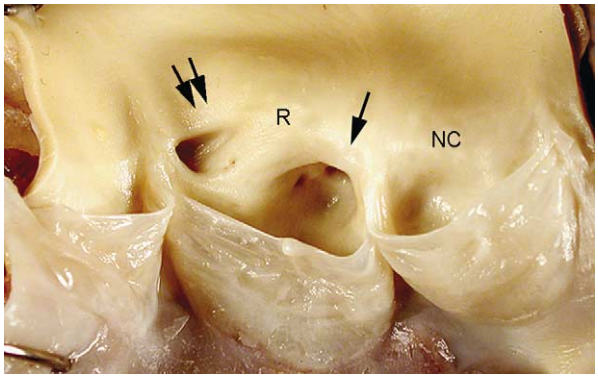

Figure 3 Anomalous left coronary artery arising in the right aortic sinus. Note the ostial valve-like ridge (double arrow) of the left main coronary artery. The ostium of the right coronary artery (single arrow) likewise arises in the right (R) sinus of Valsalva. The noncoronary cusp (NC) and left (L) cusp are shown to the right and left of the right sinus of Valsalva.

Grossly, there are two ostia located in the left sinus of Valsalva. The ostium supplying the right coronary artery may have similar features as anomalous left ostia located in the right sinus. Namely, there may be upward displacement, location near the commissure, and slitlike ostia with ostial ridges. The proximal anomalous right coronary generally also courses between the aorta and pulmonary trunk. The pathophysiology of sudden death is similar to that of anomalous left coronary artery, and, like that anomaly, evidence of acute or remote ischemia in the ventricular myocardium is not often found.

Origin from Pulmonary Trunk

The left main coronary artery arises from the pulmonary trunk in 1/50 000 to 1/300 000 autopsies. Most cases are identified in the first year of life, and sudden death occurs in about 40% of cases. Sudden death usually occurs at rest, but it may arise after strenuous activity in older children. Pathologically, the aberrant artery arises in the left pulmonary sinus in 95% of cases. Typically, the artery appears thin-walled and veinlike, and the right coronary artery, although normal in location, is tortuous.

Tunnel Coronary Arteries

A tunnel coronary artery is formed by a myocardial bridge that results in a focally intramural coronary artery that is flanked by epicardial segments. The most common location is the middle third of the left anterior descending coronary artery. Tunneled segments of the left anterior descending coronary artery are found in about 30% of hearts at autopsy. In cases of sudden death without other apparent cause, a tunnel greater than 5 mm deep may be considered a potential cause of a lethal arrhythmia.

Other Nonatherosclerotic Coronary Causes of Sudden Death

Spontaneous Coronary Dissection

Coronary artery dissection accounts for approximately 0.5% of sudden deaths in patients 30–40 years old (Table 3). Most patients are young women, and sometimes death occurs in the postpartum period. In autopsy studies of coronary dissections that result in sudden death, more than 90% of cases involve the left anterior descending coronary artery. Histologically, the dissection plane is in the outer media, with infiltrates of eosinophils, lymphocytes, neutrophils, and macrophages in the adventitia. The inflammatory infiltrate is believed to be secondary to the dissection and not a vasculitis. The etiology and genetics of spontaneous coronary dissection are unknown.

Small-Vessel Disease

Narrowing of the small arteries supplying the sinoatrial and atrioventricular nodes has been associated with sudden death. The etiology of the narrowing in a majority of these cases is a form of arterial dysplasia. Small-vessel dysplasia has also been associated with catecholamine-induced sudden death, hypertrophic cardiomyopathy, sickle-cell disease, and mitral valve prolapse. Although most cases of small-vessel disease and sudden death have involved arteries supplying the specialized conduction system of the heart, thickened arteries within the wall of the ventricular septum have also been implicated in sudden cardiac death.

Cardiomyopathies

Assessment of Cardiomegaly

Most cases of cardiomyopathy result in cardiac hypertrophy. Normal heart weight varies with body weight, which must be taken into consideration before assessing the degree of cardiomegaly. Ninety-five percent confidence intervals of normal heart weight, as based on body weight and body surface area (kg m^{-2}), are readily available and of extreme importance in the assessment of cardiac hypertrophy. Normal heart weight is about 0.45% of body weight in men.

Hypertrophic Cardiomyopathy

Sudden death is the mode of presentation for more than 50% of patients with hypertrophic cardiomyopathy. Patients at risk for sudden death are those with a

family history of sudden death and those with a history of syncope or presyncope. In children with hypertrophic cardiomyopathy, coexistent tunneling of the left anterior descending coronary artery may predispose to sudden death. Familial forms of the disease account for approximately half of the cases and are inherited as an autosomal dominant trait. Genetic defects in familial cases involve structural proteins of the sarcomere, most commonly the beta-myosin heavy chain.

Asymmetric left ventricular hypertrophy (predominantly septal), small left ventricular chamber cavity, left atrial dilatation, thickening of the anterior leaflet of the mitral valve, and evidence of left ventricular outflow tract obstruction (left ventricular outflow tract plaque) are all gross features of hypertrophic cardiomyopathy (Figure 4). Histologic features include myofiber disarray with hypertrophy and intramural myocardial artery thickening. Myofiber disarray may be accompanied by significant interstitial fibrosis, especially in advanced stages of disease.

There are several potential mechanisms of sudden cardiac death in patients with hypertrophic cardiomyopathy. The major possible mechanisms include acute ischemia secondary to subaortic stenosis, ventricular arrhythmias secondary to disordered muscle bundles in the ventricular septum, myocardial ischemia secondary to small-vessel coronary disease, altered autonomic vascular control, and myocardial hypertrophy. An increase in the collagen network of the interstitium has been implicated in sudden death due to hypertrophic cardiomyopathy.

Hypertensive Cardiomyopathy

Left ventricular hypertrophy of any cause is associated with ventricular ectopy and increased risk for ventricular tachyarrhythmias. Patients with hypertension and left ventricular hypertrophy have an increased risk of sudden death. As for other causes of cardiomegaly, the diagnosis of concentric left ventricular hypertrophy requires demonstration of increased heart weight as a function of body weight and height.

Idiopathic Concentric Left Ventricular Hypertrophy

In 10–40% of sudden deaths in young individuals, especially athletes, concentric left ventricular hypertrophy, as determined by body weight and height, is the only pathologic finding at autopsy. Some cases of idiopathic concentric left ventricular hypertrophy may represent forms of hypertrophic cardiomyopathy, lacking typical morphologic expressions of the disease, especially in patients with a family history of cardiomyopathy. The diagnosis of idiopathic concentric left ventricular hypertrophy assumes the absence

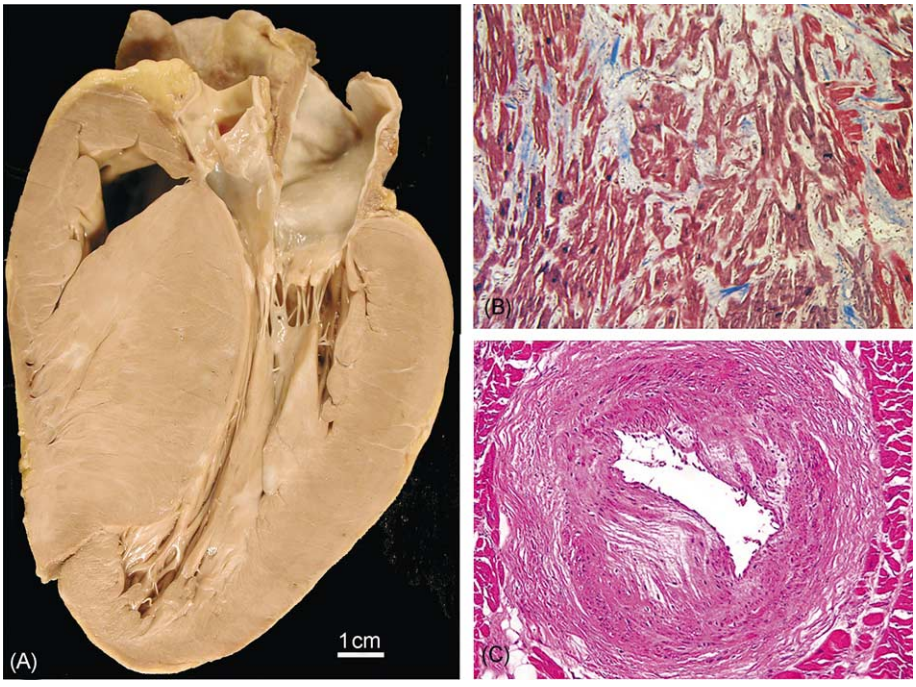

Figure 4 Hypertrophic cardiomyopathy. (A) A long-axis cut of the heart demonstrates a markedly thickened ventricular septum as well as right ventricular hypertrophy. (B) A histologic section of the ventricular septum shows myofiber disarray (Masson trichrome stain). (C) A thickened intramural coronary artery present in the ventricular septum in a patient with hypertrophic cardiomyopathy.

of systemic hypertension, as determined by history or examination of renal microvasculature.

Dilated Cardiomyopathy

Regardless of etiology, the failing heart is prone to ventricular arrhythmias, which may potentially result in sudden death. Ambulatory Holter monitoring in patients with idiopathic dilated cardiomyopathy often demonstrates ventricular arrhythmias, including nonsustained ventricular tachycardia. Although patients with dilated cardiomyopathy frequently die sudden arrhythmic deaths, death is generally not unexpected because illness is often chronic and progressive. The autopsy diagnosis of dilated cardiomyopathy rests on the identification of cardiac dilatation in the absence of significant atherosclerotic and valvular disease. The heart is moderately to significantly enlarged, there is four-chamber dilatation (ventricles more pronounced than atria), and the left ventricular wall is of normal thickness or thinned. The ventricular cavity is generally >4 cm at the level of the papillary muscles. Histologic sections are required to rule out specific causes of cardiomyopathy.

Cardiomyopathy of Obesity

The association of obesity and sudden death has been known since ancient times, as illustrated by Hippocrates' adage that "sudden death is more common in those who are naturally fat than in the lean." In a study in which morbid obesity was defined as being more than 100% or 100 lb (about 45 kg) over desired body weight, the annual sudden cardiac death mortality rate was 65/100 000 versus 1.6/100 000 in normal-weight women.

Autopsy studies of sudden death in the massively obese have shown an increase in heart weight in proportion to body weight and myocardial hypertrophy. The most common causes of death are dilated cardiomyopathy, severe coronary atherosclerosis, and concentric left ventricular hypertrophy without left ventricular dilatation. When death occurs during sleep in patients who are obese, concomitant sleep apnea, as determined by history, may be a contributing factor.

Arrhythmogenic Right Ventricular Dysplasia–Cardiomyopathy

Arrhythmogenic right ventricular dysplasia accounts for less than 5% of sudden cardiac deaths but is a relatively common cause of exertional death. Arrhythmogenic right ventricular dysplasia is familial in up to 50% of cases, in which case the mode of inheritance is autosomal dominant with variable penetrance. Most patients are younger than 40 years at the time of death, and some deaths occur in children. Pathologically, the right ventricle is often dilated, with focal thinning (Figure 5). Biventricular scars are seen in the majority of hearts from patients dying suddenly. Histologically, the right ventricle demonstrates areas of scarring and fatty infiltrates; in the left ventricle, these findings are distinctly subepicardial in location.

Right Ventricular Hypertrophy and Pulmonary Hypertension

Patients with idiopathic pulmonary hypertension are at an increased risk for sudden death, especially those with a history of syncope. Syncopal episodes and sudden death generally occur at rest but may be triggered by catheterization procedures and exercise. The mechanism of sudden death in patients with pulmonary hypertension is most likely multifactorial,

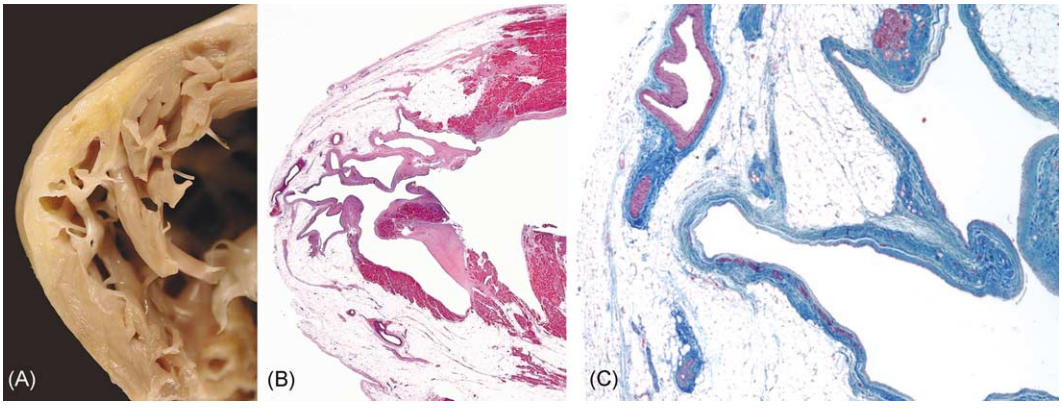

Figure 5 Arrhythmogenic right ventricular dysplasia–cardiomyopathy. (A) The right ventricle demonstrates focal fat infiltration (bright yellow). (B) The corresponding histologic section shows fat infiltration within the myocardium. (C) A Masson trichrome stain demonstrates fibrosis (blue) in addition to the fat.

including the arrhythmogenic effects of the hypertrophied right ventricle complicated by anoxia-induced bradycardia.

Myocarditis

Lymphocytic Myocarditis

Usually a sequela of viral infection, lymphocytic myocarditis is the cause of sudden cardiac death in 15–20% of children and young adolescents and less in young adults. At autopsy, a pericardial effusion is often found. Histologically, there is myocyte necrosis with an accompanying lymphocytic infiltrate. The degree of infiltration may be especially marked in infants and young children, and there may be scattered neutrophils and histiocytes, in addition to lymphocytes. Areas of scarring are not uncommon, and are indicative of chronicity and healing. Large areas of granulation tissue may be present in cases of extensive myocarditis.

Serologic and molecular studies suggest that many cases of lymphocytic myocarditis are caused by enteroviruses, especially coxsackievirus type B3, and adenoviruses, although a variety of other viruses have been implicated in isolated cases.

Giant-Cell Myocarditis

A myocardial inflammation that is an especially aggressive form of myocarditis, giant-cell myocarditis is characterized by chronic inflammation with numerous giant cells, widespread myocardial necrosis, and scarring. Sudden death may occur secondary to ventricular arrhythmias or acute heart failure. The differential diagnosis is sarcoidosis, which generally involves mediastinal lymph nodes, lacks myocyte necrosis, and demonstrates well-formed granulomas.

Sarcoidosis

Approximately 2% of sudden deaths in young adults are caused by sarcoidosis. Of patients that die suddenly with sarcoid, one-third have no previous medical history, one-third have a history of cardiac symptoms not attributed to sarcoid, and one-third have a previous diagnosis of sarcoidosis. Sarcoidosis affects the heart in 30% of patients with symptomatic pulmonary sarcoidosis, and it may result in ventricular premature beats, ventricular tachycardia, and heart block. The left ventricle is involved in all cases with cardiac involvement, and the interventricular septum is involved in 95% of cases (Figure 6).

Idiopathic Left Ventricular Scars

Occasionally, the only cardiac finding in cases of sudden cardiac death is ventricular scarring, in the absence of significant coronary artery disease or sarcoidosis. Diffuse ventricular scars are likely related to healed myocarditis; subepicardial scars in the left ventricle are frequent in cases of right ventricular dysplasia and may also be present in cases of chronic myocardial emboli. Chronic abuse of cocaine and other drugs may result in ventricular fibrosis in the absence of coronary disease.

Valvular Heart Disease

Mitral Valve Prolapse

The lifetime risk of sudden cardiac death in patients with mitral valve prolapse is 1–3%. The rate of sudden death in patients with mitral valve prolapse is greater if mitral regurgitation is present. The pathophysiology of sudden cardiac death in mitral valve prolapse and competent valves is poorly understood. Vectorcardiograms suggest that the majority of ventricular arrhythmias in patients with mitral valve prolapse arise in the posterior basilar septum of the left ventricle. Autopsy studies have provided several theories for sudden death, including endocardial friction lesions resulting in ventricular arrhythmias, traction of an abnormally inserted valve on the conduction system, deposition of proteoglycans within the

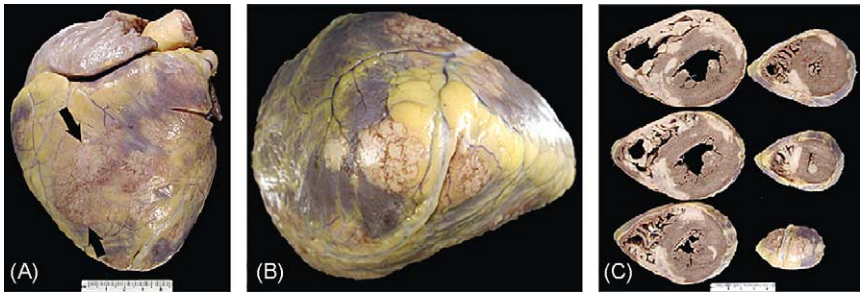

Figure 6 Cardiac sarcoidosis. (A) The heart from a man who died suddenly, without prior history, shows focal epicardial plaquing (arrows), seen more clearly in (B), a photograph of the ventricular apex. (C) Cut sections of the myocardium show multifocal infiltrates and scars, typical of sarcoidosis.

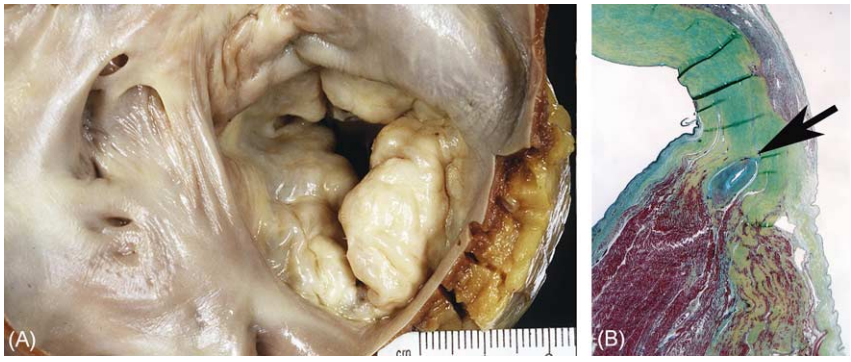

Figure 7 Mitral valve prolapse. (A) The left atrium shown from above, demonstrating the mitral valve, with characteristic billowing and redundancy of leaflets. (B) A histologic section (Movat pentachrome stain) of the atrioventricular septum posterior to the atrioventricular node shows increased proteoglycans (green) as well as a dysplastic, thickened branch of the atrioventricular nodal artery (arrow).

autonomic nerve supply to the heart, and small-vessel dysplasia at the base of the heart (Figure 7).

Aortic Stenosis

The incidence of sudden death due to aortic stenosis has decreased with the introduction of valve replacement. The principal mechanism of sudden death in aortic stenosis appears to be activation of left ventricular baroreceptors, which causes reflex bradycardia and cardiac arrhythmias. Myocardial ischemia may also contribute to terminal arrhythmias in patients with aortic stenosis via diastolic compression of intramural coronary arteries. Aortic stenosis may be the result of a variety of morphologic valve defects. The most common are calcified bicuspid aortic valves and nodular calcification in normal, trileaflet valves. Asymptomatic patients with aortic stenosis have excellent survival and prognosis. However, after angina or syncope occur, the average survival is 1–3 years. Aortic valve replacement greatly reduces the risk for sudden death but does not eliminate it: about 20% of deaths in patients with stenotic aortic valve replacement are sudden. Overall, the rate of sudden death is low, estimated to be 0.3% per year. The indications for aortic valve replacement in patients with aortic stenosis are the degree of symptoms, degree of gradient, concomitant coronary disease, degree of left ventricular dysfunction, the presence of arrhythmias, and valve area.

Cardiac Tamponade

Acute cardiac tamponade occurs when there is sudden hemorrhage into the pericardial space, resulting in impaired ventricular filling and reduced cardiac output. When massive, such as secondary to rupture of the heart, aorta, or coronary artery, electromechanical dissociation and sudden cardiac death occur.

Myocardial Rupture

Cardiac rupture generally results from acute myocardial infarction. The infarct almost always involves the left ventricular myocardium, although the epicardial rupture site may be located over the right ventricle. Rarely, cardiac rupture may result as a complication of cardiac abscess. A case of isolated ventricular rupture has been reported in the absence of myocardial necrosis, possibly precipitated by fatty infiltration.

Direct cardiac rupture secondary to trauma occurs primarily from gunshot wounds and stab wounds, and it usually involves the anterior wall of the right or left ventricle. In contrast, blunt trauma results from cardiac compression and affects all four chambers of the heart with equal frequency and less commonly results in perforation by rib fracture. Because traumatic deaths are not natural, they are not considered in the spectrum of sudden unexpected cardiac death and will not be discussed further.

Iatrogenic forms of traumatic cardiac rupture may result from catheterization procedures, including insertion of pacemakers, and tamponade may be a delayed event. Puncture of the left ventricle or atrium may occur during transvenous approaches to valvoplasty and is often fatal.

Rupture of the Aorta

The most common cause of death from type I and II aortic dissections is cardiac tamponade, because the site of rupture of the false lumen is generally within the pericardial reflection. Less commonly, type III dissections (those with the intimal tear in the descending thoracic aorta) will rupture into the pericardial space; the majority of type III dissections rupture into the left hemothorax.

Sudden Death due to Abnormalities in the Conduction System

Cystic Tumor of the Atrioventricular Node

A developmental rest originally believed to be of mesothelial origin, cystic tumor of the atrioventricular node is a collection of endodermal-derived glands in the region of the atrioventricular node (Figure 8). The condition is congenital and results in heart block from birth in most patients. Sudden death may occur at any age, from young childhood to late adulthood; in most patients, a clinical diagnosis of congenital heart block is known.

Heart Block

Cystic tumor of the atrioventricular node is a rare cause of heart block. More commonly, the condition is the result of fibrosis with interruption of the atrioventricular nodal pathways. Congenital heart block is often the result of maternal lupus autoantibodies, and inflammation and scarring, often with calcification, occur *in utero*. Acquired inflammation and scarring may occur in children and adults without known predisposing cause. The risk of sudden death in patients with congenital or acquired heart block is small, and the need for implantable defibrillators is controversial.

Sudden Death in the Absence of Morphologic Findings

Preexcitation Syndromes

The Wolff–Parkinson–White syndrome results from preexcitation caused by an abnormal muscular communication (the bypass tract avoiding the atrioventricular node) between either atrium and ventricle. The most common arrhythmias are benign, but sudden death may occur. The incidence of sudden death in patients with the Wolff–Parkinson–White syndrome is estimated to be less than 1 per 100 patient-years follow-up; 70% of patients who experience ventricular tachyarrhythmias have a previous history of symptoms. In symptomatic patients, curative ablative therapy prevents recurrent arrhythmias, including atrial fibrillation. In cases of sudden death in patients with known Wolff–Parkinson–White syndrome, histologic confirmation of the bypass tract is difficult, and the most important task facing the forensic pathologist is the exclusion of other potential causes of death.

Ion Channel Disorders

Mutations resulting in an inactivation of the cardiac potassium channel subunits (encoded by *KCNQ1, KCNH2, KCNE1*, and *KCNE2*) cause electrocardiographic prolongation of the QT interval, ventricular tachyarrhythmias, syncope, and sudden death. A ventricular tachyarrhythmia characteristic of the long QT syndrome is torsade de pointes. *KCNQ1* and *KCNE1* encode for alpha and beta subunits of the slow delayed rectifier potassium current (KvLQT1 and minK); *KCNH2* and *KCNE2* encode for alpha and beta subunits of the rapid delayed rectifier potassium current (HERG and MiRP1). HERG and MiRP1 are alpha and beta subunits of the same channel protein; likewise for *KCNQ1* and minK, respectively. Mutations in the *KCNQ1*, or *LQT1* (long

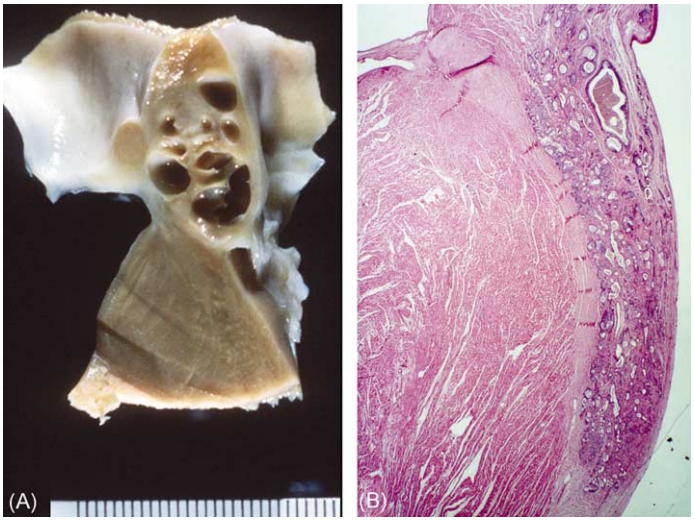

Figure 8 Cystic tumor of the atrioventricular node. (A) An uncommon cause of congenital heart block and sudden death, atrioventricular nodal tumors are occasionally grossly visible. (B) A histologic section of a different tumor, in which the cystic spaces are of microscopic size.

QT-1), gene have been identified as the cause of Romano–Ward syndrome, an autosomal dominant condition characterized by familial premature sudden death. There are several long QT syndromes; the *KCNH2* (HERG) gene corresponds to LQT2, *KCNE1* (minK) corresponds to LQT5, and *KCNE2* (MiRP1) corresponds to LQT6. Mutations in any of these genes may cause ventricular arrhythmias and sudden death. The genes are on different chromosomes (with the exception of minK and MiRP, which share sequence identity) and are composed of multiple exons. Homozygous mutations in the *KCNQ1* gene are the cause of the Jervell and Lange–Nielsen syndrome, an autosomal recessive disorder characterized by marked prolongation of the QT interval, sudden death, and sensorineural deafness. Mutations resulting in activation (as opposed to inactivation) of the cardiac sodium channel gene (*SCN5A*, or the *LQT3* gene) also cause long QT syndrome, torsade de pointes, and sudden cardiac death. There are some differences in typical clinical presentation according to the type of long QT syndrome (Table 5).

The Brugada syndrome is characterized by electrocardiographic findings of right bundle-branch block with ST segment elevation in leads V1–V3, ventricular arrhythmias, syncope, and sudden death. The syndrome is related to sudden unexpected nocturnal death syndrome in Southeast Asia and Japan, where it has many synonyms, including bangungut, nonlaitai, laitai, and pokkuri. Most cases are autosomal dominant. There have been reports of mutations in the *SCN5A* gene, the gene responsible for LQT3, with decreased, instead of increased, activity of the sodium current. A relationship between Brugada syndrome and arrhythmogenic right ventricular dysplasia has been proposed, but is questionable.

Mutations of the cardiac ryanodine receptor (*RyR2*) gene result in familial polymorphic ventricular tachycardia, an autosomal dominant syndrome characterized by ventricular arrhythmias, slight prolongation of the QT interval, and sudden death. Cardiac events, including sudden death, are often precipitated by exertion or adrenergic stimuli (Table 5).

The autopsy diagnosis of channel diseases may be accomplished by genetic analysis with sequencing of potential culprit genes, especially the *KVLQT1* gene. In selected cases with a strong suspicion, such as unexplained drowning deaths or patients with a family history of unexplained sudden death or LQT syndrome, sequencing of the *KVLQT1* or other candidate genes may be possible.

Pulmonary Embolism

Incidence

The incidence of pulmonary embolism is from 23 to more than 200 per 100 000 population annually, and it is the cause of death in 0.2–5% of people. Approximately 10% of sudden deaths due to cardiovascular causes are due to pulmonary emboli, and about 5% of cardiac arrests are due to pulmonary embolus. The major risk factors for pulmonary embolism are deep venous thrombosis, trauma, postoperative state

Table 5 Characteristics of selected channel disorders that may result in sudden cardiac death without morphologic abnormalities

Syndrome[a]	*Chromosome*	*Gene*	*Current*	*Triggers*	*Events by age 40 (%)*	*Lethality of event (%)*	*Median age at first event (years)*
LQT1	11p 15.5	*KCNQ1* (KV LQT1)	$\Downarrow I_{Ks}$	Exertion, near drowning	62	4	9
LQT2	7q 35–36	*KCNH2* (HERG)	$\Downarrow I_{KR}$	Auditory stimuli	46	4	12
LQT3	3p 21–24	*SCN5A*	$\Uparrow I_{Na}$	Rest, sleep	18	20	16
LQT5	21q 22.1–22.2	*KCNE1* (MinK protein)	$\Downarrow I_{Ks}$				
LQT6	21q 22.1–22.2	*KCNE2* (MiRP1 protein)	$\Downarrow I_{KR}$				
JLN1	11p 15.5	*KCNQ1* (KV LQT1)	$\Downarrow\Downarrow I_{Ks}$	Exertion	75	50	6
Brugada	3p 21–24	*SCN5A*	$\Downarrow I_{Na}$	Sleep			35
FPVT	1q 42–43	*RyR2*	$\Uparrow Ca$[b]	Exertion, adrenergic stimuli	64	10	25

[a]All are autosomal dominant, with the exception of JLN (autosomal recessive).
[b]Mutations associated with FPVT result in increased sensitivity of calcium-induced activation of the calcium-release channel complex (L-type calcium channel).
LQT, long QT; HERG, human ''ether-a-gogo'' related gene; I_{Ks}, slowly activating component of delayed rectifier potassium current; I_{KR}, rapidly activating component of delayed rectifier potassium current; $\Uparrow I_{Na}$, sodium current; JLN, Jervell and Lange–Nielsen syndrome; MiRP1, MinK-related peptide 1; SCN5a, cardiac voltage-dependent sodium channel gene; FPVT, familial polymorphic ventricular tachycardia; RyR2, cardiac ryanodine receptor.
Blank fields indicate insufficient data.

(accounting for approximately 25% of hospital deaths due to pulmonary embolism), obesity, malignancy, old age, female gender, and chronic heart disease. After surgery, death from pulmonary embolism may occur within 24 h of the procedure and up to 30 days thereafter.

Deficiencies in protein C and S may be first diagnosed in patients who present with pulmonary embolism at a young age, often postoperatively. Affected members of families with protein S deficiency suffer pulmonary embolism at a high rate, from 7% to 26%, depending on other genetic factors. A large study from a medical examiner did not show an increased frequency of factor V Leiden in a series of patients who died with unexpected pulmonary embolism, and neither did a retrospective study of medical autopsies. The lack of association between pulmonary embolism and factor V Leiden is perplexing, given the established increased risk for deep venous thrombosis. Other thrombogenic factors that have been implicated in pulmonary embolism include a polymorphism of plasminogen activator inhibitor-1, which may increase the risk of pulmonary embolism in protein S-deficient individuals, and polymorphism for factor II (prothrombin G20210A polymorphism).

Pathologic Findings

The point of origin is usually in the lower veins (legs and abdomen). In a large series, 60% of thrombi were located in the lower venous tree, 12% in the upper venous tree, and no source could be detected in 28% of cases. The originating thrombi may be overlooked in an attempt to prevent disfigurement of the body, or the entire clot may have dislodged or lysed.

Although saddle emboli are invariably fatal, pulmonary emboli in cases of sudden death may be segmental, only involving muscular arteries. Often, a fatal embolus is relatively small but hardly tolerated because of the underlying cardiopulmonary situation. There is a wide variety of patterns of pulmonary embolism, but there is a predisposition to the right lung and lower lobes, and multiple emboli are the rule.

Because of the dual blood supply of the lungs, infarction only occurs if there is associated heart disease, especially mitral stenosis. Pulmonary infarction occurs in approximately 15% of cases, is more common in females, and is rare in patients without underlying cardiac diseases.

Of pulmonary emboli found at autopsy, 30–40% are considered the cause of death, 25% contribute to death, and the remaining are incidental. Symptomatic deep-vein thrombosis or pulmonary embolism is uncommon prior to autopsy-documented pulmonary embolism, partly because these patients are treated with anticoagulation.

See Also

Children: Sudden Natural Infant and Childhood Death; **Sudden Natural Death:** Central Nervous System and Miscellaneous Causes; Infectious Diseases

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Central Nervous System and Miscellaneous Causes

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Introduction

The investigation of sudden natural death occupies a significant proportion of the workload of the forensic pathologist. Sudden natural death as investigated by a coroner or medical examiner may have significant medicolegal ramifications in addition to providing valuable information to the deceased's immediate family and the community as a whole.

Cardiovascular disease and, in particular, coronary artery atherosclerosis is the most common cause of sudden and unexpected natural death in western societies. This review will concentrate on the important causes of noncardiac death, with particular emphasis on the central nervous system. Meningoencephalitis has been discussed elsewhere.

Definition

The definition of sudden natural death varies between organizations and jurisdictions. Although the World Health Organization defines sudden death as occurring within 24 h of the onset of symptoms, many forensic pathologists would only include cases where the death has occurred within hours of signs and symptoms or when the immediate clinical history is unknown.

Systems

Central Nervous System

The optimum investigation of deaths resulting from intracranial pathology involves formalin fixation of the brain and examination by a neuropathologist. Unfortunately this level of investigation is becoming available only at specialist institutions. A further significant issue of relevance to neuropathological examination is organ retention. However, with sensitive and open discussion with the deceased's family and by using rapid fixation techniques, these problems can be addressed. The forensic and general pathologist can facilitate later expert review of a particular case if generous labeled sections are taken for histology along with adequate notation and photographs.

Intracranial hemorrhage Sudden and unexpected death attributable to the central nervous system usually occurs as a consequence of intracranial hemorrhage. The two common natural anatomical sites of intracranial hemorrhage are intraparenchymal hemorrhage and subarachnoid hemorrhage. Less commonly, the hemorrhage may involve the extradural or subdural spaces or the ventricular system. The site of the hemorrhage will tend to vary with respect to the deceased's age and the underlying pathology.

Intraparenchymal hemorrhage Intraparenchymal hemorrhage incorporates intracerebral and brainstem hemorrhages. The vast majority of cases are associated with systemic hypertension. The common sites for hypertensive intraparenchymal hemorrhage are basal ganglia, thalamus, the hemispheres, pons, and cerebellum (**Figure 1**). The clinical evolution of intraparenchymal hemorrhage tends to be sudden with rapid decline in neurological function. The clinical symptoms range from sudden onset of headache to immediate loss of consciousness in pontine hemorrhage. Supratentorial hematomas within the rigid confines of the skull will displace the brain in a predictable way. The volume of blood within the brain required to cause critical brain compression is 75–100 ml. After the ventricles are compressed there will be subfalcine, transtentorial, and finally cerebellar tonsillar herniation. Cerebellar hemorrhage may result in headache, ataxia, and vomiting with loss of consciousness occurring due to brainstem compression. Pathological examination of the brain may reveal lipohyalinotic degeneration of blood vessels in sites of predilection for hemorrhage. It has

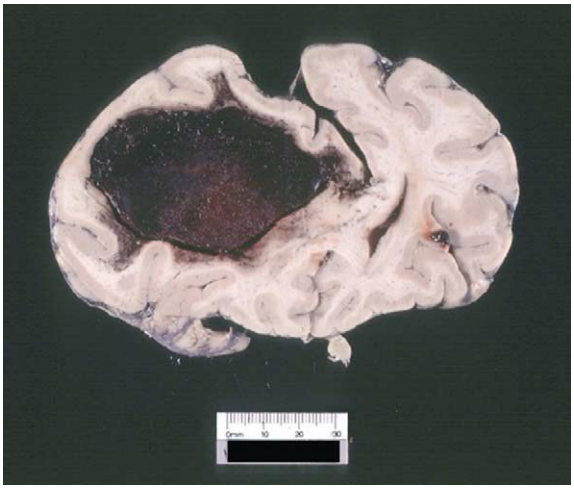

Figure 1 Hypertensive brain hemorrhage.

been recently reported that an acute vascular lesion in intracerebral hemorrhage is fibrinoid necrosis of arterioles.

In general, individuals who die from a hypertensive hemorrhage will have a clinical history of longstanding hypertension. The postmortem examination may show systemic effects of the disease including concentric left ventricular hypertrophy and benign nephrosclerosis. The brain may also show evidence of old lacunar infarcts within the basal ganglia.

Cerebral amyloid angiopathy causes about 12% of primary nontraumatic intracerebral hemorrhage. The disorder occurs as the result of the deposition of amyloid protein within small- and medium-sized cortical arteries and results in often multifocal peripheral and lobar hemorrhage. The deposition of amyloid into the vessel walls renders them leaky. Cerebral amyloid angiopathy is seen in elderly, normotensive individuals and is associated with both Alzheimer disease and Down syndrome.

Unusual anatomical sites of hemorrhage may suggest an underlying vascular malformation. The most frequent of these lesions is the arteriovenous malformation, a collection of tangled arteries, veins, and vascular channels that commonly occur over the cerebral hemispheres but also deep within the basal ganglia and thalamus. Arteriovenous malformations may cause both subarachnoid and intraparenchymal hemorrhage.

Other less common causes of intraparenchymal hemorrhage include bacterial endocarditis, vasculitides, connective tissue disorders, blood dyscrasias, and tumors.

In young adults the presence of an intraparenchymal hemorrhage should raise the possibility of an association with recent use of illicit drugs, including amphetamines and cocaine.

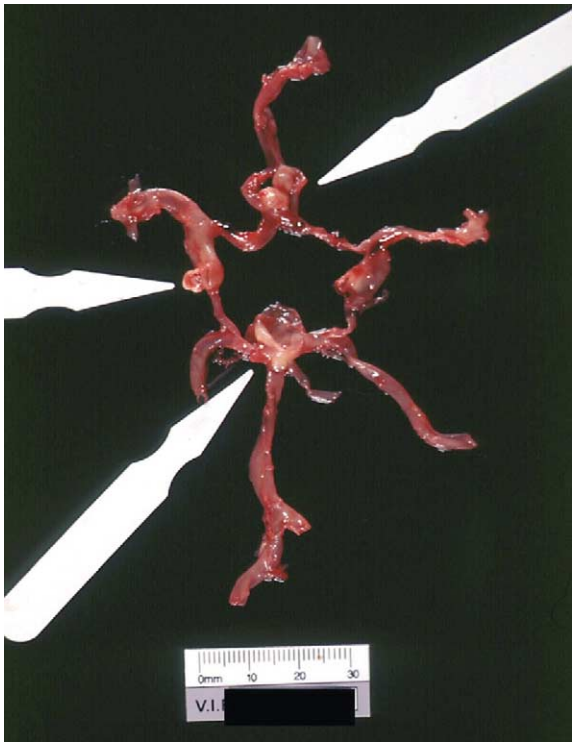

Figure 2 Aneurysms within the circle of Willis.

Subarachnoid hemorrhage Nontraumatic subarachnoid hemorrhage arises primarily from berry aneurysms arising from bifurcation points within the circle of Willis at the base of the brain (Figure 2). Berry aneurysms are believed to originate from a congenital defect in the media of the artery at a branching point. The elastic lamina and muscularis of the artery terminates at the neck of the aneurysm with the wall of the aneurysmal sac formed by thickened hyalinized intima and adventitial tissue. It is believed that the most critical factor leading to rupture of an aneurysm is its size, with diameters greater than 1 cm at significant risk of rupture and subsequent death. The rupture of such an aneurysm is more likely to occur during the day and may be associated with acute stress causing an elevation of blood pressure. The rupture is usually from the tip of the aneurysm and results in blood entering the subarachnoid space and manifests as sudden onset of severe headache or collapse. It is not uncommon for the deceased individual to have complained of symptoms including severe and persistent headache during the weeks leading to death and this is due to the aneurysm leaking.

The ruptured aneurysm results in extensive basal subarachnoid hemorrhage and may be associated with intraventricular hemorrhage, and sometimes intracerebral hemorrhage if the aneurysm ruptures directly into the brain parenchyma.

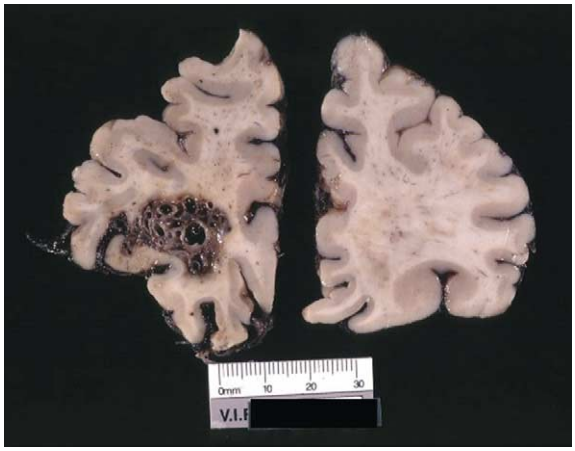

Figure 3 Arteriovenous malformation of the brain.

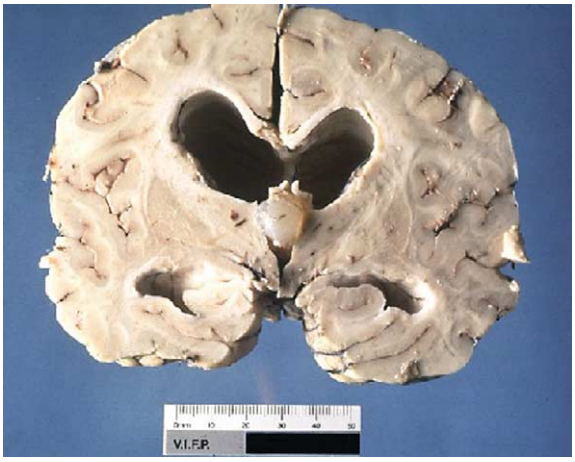

Figure 4 Hydrocephalus from colloid cyst of third ventricle.

At the postmortem examination it is imperative to examine the brain before fixation. The arachnoid is gently removed with fine forceps and the blood displaced with a gentle stream of running water.

Removal of the blood may be facilitated by a dampened swab. In most cases the aneurysm can be identified; however, in some cases, no aneurysm can be detected and one assumes the rupture has completely destroyed a small aneurysm.

Rupture of an arteriovenous malformation causes approximately 10% of subarachnoid hemorrhage and this is more often associated with intraparenchymal and intraventricular extension (Figure 3).

Sudden and Unexpected Death in Epilepsy

Sudden and unexpected death in epilepsy (SUDEP) may be defined as a death occurring in an individual with a documented clinical history of epilepsy, not associated with trauma, drowning, or status epilepticus, and associated with a normal complete postmortem examination with toxicological examination. Most of these deaths occur in the 20–40-years age group with a slight male preponderance.

Whilst witnessed deaths occur, including those following a seizure, most affected individuals are found deceased in bed. Evidence of seizure activity such as tongue injuries and incontinence are relatively nonspecific and may also occur following terminal seizure activity in deaths from other causes. Risk factors for SUDEP include early onset of seizures, poor seizure control, and generalized tonic/clonic seizures. The weight of evidence would suggest that the deaths may be a result of seizure-related apnea and cardiac arrhythmias.

The identification of pathological processes within the central nervous system varies with the level of neuropathological investigation. In one prospective study of 50 cases of SUDEP with formal neuropathological examination, no structural cause of epilepsy was found in 28 cases. Old head injury accounted for eight cases. Mesial temporal sclerosis was identified in eight cases. The remaining cases showed arteriovenous malformations, ectopic gray matter, cortical dysplasia, Sturge–Weber syndrome, and multicystic encephalopathy.

Temporal sclerosis is believed to be a consequence of seizure activity rather than the underlying cause. Toxicological examination may show therapeutic or subtherapeutic levels of anticonvulsant medications with conflicting reports presented in regard to the incidence of subtherapeutic levels of anticonvulsant therapies in SUDEP. These discrepancies may also relate to postmortem drug redistribution that occurs with many therapeutic drugs, including anticonvulsants, in the postmortem period.

Tumors and tumor-like conditions In rare circumstances an individual may die suddenly and unexpectedly from an undiagnosed central nervous system tumor. When this occurs, it is most commonly associated with hemorrhage into the tumor or sudden obstruction to cerebrospinal fluid, resulting in acute hydrocephalus. Hydrocephalus may also be seen in association with the rare colloid cyst of the third ventricle which may cause sudden death in young individuals (Figure 4).

Respiratory System

Sudden death from asthma is well described in the forensic and respiratory medicine literature. Uncommon causes of sudden death include acute epiglottitis, pneumonia, massive pulmonary hemorrhage, and pulmonary hypertension.

Sudden death in asthma Individuals with asthma may suffer sudden and unexpected death not associated with status asthmaticus. The death rate increases with age. The true incidence is difficult to determine as the presence of other diseases, especially ischemic heart disease and chronic obstructive airways disease, may cause a falsely reduced reporting of acute asthma on death certificates.

In general, individuals who die from asthma have a history of significant disease with multiple hospital admissions, low FEV_1 (forced expiratory volume in one second), peripheral blood eosinophilia, and a high degree of irreversibility of bronchospasm with a bronchodilator, all factors which suggest severe or uncontrolled asthma. There is a weak association with prior use of oral corticosteroids. However, a significant proportion of the deaths occur in individuals whose asthma has been clinically stable.

An acute asthmatic attack results in airway obstruction by mucus and bronchospasm with subsequent ventilation–perfusion imbalance, leading to hypoxia and hypercapnia. It is believed that death is ultimately related to a cardiac arrhythmia, most probably occurring in the setting of hypoxia and acidosis in a myocardium sensitized by catecholamines.

Postmortem radiology may reveal pneumothorax and mediastinal emphysema reflecting severe obstruction with raised intrathoracic pressures. Macroscopic examination of the lungs reveals voluminous lungs with mucus plugs in bronchi and bronchioles (Figure 5). There may be regions of collapse. Microscopic examination of the lung tissue shows a thickened basement membrane within bronchi, smooth-muscle hyperplasia, and an infiltrate of inflammatory cells, including neutrophils and eosinophils. Eosinophils are prominent within the mucosa and within the bronchial lumen. Some studies have suggested the presence of numerous neutrophils as a marker for an acute attack. Rarely one may see desquamated mucosal epithelium (Curschmann spirals) within the bronchus.

Occasionally, the initial diagnosis of asthma will be made at the postmortem examination. More commonly, information from the scene may include a bronchodilator in close proximity, the presence of cigarettes at the scene, and other medications such as aspirin or beta-blocking medications that could potentially precipitate an acute attack.

Acute epiglottitis Acute epiglottitis is an acute infection of the epiglottis that is well recognized in children but which may also occur in adults. The causative organism is usually *Haemophilus influenzae*. Despite immunization with the *H. influenzae* type B (HiB) vaccine, isolated cases are still recorded. The disease is characterized clinically by high fever, severe sore throat, and painful dysphagia. Death results from acute upper-airway obstruction. The postmortem examination shows edematous mucosa with a pronounced acute inflammatory infiltrate (Figure 6).

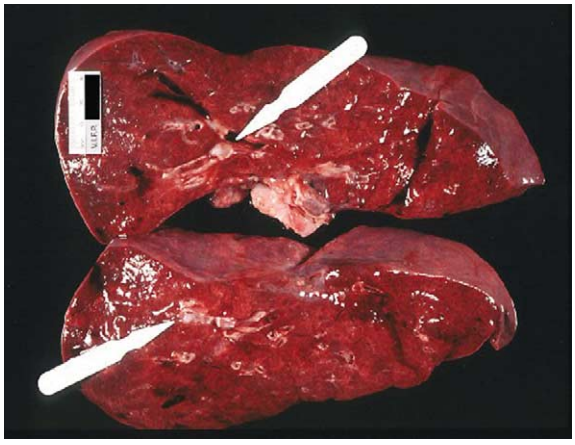

Figure 5 Mucus plugs within bronchi in asthma.

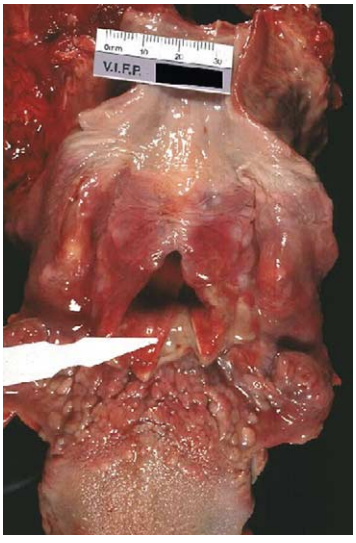

Figure 6 Purulent exudative epiglottitis in an adult with only moderate edema.

Pneumonia In developed countries most individuals with significant lower respiratory tract infections will consult their medical practitioner and receive appropriate care. However, individuals who live a marginal existence, or those with significant underlying natural disease, may succumb to pneumonia before a diagnosis is established and thus be referred to the coroner. The most common cause of community-acquired pneumonia is *Streptococcus pneumoniae*. Infections

with organisms such as *Legionella pneumophila* may result in sporadic deaths in addition to occasional outbreaks.

Massive pulmonary hemorrhage Massive pulmonary hemorrhage leads to death as a consequence of profound hypoxemia secondary to upper-airway obstruction. The most common cause is erosion of a large artery by a lung malignancy. Rarely vasculitides, infectious, and other inflammatory disorders may be the underlying cause.

Pulmonary hypertension Pulmonary hypertension is usually a secondary manifestation of primary myocardial or cardiac valve diseases, underlying pulmonary disease, or chronic pulmonary thromboembolism. Sudden and unexpected death is seen in primary pulmonary hypertension, a rare progressive disorder characterized by the presence of intimal fibrosis, medial hypertrophy, microthrombosis, and plexiform lesions in precapillary pulmonary arteries. The disease is twice as common in females and usually presents in the third decade of life.

Gastrointestinal Tract

Sudden and unexpected death attributable to the gastrointestinal tract often involves a catastrophic complication of an underlying chronic disease process. Massive gastrointestinal hemorrhage, perforated viscus, hemoperitoneum, and pancreatitis are the more common causes of death.

Gastrointestinal hemorrhage The etiological factors in gastrointestinal hemorrhage are protean and include esophageal varices, peptic erosions and ulceration, angiodysplasia, diverticular disease, ischemic colitis, and tumors. Hemorrhage arising from the upper gastrointestinal tract may result in hematemesis, the vomiting of frank blood. Blood acted upon by gastric acid becomes a sticky black stool called melena. The scene of death in such cases may demonstrate a large volume of fresh blood and/or show melena stool.

The hemorrhage may be entirely internal with no significant scene findings.

Individuals with cirrhosis of the liver from any cause may develop varices of submucosal esophageal veins, which are prone to trauma and sudden massive hemorrhage. The concomitant liver disease results in coagulation abnormalities, which exacerbate the hemorrhage. The postmortem examination may not show any macroscopic abnormality in the esophagus as the varices will collapse with the absence of blood pressure. Blind sections for histology should demonstrate dilated submucosal veins.

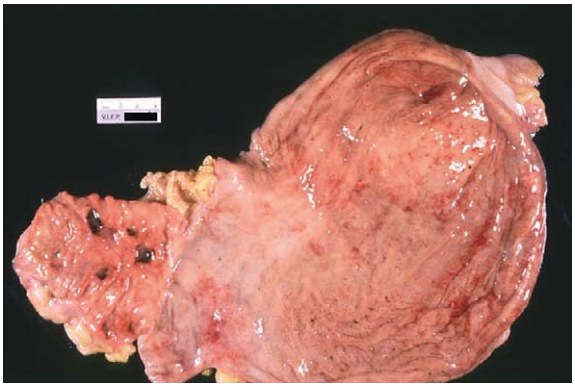

Figure 7 Peptic ulcers within the duodenum.

Peptic ulceration is often associated with the colonization of the stomach with the bacterium *Helicobacter pylori*. Ulceration also occurs with ingestion of alcohol and therapeutic medications, including nonsteroidal antiinflammatory drugs (Figure 7). Torrential hemorrhage can occur if there is erosion of a submucosal artery. Widespread gastric erosions are seen in severe "stress" of any cause and is believed to relate to increased circulating glucocorticosteroids. Rarely, both benign and malignant gastrointestinal tumors may cause fatal hemorrhage. Meckel diverticulum in the small bowel may contain acid-secreting gastric mucosa and develop ulceration.

Angiodysplasia and other vascular disorders have been described in the stomach and more commonly in the right colon. The source of the bleeding can be extremely difficult to define at the postmortem examination. Angiographic techniques have shown success in identifying the abnormal vessels. Microscopic examination shows dilated mucosal capillaries with associated dilated submucosal capillaries and venules.

Ischemic colitis leads to shock from a combination of hemorrhage and sepsis related to the ischemic mucosa, and is well recognized in elderly individuals with generalized atherosclerosis. The condition may also occur acutely when emboli from the heart or aorta occlude the superior mesenteric artery.

Peritonitis Perforation of a viscus is most commonly seen from full-thickness ulceration in the stomach or duodenum. Occasionally a perforated appendix, diverticulum, or tumor can cause death from generalized peritonitis. Spontaneous bacterial peritonitis is a serious complication of ascites in individuals with chronic liver disease.

Spontaneous hemoperitoneum Spontaneous hemoperitoneum is a rare condition with a number of etiologies. The intraperitoneal hemorrhage may

occur from rupture of the spleen, liver, or from dysplasias and inflammatory disorders of the splanchnic arteries. Infectious mononucleosis and lymphoid malignancies of the spleen have been associated with rupture, as have adenomas and sarcomas of the liver. Arterial dysplasia and vasculitides such as polyarteritis nodosa may result in splanchnic artery rupture.

Pancreatitis Acute and chronic pancreatitis is most commonly related to the presence of gallstones or excessive alcohol intake but is also seen in hyperlipoproteinemia, the vasculitidies, and other inflammatory conditions. The severe end of the spectrum of acute inflammation, hemorrhagic pancreatitis, can lead to death due to gross metabolic disturbance and multiple-system failure induced by systemic inflammatory mediators in the systemic inflammatory response syndrome.

Endocrine System

Sudden and unexpected death attributable to the endocrine system mainly involves metabolic complications of diabetes mellitus and, rarely, adrenocortical insufficiency.

Diabetes mellitus Diabetes is a major risk factor for atherosclerosis and subsequently acute myocardial infarction and cerebrovascular events. Furthermore, diabetes mellitus may cause sudden and unexpected death in young individuals from profound metabolic disturbance associated with the presence of marked hyperglycemia.

Diabetes mellitus may lead to sudden unexpected death as a consequence of diabetic ketoacidosis or, rarely, nonketotic hyperosmolar hyperglycemia. Often in retrospect there may have been a history of polydipsia and polyuria, weight loss, and a sense of being generally unwell. Postmortem toxicological examination can reveal a raised glucose concentration within the vitreous humor of the eye. This will be associated with a markedly raised acetone level in blood in cases of ketoacidosis. Microscopic examination of the kidney in cases of diabetic ketoacidosis may show vacuolization of the tubules (Armanni–Ebstein lesion).

Adrenocortical insufficiency Adrenocortical insufficiency refers to adrenal gland cortical failure. Patients with clinically stable adrenocortical insufficiency may succumb to an Addisonian crisis from acute illness. Rarely an individual with undiagnosed adrenocortical insufficiency may die suddenly and be referred for coronial postmortem examination. In the first instance the examination is tailored to identify any acute illness that could have precipitated the death. In the undiagnosed case histological sections may reveal granulomas in tuberculosis, or lymphocytic inflammation in autoimmune disease.

Serological examination can confirm the presence of autoantibodies and biochemical analysis can measure adrenocorticotropic hormone and cortisol levels.

Metabolic and Inherited Causes of Sudden Death

Disorders of connective tissue are a group of uncommon and rare genetically determined diseases that may present as sudden unexpected death.

Marfan syndrome is an autosomal dominant disorder of connective tissue with high penetrance and variable severity which affects multiple organ systems. The common clinical findings are bilateral subluxation or dislocation of the lens of the eye, a tall thin stature with arachnodactyly, with 90% of affected individuals having cardiovascular involvement, including mitral valve regurgitation and mitral valve prolapse. Dissection and rupture of the aortic root are the most common causes of sudden death. The underlying changes in connective tissue are caused by mutations in extracellular matrix glycoprotein fibrillin-1, which is encoded at chromosome 15.

Ehlers–Danlos syndrome (EDS) is a heterogeneous group of rare autosomal dominant inherited disorders of connective tissue caused by mutations in the gene encoding type III collagen. The more common clinical findings are tissue fragility with easy bruising, excessive skin elasticity, and joint hypermobility. Eleven types of EDS have been described. In type IV EDS vascular involvement can lead to fatal vascular, intestinal, and obstetric complications. Arterial rupture is the most common cause of sudden unexpected death.

Inborn errors of metabolism encompass a wide range of inherited disorders, including the organic acidemias, urea cycle defects, and disorders of amino acid metabolism. These disorders typically present in the infant with lethargy, poor feeding, recurrent vomiting, and failure to thrive. Metabolic acidosis and hypoglycemia are common clinical findings in many of these conditions. Clinical investigation in the infant suspected of having an inborn error of metabolism includes blood-gas analysis, serum, urea and electrolytes, blood glucose, urinary reducing substances and ketones, plasma and urine amino acids, and urine organic acid analysis. Further investigations include liver biopsy, skin biopsy with fibroblast culture, enzyme assay, and molecular analysis.

See Also

Sudden Natural Death: Cardiovascular; Infectious Diseases

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Infectious Diseases

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Introduction

A wide range of deaths from natural causes is encountered in the field of forensic medicine. Despite the advances in the diagnosis and treatment of infectious diseases, a substantial number of sudden and unexpected deaths are caused by infections. In most medicolegal systems these deaths are subject to a forensic investigation.

The World Health Organization defines sudden death as that occurring within 24 h of the onset of symptoms. Some authors variably define sudden death as that occurring within 1, 6, and 12 h of the onset of symptoms.

Forensic pathologists should be aware of the importance of infectious causes of sudden death in the present era of bioterrorism and emergent and reemergent diseases. Genetic engineering has led to the development of highly infectious and virulent strains of microorganisms (e.g., anthrax). Emerging infectious diseases are infections whose incidence has increased in recent years and/or threatens to increase in the near future. Reemergence refers to the reappearance of a known infection after a period of disappearance or decline.

Death from infectious agents may occur as a direct consequence of the infection or from complications such as immunosuppression caused by the infection and adverse reactions to therapeutic drugs. Sudden death due to infectious disease may be classified by organ system involvement (e.g., cardiac – myocarditis; nervous system – meningitis and encephalitis) or according to the etiological agent (e.g., viral, chlamydial, bacterial, fungal, protozoal, or helminthic). The common infectious causes of sudden death by organ system are listed in **Table 1**.

The morphological findings at autopsy will depend on the type of organism, the site involved, and the host's response to the organism. Microbiological demonstration of an organism does not equate to disease, as a host may be colonized by bacteria or the patient may have an asymptomatic viral infection. The exquisite sensitivity of molecular tests, e.g., polymerase chain reaction, may exacerbate this problem if the results are not correlated with the pathological findings at autopsy.

Infectious Causes of Sudden Death

Categories of human pathogens include prions; viruses; chlamydiae, rickettsiae, and mycoplasmas;

Table 1 Common infectious causes of sudden death

Cardiovascular system	
Myocarditis	Coxsackie A and B *Chlamydia pneumoniae* *Corynebacterium diphtheriae*, *Neisseria meningitidis, Borrelia burgdorferi, Mycobacterium tuberculosis* Chagas disease (*Trypanosoma cruzi*) Hydatid disease (*Echinococcus granulosus*)
Infective endocarditis	*Staphylococcus, Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella, Candida*
Respiratory system	
Acute epiglottitis	*Haemophilus influenzae*
Pneumonia	Respiratory syncytial virus, parainfluenza virus, adenovirus, influenza A and B, severe acute respiratory syndrome (SARS), *Streptococcus pneumoniae,* staphylococci, *H. influenzae*, *Pseudomonas aeruginosa,* coliform bacteria, *Legionella pneumophila, Pneumocystis carinii*
Central nervous system	
Meningitis	*H. influenzae, S. pneumoniae, N. meningitides, Cryptococcus*
Encephalitis	Herpes simplex virus-1 Toxoplasmosis, malaria
Gastrointestinal system	
Peptic ulcer	*Helicobacter pylori*
Enterocolitis	*Vibrio cholerae*, *Clostridium perfringens, Salmonella*, *Shigella*, enteroinvasive *Escherichia coli, Entamoeba histolytica*

bacteria; fungi; protozoans; and helminths. Infection by prions, rickettsiae, and mycoplasmas is not normally associated with sudden and unexpected death.

Viral Causes of Sudden Death

Viruses are ubiquitous and cause a spectrum of disease in humans. These may range from asymptomatic infection, severe debilitating illness, to sudden death. Viral infections causing sudden death usually involve the cardiac, respiratory, or the central nervous system. Morphologic findings in viral infections may include intranuclear and/or intracytoplasmic inclusions, multinucleate giant cells, and tissue necrosis (cytopathic effect). In many cases the diagnosis can only be made on special investigations, e.g., culture, electron microscopy, serology, or molecular testing.

Viral hemorrhagic fevers such as Marburg, Lassa, and Ebola virus may cause sudden death in children. If there is any suspicion of a viral hemorrhagic fever, special care must be taken to avoid unwarranted exposure to health workers. The local public health officials must be informed and consideration given to limited autopsy examination in consultation with a virologist (e.g., postmortem blood sampling and liver biopsy).

Viral infections of the cardiovascular system Cardiac involvement usually takes the form of myocarditis. Although many viruses may cause myocarditis (Table 2), coxsackie A and B are responsible for most cases. Fulminant coxsackievirus infection may also cause leptomeningitis, florid interstitial pneumonitis, pancreatitis, and focal hepatic necrosis. Coxsackie B viruses should also be considered as a cause of sudden infant death.

At autopsy, the myocardium is usually mottled and flabby. Histology reveals focal infiltrates of inflammatory cells (neutrophils and/or lymphocytes, plasma cells, and macrophages). At least two foci of individual myofiber necrosis associated with 5–10 inflammatory cells are required for the histological diagnosis of myocarditis. Focal aggregates of lymphocytes not associated with necrosis may be seen in elderly patients and are not diagnostic of myocarditis. Myocardial involvement may be patchy. For adequate histological sampling, it is recommended that at least six sections be taken from various areas of the myocardium, including the left ventricle and nodal tissue.

Indirect damage to the myocardium may occur as an allergic response to a viral infection and eosinophilia, e.g., in eosinophilic myocarditis. This is a rare cause of sudden death in apparently healthy children due to the cardiac toxicity of eosinophils.

Studies have shown that persons undergoing severe mental or physical stress may have reduced immunity to viral infections. In the investigation of sudden death in athletes, the diagnosis of viral myocarditis must be considered.

Enteroviral infection may also play an important role in coronary plaque instability and may precipitate coronary thrombosis, leading to ventricular tachyarrhythmias and sudden death.

Table 2 Viral causes of myocarditis

Adenovirus
Cytomegalovirus
Epstein–Barr virus
Herpes simplex virus 1 and 2
Human immunodeficiency virus 1 (HIV-1)
Influenza A and influenza B
Parvovirus
Picornavirus (e.g., enterovirus and coxsackievirus A and B)
Respiratory syncytial virus
Rotavirus
Varicella-zoster virus

Viral infections of the respiratory system Sudden death due to viral involvement of the respiratory system may be due to fulminant viral pneumonitis or bacterial pneumonia complicating an initial viral pneumonitis. Viruses implicated include respiratory syncytial virus, human herpesvirus-6, and parainfluenza virus in children, and adenovirus and influenza A and B in adults.

Microscopically, the findings of a viral pneumonitis are usually nonspecific and include edema and widening of the interstitial septa with a mononuclear cell infiltrate. In some cases, diagnostic viral inclusions may be demonstrated.

Emergent diseases such as severe acute respiratory syndrome (SARS) have a high mortality and may cause death within hours. SARS refers to an acute respiratory illness caused by infection with a novel coronavirus currently known as the SARS virus.

Postmortem histopathological evaluations of lung tissue show diffuse alveolar damage consistent with the pathologic manifestations of acute respiratory distress syndrome. There is usually mild interstitial inflammation with scattered alveolar pneumocytes showing cytomegaly, and enlarged nuclei with prominent nucleoli.

When faced with the finding of diffuse alveolar damage at autopsy, the pathologist should consider other infective causes such as influenza, para influenza, respiratory syncytial, and adenoviruses, *Chlamydia, Mycoplasma, Pneumococcus, Legionella,* and *Pneumocystis*.

Viral infections of the central nervous system Sudden death may occur due to direct infection of the nervous system or a complication of a viral infection such as toxoplasmosis in human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS). Herpes simplex virus-1 encephalitis is usually due to reactivation of latent infection. Commonly affected sites include the temporal lobe(s) (medial before lateral), the inferior frontal lobe(s), and the Sylvian cortex(es). At autopsy there is widespread and asymmetrical necrosis. In fulminant cases there is prominent hemorrhage and swelling with raised intracranial pressure and brain herniation. Histological findings include perivascular cuffing by mononuclear cells (Figure 1) and, in a small number of cases, intranuclear inclusions may be seen in astrocytes and neurons.

In adult HIV infections, sudden death from infective causes may be due to opportunistic infections (e.g., toxoplasmosis) or rupture of mycotic aneurysms.

In viral central nervous system infections the brain may appear macroscopically normal, especially in very young, elderly, debilitated, and immunocompromised individuals. Specimens should be taken for microbiology and histology. Serum and cerebrospinal fluid (CSF) should be sent for antibody studies. Tissue for histological examination should be taken from normal, obviously abnormal, and transition areas. Routine sections should be taken from the cerebral cortex (all four lobes), thalamus, basal ganglia, hippocampus, brainstem, and cerebellum. As poliomyelitis has been described as a cause of sudden death in infants, autopsy protocols in sudden death should include histological examination of spinal cord and dorsal root ganglia.

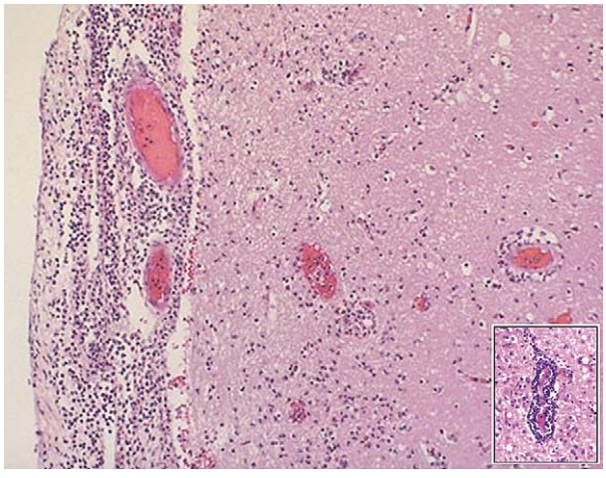

Figure 1 Viral meningoencephalitis. Insert: perivascular cuffing by lymphocytes.

Chlamydial Causes of Sudden Death

Chlamydia pneumoniae may be associated with myocarditis and sudden unexpected death.

Bacterial Causes of Sudden Death

Bacterial infections are responsible for sudden unexpected death in adults and children. In the pediatric population bacterial infections of the respiratory, gastrointestinal, and central nervous system account for the majority of cases of sudden death.

Bacterial infections of the cardiovascular system Bacterial causes of myocarditis include *Corynebacterium diphtheriae*, *Neisseria meningitidis*, and *Borrelia burgdorferi*. In *B. burgdorferi*, cardiac involvement occurs in 1–8% of cases and death may occur as a result of conduction disturbances. In diphtheritic myocarditis myocardial damage is caused by the release of toxins. *Bartonella*-induced silent myocarditis has been described as a cause of sudden unexpected cardiac death in athletes.

Granulomatous myocarditis may also lead to sudden death (Table 3). The mechanism of death includes arrhythmias, cardiac rupture, coronary occlusion, obstruction to pulmonary blood flow leading to fatal hemorrhage, and impaired myocardial contractility.

Cardiac tuberculosis is usually an autopsy diagnosis. Histological examination of the myocardium shows a nodular, miliary, or diffuse infiltrative pattern. The coronary arteries may show narrowing or complete occlusion due to an intimal or diffuse tuberculous arteritis. It is uncommon to demonstrate acid-fast bacilli within the lesions. Molecular tests such as the ligase chain reaction (LCR) and polymerase chain reaction (PCR) may be used to demonstrate the organism.

Table 3 Differential diagnosis of granulomatous myocarditis

Disease	*Histological features*
Giant-cell/ Fiedler's myocarditis	Noncaseating granulomas with adjacent muscle necrosis ± giant cells
Tuberculosis	Caseous necrosis with Langhan's giant cells
Sarcoidosis	Noncaseating granulomas with myocardial fibrosis Schaumann and asteroid bodies Calcium oxalate crystals within giant cells
Syphilis	Gummata with necrosis Sparse epithelioid cells
Brucellosis	Myocardial abscesses and endocarditis
Tularemia	Tuberculoid granulomas
Fungi	Granulomas with or without necrosis Hyphae and yeasts

Sudden death in infective endocarditis occurs as a result of perforation of a free-wall myocardial abscess or rupture of a valve leaflet. *Staphylococcus aureus* is responsible for 10–20% of cases and is the major cause in intravenous drug abusers. Other bacterial causes include *Haemophilus, Actinobacillus, Cardiobacterium, Eikenella*, and *Kingella* (HACEK group). Negative bacterial cultures may be found in 10% of cases as a result of prior antibiotic therapy. The most common sites of infection are the aortic and mitral valves, except in intravenous drug abusers, where the right-sided valves are primarily affected.

Tertiary syphilis causing aortitis may cause sudden death from rupture of aortic aneurysms with aortic dissection. The mechanism of death is either blood loss with hypovolemic shock or a fatal cardiac tamponade from intrapericardial rupture.

Figure 2 Lobar pneumonia. Left lung, showing consolidation of the lower lobe. Insert: alveolar spaces filled with acute inflammatory exudate.

Bacterial infections of the respiratory system

Sudden death from acute epiglottitis occurs from respiratory obstruction caused by swelling of the epiglottic folds, uvula, and vocal cords. The most common cause of acute epiglottitis in developing countries is *Haemophilus influenzae* type B. In countries with established immunization programs, the incidence of *H. influenzae* epiglottitis has decreased and other bacteria, such as streptococcus, staphylococcus, and pneumococcus, have been implicated as possible causes. Postmortem blood cultures are positive in 50–75% of cases.

Lobar pneumonia (Figure 2) and confluent bronchopneumonia are the most frequent cause of sudden death from acute pulmonary disease. Some 90–95% of lobar pneumonia is due to *Streptococcus pneumoniae* type 3. Bronchopneumonia is caused by staphylococci, streptococci, *H. influenzae*, *Pseudomonas aeruginosa*, and coliform bacteria.

Pulmonary tuberculosis may result in hemoptysis, which can cause hypovolemic shock and sudden death. Histologically, caseating granulomas are found. Acid-fast bacilli are demonstrated using the Ziehl–Neelsen stain (Figure 3).

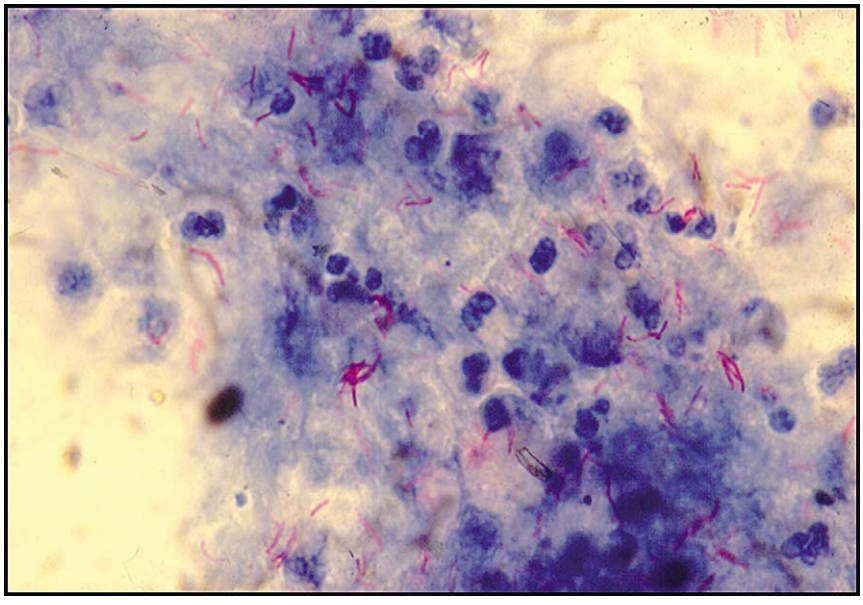

Figure 3 Tuberculosis. Acid-fast bacilli demonstrated using a Ziehl–Neelsen stain.

Corynebacterium diphtheriae produces a gray pseudomembrane from the pharynx to the larynx, and this may lead to respiratory obstruction and sudden death.

Legionnaire's disease is associated with outbreaks of sudden death. The disease is caused by *Legionella pneumophila*, a facultative intracellular organism. It causes severe pneumonia in the elderly, in smokers, and in immunocompromised patients. The organisms may be transmitted via droplet spread from contaminated air-conditioning units and water coolers. The organism may be demonstrated by a modified silver stain (Dieterle stain) or by immunofluorescence and culture.

Bacterial infections of the central nervous system Pyogenic meningitis may cause sudden death. The causative organism varies according to the age of the patient (Table 4).

The location of the exudates depends on the organism. In *H. influenzae* it is basally located. In pneumococcal meningitis it occurs over the convexities of the brain in the parasagittal region (Figure 4). Microscopic examination reveals neutrophils filling the subarachnoid space with extension of the inflammation into the leptomeningeal veins in fulminant cases.

Blood spread is the most common means of entry; however other routes of infection include local extension of infection, e.g., paranasal sinusitis, osteomyelitis, direct implantation, and via the peripheral nervous system.

Diffuse bacterial meningitis may follow rupture of a brain abscess, which may lead to sudden death.

The organisms may be demonstrated by microbiological culture of the CSF and examination of Gram stains of the CSF and brain tissue.

Table 4 Bacterial causes of acute meningitis according to age group

Age group	*Organisms*
Neonates	*Escherichia coli* Streptococci *Listeria monocytogenes*
Children	*Haemophilus influenzae* *Neisseria meningitidis*
Adults	*Neisseria meningitidis* *Streptococcus pneumoniae*
Elderly	*Streptococcus pneumoniae* *Listeria monocytogenes*

Bacterial urogenital tract infections Fulminant acute bacterial pyelonephritis may lead to septicemia, causing sudden death. At autopsy, the kidneys show tubular necrosis with interstitial suppurative inflammation. Renal papillary necrosis may also be present.

Bacterial infections of the gastrointestinal tract Severe bacterial enterocolitis may lead to sudden death, especially in the young. The pathogenesis of the diarrhea depends on the cause. *Vibrio cholerae* and *Clostridium perfringens* cause diarrhea by ingestion of a preformed toxin that is present in contaminated foods. Enteroinvasive organisms such as *Salmonella*, *Shigella*, and enteroinvasive *Escherichia coli* invade and destroy mucosal epithelial cells. Death occurs as a result of dehydration and electrolyte imbalance.

Bleeding peptic ulcers that are caused by *Helicobacter pylori* may be the first indication of an ulcer and account for 25% of ulcer deaths, many of which are sudden and unexpected.

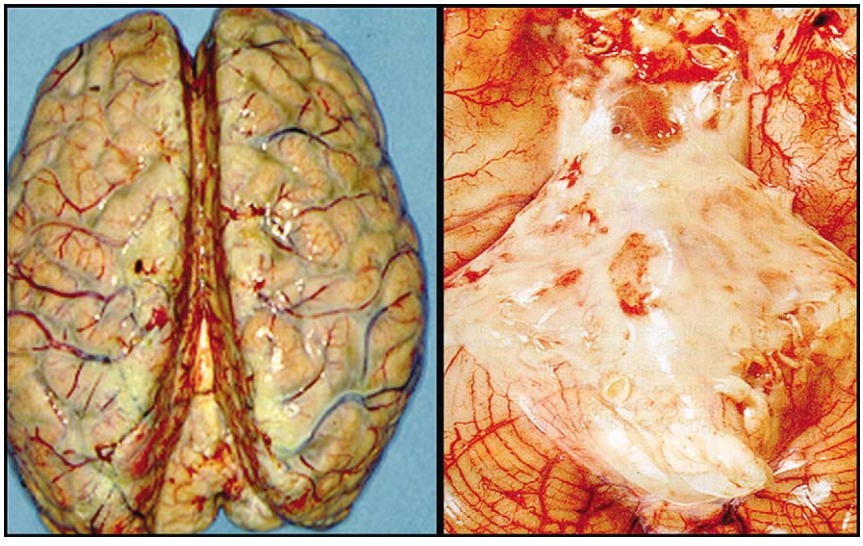

Figure 4 Bacterial meningitis. Exudate demonstrated over convexities and base of the brain.

Fulminant bacterial peritonitis secondary to acute appendicitis, acute salpingitis, ruptured peptic ulcer, diverticulitis, strangulated bowel, and cholecystitis may cause sudden death. Primary peritonitis may occur postsplenectomy and in patients with splenic hypoplasia. Patients with sickle-cell disease may have anatomical or functional asplenia. The former is due to repeated bouts of infarction leading to autosplenectomy. The latter is due to a defect in opsonization of encapsulated bacteria.

Massive bilateral adrenal hemorrhage with adrenocortical insufficiency may occur as a result of septicemic shock from overwhelming bacterial infection (Waterhouse–Friderichsen syndrome). The most common association is with *Neisseria meningitidis* septicemia; however, other virulent organisms, e.g., *H. influenzae* and *Pseudomonas* species, may also lead to this syndrome.

Fungal Causes of Sudden Death

Sudden death due to fungal infection may occur in an immunocompromised host such as in HIV/AIDS. Organisms include *Cryptococcus* (meningitis or disseminated disease) and *Pneumocystis carinii* (pneumonia).

Intravenous drug abusers are susceptible to endocarditis due to fungi such as *Candida*. These patients are prone to fungal thromboembolism, leading to sudden death.

Sudden death may also be due to a complication of fungal diseases such as fatal subarachnoid hemorrhage complicating actinomycotic meningitis or fatal hemoptysis complicating pulmonary mucormycosis.

Diagnostic modalities include culture of the organism and the histological demonstration of the organisms in tissue. This may be facilitated by special stains such as the periodic acid–Schiff (PAS) or Grocott's methenamine silver stain.

Protozoal Causes of Sudden Death

Fatal cardiac tamponade may occur with intrapericardial rupture of an amebic liver abscess due to *Entamoeba histolytica*. Fatal amebic meningoencephalitis may be caused by *Naegleria fowleri*. The organism enters the arachnoid space through the cribriform plate of the nose. There is meningeal hemorrhage with fibrinoid necrosis of blood vessels.

Cerebral malaria does not usually cause sudden death. However, it may be the primary cause of sudden death in nonimmune persons. Susceptible individuals are tourists, business travelers, and sailors. At autopsy, the brain is swollen and may have a "slate gray" color due to the brown-black malarial pigment called hemozoin. Histology reveals petechial hemorrhages as well as intravascular parasitized red cells. Small perivascular inflammatory foci called malarial or Dürck's granulomas may be present. Sudden death in malaria may also be due to rupture of an enlarged spleen. An enlarged spleen is fragile and more vulnerable to rupture. Other infections that may lead to splenic rupture and sudden death are infectious mononucleosis and typhoid.

Sudden death due to cardiac involvement in Chagas disease (*Trypanosoma cruzi*) occurs in 5–10% of acute cases. The damage to the myocardium causes fatal ventricular tachycardia. Histological examination shows myofiber necrosis with an acute inflammatory reaction. Clusters of organisms may be found within dilated myofibers, resulting in intracellular pseudocysts.

Helminthic Causes of Sudden Death

Clinically occult helminthic diseases such as hydatid disease (*Echinococcus granulosus*) and neurocysticercosis (*Taenia solium*) may cause sudden death. In neurocysticercosis death may occur due to epilepsy or raised intracranial pressure. Parasitic cysts containing scolices are present, especially in the subarachnoid space, cortical sulci, and cortical gray matter. Large multilocular cysts (racemose cysts) may be present in the basilar cisterns near the cerebellopontine angle (Figure 5).

Isolated cardiac hydatid cyst is an uncommon manifestation and accounts for fewer than 3% of all hydatid disease. Sudden death may be the initial manifestation of the disease. Death may be due to involvement of the left ventricular myocardium or to massive pulmonary embolism.

Autopsy in Cases of Sudden Death due to Infectious Causes

All autopsies must be approached using universal precautionary principles.

In sudden deaths complete autopsy examination is recommended with appropriate tissue and body fluid sampling for special investigations.

Autopsy sampling for microbiological investigations is indicated in the following circumstances: sudden unexpected deaths in children and adults, deaths in immunocompromised patients, deaths in patients with clinically suspected infections, and deaths with organ changes of infection. The problems encountered with autopsy microbiological testing are contamination during procurement of the sample because of poor technique or due to the postmortem spread of commensals.

To prevent false-positive postmortem blood cultures the following should be observed: the body should be refrigerated as soon as possible; and movement of

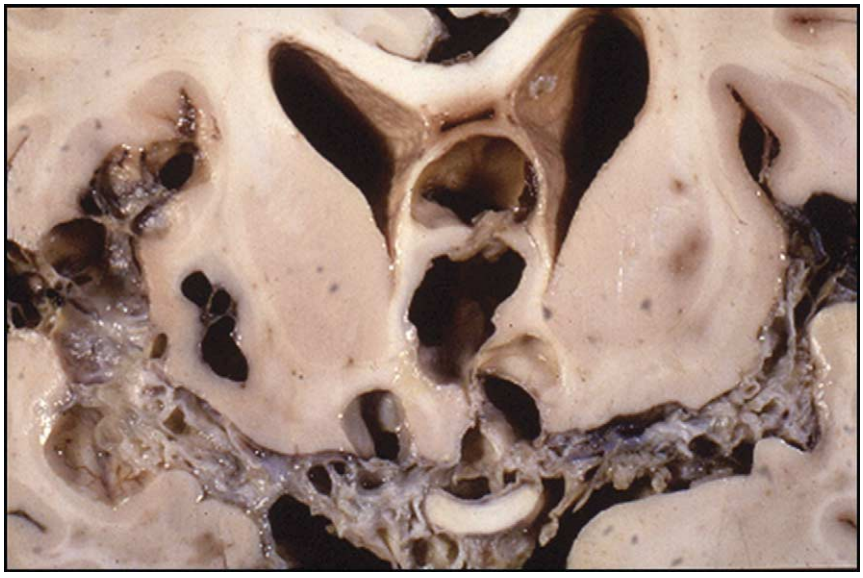

Figure 5 Hydrocephalus with basal obliterative, granulomatous cysticercus meningitis. Courtesy of Professor RH Hewlett, University of Stellenbosch.

the body should be limited to decrease the possibility of postmortem bacterial spread. An aseptic technique should be used to collect the sample, which should be stored and transported in the correct medium and temperature.

Close liaison with the microbiology and virology laboratories is important to guide collection, preservation, transport, and evaluation of specimens. This is particularly important in cases where there are positive cultures with negative histological findings. Sampling at multiple sites and determining the antibiotic sensitivities may be helpful in determining the significance of positive cultures. The finding of a "pure" as opposed to "mixed" culture helps to determine the significance of the findings. The type of organism in relation to the site where it was cultured also helps to differentiate contaminants from significant positive cultures.

Relevant special techniques should be used by the pathologist in order to improve the diagnostic yield in infectious diseases (Table 5).

In a small group of cases (so-called negative autopsies) no obvious cause of death is apparent after detailed initial external and internal examination. The incidence of negative autopsies is 5%–10%; this figure improves to about 5% when special tests such as postmortem chemistry and microbiology are carried out.

Table 5 Special techniques used to demonstrate infectious agents

Organism	*Special technique*	*Comment*
Viruses	Hematoxylin & eosin, antibody probes, culture and DNA probes	Intranuclear and/or cytoplasmic inclusions, giant cells
Chlamydia	Giemsa, culture	Necrotizing granulomas with stellate abscesses
Bacteria	Gram stain, silver stain, acid-fast stain, culture, DNA probes	Polymerase chain reaction and ligase chain reaction for mycobacteria
Fungi	Periodic acid–Schiff, silver stain, Giemsa, culture	Mucicarmine for capsule of cryptococcus
Protozoans	Giemsa, periodic acid–Schiff, DNA probes	
Helminths	Modified acid-fast stain	In bilharzia, acid-fastness is concentrated in the spine of the egg

Conclusion

Infectious agents are not a common cause of sudden death. Even in cases with little or no morphological changes, investigation of appropriate autopsy samples by recently developed laboratory techniques may prove invaluable and shed light on the cause of death.

See Also

Children: Sudden Natural Infant and Childhood Death; **Sudden Natural Death:** Cardiovascular; Central Nervous System and Miscellaneous Causes

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