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Forensic Considerations in Cases of Neurofibromatosis—An Overview

ABSTRACT: Neurofibromatosis types 1 and 2 are inherited neurocutaneous disorders characterized by a variety of manifestations that involve the circulatory system, the central and peripheral nervous systems, the skin, and the skeleton. Significant reduction in lifespan occurs in both conditions often related to complications of malignancy and hypertension. Individuals with these conditions may also be the subject of medicolegal autopsy investigation if sudden death occurs. Unexpected lethal events may be associated with intracranial neoplasia and hemorrhage or brainstem compression. Vasculopathy with fibrointimal proliferation may result in critical reduction in blood flow within the coronary or cerebral circulations, and aneurysmal dilatation may be associated with rupture and life-threatening hemorrhage. An autopsy approach to potential cases should include review of the history/hospital record, liaison with a clinical geneticist (to include family follow-up), a full external examination with careful documentation of skin lesions and nodules, measurement of the head circumference in children, photography, possible radiologic examination, a standard internal autopsy examination, documentation of the effects of previous surgery and/or chemo/radiotherapy, examination for specific tumors, specific examination and sampling of vasculature (renal, cerebral, and cardiac), formal neuropathologic examination of brain and spinal cord, possible examination of the eyeballs, examination of the gastrointestinal tract, histology to include tumors, vessels, gut, and bone marrow, toxicological testing for anticonvulsants, and sampling of blood and tissue for possible cytogenetic/molecular evaluation if required.

KEYWORDS: forensic science, neurofibromatosis, von Recklinghausen, sudden death

Neurofibromatosis types 1 and 2 (NF1 and NF2) are inherited neurocutaneous disorders characterized by multiple abnormalities involving a variety of systems. While affected individuals may have lives of normal duration, the manifestations of these disorders may result in a reduction in lifespan. Some cases are associated with sudden and unexpected death. Despite the fact that NF1 is one of the most commonly inherited diseases, cases are not frequently encountered in forensic practice and so physical characteristics and possible mechanisms of death may not be well understood by pathologists. The following paper provides an overview of these conditions with a description of the features of neurofibromatosis that may be encountered at autopsy, forensic implications, and an analysis of possible mechanisms of sudden death.

Neurofibromatosis 1

Incidence

Although neurofibromatosis 1 (NF1 MIM 162200) was described by von Recklinghausen in 1882, it had been previously reported by Smith in 1849, and even earlier illustrations of probable cases exist. It occurs in approximately one in 3000–4000 individuals with no gender or racial predilection (1–4).

Etiology

Neurofibromatosis 1 is caused by mutations in, or deletions of, the *NF1* gene that is located on 17q11.2. This gene controls neurofibromin, a GTPase-activating protein that is thought to have a possible tumor-suppressor function by maintaining the ras proto-oncogene in an inactive form. Once activated, the ras oncogene causes proliferation and tumor formation in neurocutaneous tissues. Over 250 mutations in the *NF1* gene have been identified. The inheritance is autosomal dominant with 50% of cases representing new mutations. While there is 100% penetrance, there is considerable phenotypic variability with genetic mosaicism (5). The possibility of heritability underscores the need for accuracy in postmortem diagnosis.

Features

The manifestations of NF1 vary greatly among affected individuals, even within the same family, and so clinical predictions about prognosis are difficult. It is fully penetrant by the age of 8 years (6).

At autopsy an affected individual may be short with a mild kyphoscoliosis and macrocephaly with asymmetry of the chest and prominence of the inferior ribs. Macrocephaly may be due to hydrocephalus secondary to aqueduct stenosis or to increased amounts of cerebral white matter (7). Chiari 1 malformations of the hindbrain may be present. There is an increased incidence of epilepsy in patients with NF1, occurring at a rate twice that of the general population (in 4.2% of cases). A history of mild intellectual impairment may be present. The seizures are not related to cortical dysplasia (8).

Hyperpigmented macules or so-called café-au-lait macules (CALM) may be present on the skin, along with ephiledes (freckles) in the groin and axillae, and urticaria pigmentosa. CALM are often the initial presenting feature of NF1 and develop during infancy or early childhood. They are smooth-edged, oval, hyperpigmented macules that measure ~10–40 mm in diameter (Fig. 1). Most patients have them by 1 year of age and the number and size increase during puberty with loss of pigment in later life. Approximately 95% of patients with NF1 have these macules at some stage, compared to 25% of the general population. Freckling in NF1 has a distinctive pattern with involvement of the inguinal and axillary regions in about 90% of cases and also in other

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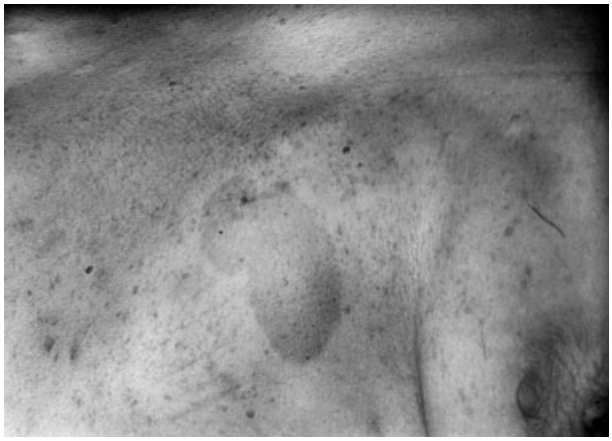

FIG. 1—*A typical lightly pigmented café-au-lait spot near the breast in a case of neurofibromatosis 1.*

intertriginous areas, rather than in the usual sun-exposed areas. Sometimes the skin may become diffusely hyperpigmented or covered with freckles. Opthalmic manifestations include hypo- or hyperpigmented iris hamartomas, so-called Lisch nodules, that are present in 80% of affected patients (9,10).

Children may show precocious puberty associated with tumors of the optic chiasm that disrupt the hypothalamic-pituitary axis. Gynecomastia is a rare finding in prepubertal boys (11). Radiological examinations may reveal long bone bowing with intramedullary fibrosis and cortical thinning and sphenoid bone dysplasia. Pseudarthroses may develop from impaired healing of long bone fractures associated with cortical thinning (4).

A variety of benign and malignant tumors may be identified ranging from cutaneous/subcutaneous neurofibromas (Fig. 2) to spinal cord and optic nerve gliomas, meningiomas, central gliomas, plexiform neurofibromas, malignant peripheral nerve sheath tumors (MPNST), pheochromocytomas, rhabdomyosarcomas, and hematopoietic conditions such as chronic myeloid leukemia (4,12). Histologic features of these tumors are available in standard texts. Although astrocytomas usually manifest in early childhood, there is an increased risk of developing gliomas throughout life. Most are low grade pilocytic astrocytomas that are localized to the optic nerve and chiasm, the hypothalamus and less often the brainstem and cerebellum (13).

Neurofibromas arise within nerve fibers and consist of an admixture of proliferating Schwann cells, fibroblasts and pericytes (Fig. 3) and appear in NF1 as cutaneous or subcutaneous neurofibromas or nodular or diffuse plexiform neurofibromas. Cutaneous neurofibromas can be soft, fleshy, sessile, or pedunculated and may grow to quite a large size. Subcutaneous neurofibromas are palpable firm and sometimes tender nodules under the skin. Both of these types of tumors grow quite slowly and are always benign; however, subcutaneous neurofibromas and male gender have been found to be independent predictors of mortality after adjustment for age (6).

Plexiform neurofibromas may be either nodular or diffuse. Nodular plexiform neurofibromas are discrete tumors that may arise in clusters around nerve roots. Extension along nerve roots may involve spinal foramina i.e., the classical "dumbbell tumor" with neurological effects due to compression of nerve roots and/or the cord. Diffuse plexiform neurofibromas are much more extensive tumors that grow along nerve fibers into organs and tissues. This type of tumor may damage organ or limb function and occasionally undergoes malignant transformation into a MPNST. The risk of malignant transformation is 5–13% (7,14).

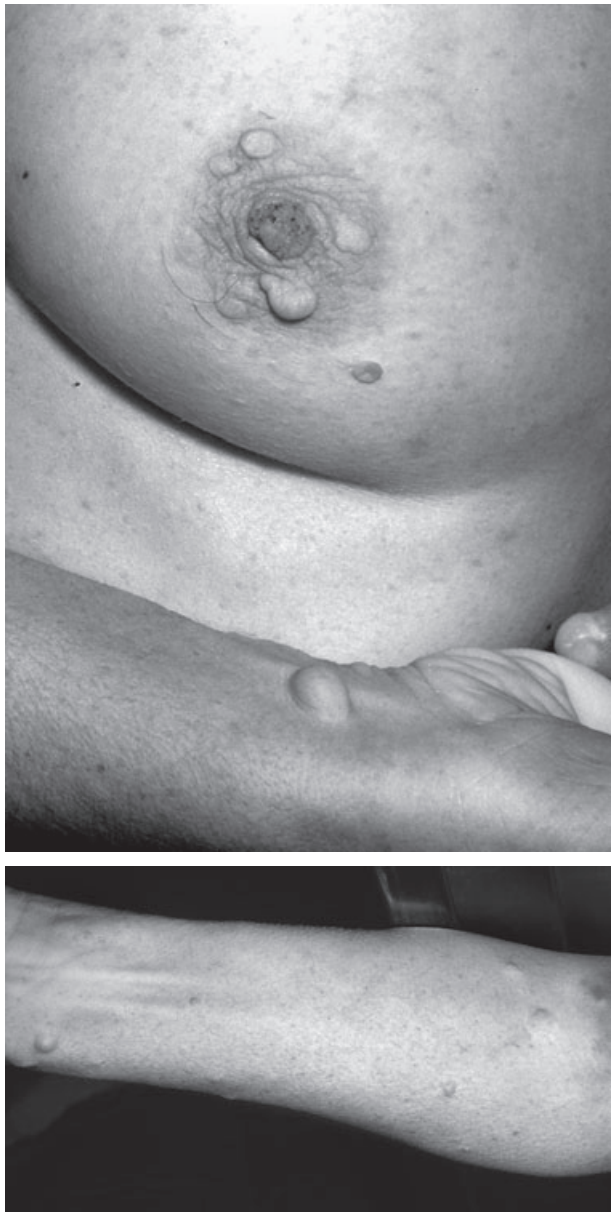

FIG. 2—*Multiple-scattered cutaneous neurofibromas in a case of neurofibromatosis 1 in a 46-year-old woman involving the breast and forearms.*

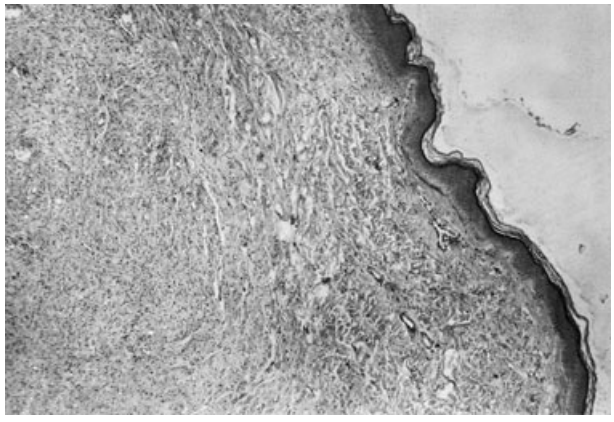

FIG. 3—*A section of a subcutaneous neurofibroma showing aggregates of benign spindle cells (hematoxylin & eosin 800×).*

Optic nerve gliomas are the most commonly diagnosed central nervous system tumor in NF1, occurring in 15% of affected children. They are generally low grade and slow growing resulting in visual impairment (7). Studies have shown that the clinical features of NF1 tend to group into three categories: (i) café-au-lait spots, intertriginous freckling, and Lisch nodules, (ii) cutaneous, subcutaneous, and plexiform neurofibromas, and (iii) macrocephaly, optic gliomas, and other tumors (15).

Eleven to 25% of individuals with NF1 have involvement of the gastrointestinal tract, with the majority of tumors consisting of benign neurofibromas and leiomyomas. Complications include hemorrhage, obstruction, or perforation. Bleeding may be chronic and occult, resulting in iron deficiency anemia, or sudden and massive (16).

Abnormalities of blood vessels consist of arterial ectasia and aneurysms, stenoses, and fibromuscular dysplasia. All arteries may be involved and very rarely veins, with occasional arteriovenous fistula formation and aneurysm rupture (17,18). It is believed that the incidence of vascular pathology is underestimated, as most of the vascular features are asymptomatic (3,19). Involvement of the renal arteries may cause marked hypertension, particularly in children and examination of the renal vasculature may reveal stenoses and aneurysms at all levels of the renal artery including the intraparenchymal branches (20,21). Cardiovascular complications may involve an underlying vasculopathy, hypertension, or congenital cardiac defects (3).

Moyamoya disease involves proliferation of a web-like net of arterioles at the base of the brain with an angiographic appearance of a "puff of smoke." Involved vessels may show eccentric intimal proliferation with luminal narrowing and microaneurysm formation, and this may result in subarachnoid hemorrhage, ischemia, or intraparenchymal hemorrhage. Moyamoya occurs in NF1 with 2.5% of affected children in one study of brain magnetic resonance imaging having abnormal vasculature (22).

Meningioangiomatosis is a rare disorder characterized by leptomeningeal vascular proliferation and calcification that has been associated with NF1. However, there now appears to be an increasing evidence for an association with NF2. While sporadic cases often present with seizures, those associated with neurofibromatosis are often asymptomatic (23).

Interstitial fibrosing alveolitis associated with bullous changes has been described in the lungs, in addition to fibromuscular dysplasia associated with severe pulmonary hypertension (24,25). Pregnancy in NF1 may result in severe hypertension with marked intrauterine growth retardation and fetal death (26,27).

Associated syndromes

Some individuals with NF1 may also manifest features of Noonan syndrome with hypertelorism, down-slanting palpebrae, low-set, rotated ears, short necks sternal deformities, and cardiac problems such as atrial septal defects, pulmonary stenosis, and hypertrophic cardiomyopathy. This has been called the Watson phenotype of NF1. In a review of 2322 patients with confirmed NF1 from the National Neurofibromatosis Foundation International Database, four patients had Watson syndrome, 25 had pulmonary stenosis and five had aortic coarctation. Conotruncal abnormalities were rare (28). Congenital cardiac defects have occurred in 0.4–6.4% of patients with NF1 (3).

Diagnosis

Two of seven criteria are required to make the clinical diagnosis of NF1. The criteria include: two or more typical neurofibromas or one plexiform neurofibroma; at least six café-au-lait spots or pigmented macules (>5 mm in diameter in children before puberty and >15 mm in postpubertal individuals); axillary or inguinal freckles; two or more iris hamartomas; an optic nerve glioma; long bone abnormalities such as cortical thinning with or without pseudarthrosis or sphenoid dysplasia; and a first degree relative (sibling, parent, or child) with NF1 by the above criteria (29). Detection of these abnormalities at autopsy should prompt consultation with a medical geneticist, the consideration of molecular diagnostic studies and family interview and follow-up. It should be noted, however, that 40% of people who have more than six CALM and other features of NF1 do not develop the condition and that young children may not have many of these features (30).

Mechanisms of Death

Affected individuals may have a 15-year reduction in lifespan predominantly due to the effects of vascular disease and malignancy (31,32). Hypertension may be essential or due to the effects of catecholamine secretion from a pheochromocytoma or to renal artery stenosis associated with fibromuscular dysplasia. As noted above, hypertension may be exacerbated by pregnancy (26). Deaths from hypertension result from intracerebral hemorrhage, cardiac arrhythmias secondary to compensatory cardiomegaly, and aortic dissections.

Other mechanisms of death include cerebrovascular accidents or seizures due to fibromuscular dysplasia with narrowing of major cerebral vessels. Fibromuscular dysplasia has been classified into intimal, intimal aneurysmal, periarterial nodular, and epithelioid forms depending on the degree and type of proliferation, and also into circumscribed, nodular, and diffuse subtypes (33). Vasculopathy resulting in aneurysms may be associated with dissection, rupture, and exsanguination. Alternatively, hemorrhage into the chest cavity may result in sudden death from hemothorax (34,35). Compression of neck structures due to a massive cervicomediastinal hematoma from vessel hemorrhage may occur and bleeding may also result from infiltrating tumors, from gastrointestinal tumors, or from pressure necrosis on large vessel walls. Sudden death may be due to hemorrhage into the brain or into tumors (16,36–39). Although gliomas tend to be of low grade in NF1, reported sudden death in childhood has been due to hemorrhage into such tumors of the optic chiasm (40).

A range of other cardiovascular anomalies have been reported that may cause sudden death. Fibromuscular dysplasia has caused narrowing of epicardial and intramural coronary arties and has been associated with evidence of previous ischemic damage with fibrosis and acute myocardial infarction (19). Coronary artery aneurysm formation may occur in the very young and may be associated with sudden death (41). Hypertrophic cardiomyopathy and floppy mitral valve may also occur (19,42,43). As has been noted, vascular involvement of the lungs is a rarely reported occurrence that may result in significant pulmonary hypertension (25).

Death has been associated with upper spinal cord compression from neurofibromas and unstable dysplastic scoliosis (6) and from compression of the airway and vagus nerve (44,45). Neurofibromas may also obstruct blood flow by compressing large vessels or the heart (3). Features that may be associated with unexpected death in NF1 are summarized in Table 1.

While seizures occur in a small percentage of patients, these are usually controllable by medication. As with any underlying seizure disorder however, unexpected death may result, with minimal findings at autopsy. Toxicological analysis of blood for anticonvulsant medication in individuals with neurofibromatosis may give an

TABLE 1—*Autopsy findings that may be associated with unexpected death in neurofibromatosis 1.*

Vascular
Vasculopathy:
i) Aneurysm dissection/rupture:
Soft tissue hemorrhage
Hemothorax
Intracerebral hemorrhage
ii) Fibrointimal hyperplasia:
Renal artery stenosis
Coronary artery stenosis
Cerebral artery stenosis/moyamoya disease
Pulmonary hypertension
Meningioangiomatosis:
Congenital malformation:
Aortic coarctation
Extra-cranial tumors
Pheochromocytoma:
i) Hypertension:
Intracerebral hemorrhage
Aortic dissection
Cardiomegaly
Nerve/stromal tumors:
i) Vascular invasion/compression/abnormal vessels:
Mediastinal/soft tissue/gastrointestinal hemorrhage
Hemothorax
ii) Local growth
Vagal compression
Airway obstruction
Central nervous system
Tumors:
Hemorrhage
Brainstem compression
Hydrocephalus
Vasculopathy:
Congenital malformation:
Chiari 1 malformation
Cardiac
Coronary artery vasculopathy:
Acute myocardial infarction
Myocardial fibrosis
Hypertrophic cardiomyopathy:
Floppy mitral valve:
Congenital malformation:
Watson syndrome
Pulmonary stenosis
Miscellaneous
Pregnancy:
i) Exacerbation of hypertension
Intracerebral hemorrhage
Aortic dissection
Cardiomegaly
Placental pathology
Fetal death

indication that epilepsy was present, even if not specified in the history. Subtherapeutic drug levels may also be identified.

Neurofibromatosis 2

Incidence

Neurofibromatosis 2 (NF2 MIM 101000) was first clearly delineated from NF1 in 1981, although the first probable case was described by Wishart in 1820. It occurs in approximately one in 40,000 individuals with no sex or racial predilection and has almost complete penetrance by the age of 60 years (46,47).

Etiology

Neurofibromatosis 2 is caused by mutations in, or deletions of, the *NF2* gene that is located on 22q12.2. This gene product is known as merlin and is thought to regulate cellular remodeling, motility and growth by interfering with extracellular mitogenic signals. As with NF1 the inheritance is autosomal dominant with 50% of cases representing new mutations. Again there is also nearly 100% penetrance, but with considerable phenotypic variability and genetic mosaicism (48).

Features

The manifestations of NF2 largely result from peripheral and central nervous system tumors, in particular schwannomas. Intracranial schwannomas most often arise from the vestibular branch of the VIIIth cranial nerve resulting in the typical presentation of loss of balance due to vestibular disturbance and progressive deafness (47). Bilateral schwannomas at the cerebellopontine angle are a pathognomonic feature of NF2 and account for considerable morbidity and mortality when there is brainstem compression and obstructive hydrocephalus (49). They account for approximately 8% of intracranial neoplasms (48). Malignant tumors may also occur (Fig. 4). Spinal root schwannomas are usually asymptomatic,

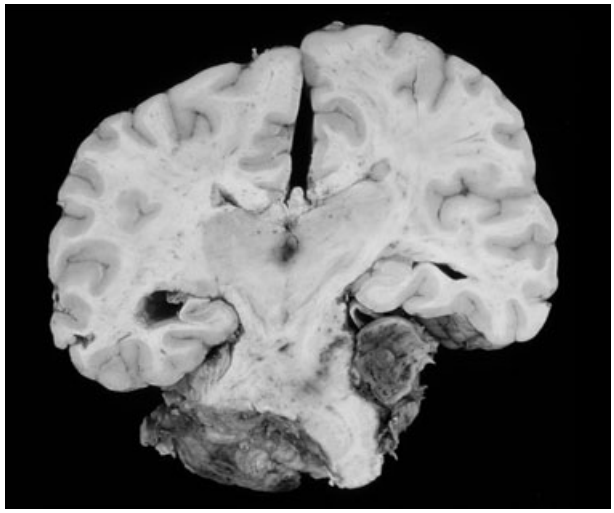

FIG. 4—*A malignant schwannoma of the cerebellopontine angle with central necrosis and compression of the adjacent brain in a case of neurofibromatosis 2.*

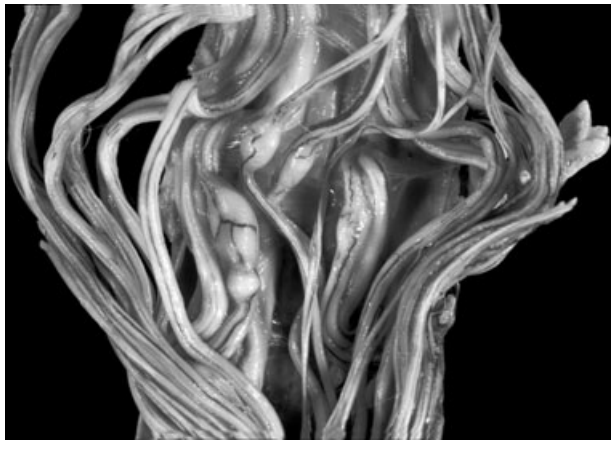

FIG. 5—*Multiple schwannomas of the cauda equina in a case of neurofibromatosis 2.*

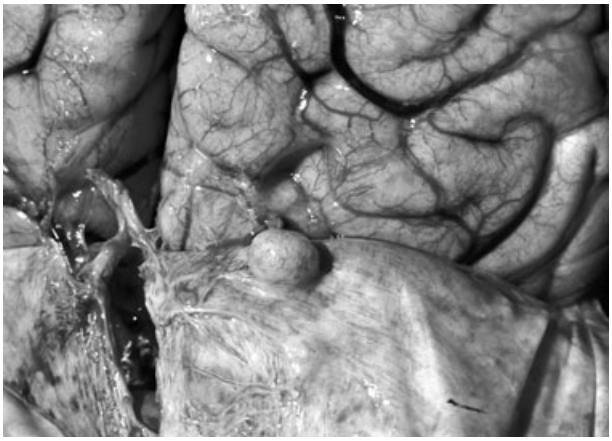

FIG. 6—*Indentation of the brain by an incidental small parasagittal meningioma in a 16-year-old girl with neurofibromatosis 2.*

but if large may compress the adjacent cord. Peripheral schwannomas (Fig. 5) occur in up to 50% of affected individuals and may be identified as cutaneous nodules or swellings. Nearly 50% of individuals with NF2 develop meningiomas (Fig. 6) that are generally slow growing and amenable to surgical treatment. There is also an increased incidence of other tumors such as ependymomas and astrocytomas that may be diagnosed in up to one-third of cases, most often within the spine or cauda equina, but occasionally within the brain.

Visual disturbances during life may be due to cataracts (in 67%) or to corneal damage associated with facial paresis. Retinal hamartomas are also not uncommon (in 22%) (50).

Schwannomatosis is a recently recognized third form of neurofibromatosis in which multiple schwannomas occur in the absence of the vestibular schwannomas characteristic of NF2. Diagnostic criteria have been proposed to help distinguish it from NF2. The clinical manifestations do not appear to be lethal (51,52).

Diagnosis

It has been proposed that a definite diagnosis of NF2 can be made clinically in an individual who has bilateral VIIIth nerve schwannomas or who has a unilateral VIIIth nerve schwannoma under the age of 30 years or any two of the following: schwannoma, meningioma, glioma, juvenile posterior subcapsular lenticular opacities, with a first-degree relative who has neurofibromatosis (53). A probable diagnosis can be made if an individual has a unilateral VIIIth nerve schwannoma under the age of 30 years with at least one of the following: schwannoma, meningioma, glioma, or juvenile posterior subcapsular lenticular opacities, or who has multiple meningiomas with either a unilateral VIIIth nerve schwannoma under the age of 30 years or one of the following: schwannoma, meningioma, or glioma, juvenile posterior subcapsular lenticular opacities (53). Detection of these abnormalities at autopsy should again prompt consultation with a medical geneticist, the consideration of molecular diagnostic studies and family interview and follow-up.

TABLE 2—*Autopsy findings that may be associated with unexpected death in neurofibromatosis 2.*

Central nervous system
Tumors:
i) Cranial nerve schwannomas
Brainstem compression
Hydrocephalus
ii) Primary brain tumors:
Hemorrhage
Brainstem compression
Hydrocephalus

TABLE 3—*Autopsy considerations in cases of possible neurofibromatosis.*

Review of history/hospital record
Liaison with Clinical Geneticist (to include family follow-up)
Full external examination with careful documentation of skin lesions and nodules
Measurement of head circumference in children
Photography
Consider radiologic examination
Standard internal autopsy examination
Documentation of effects of previous surgery and/or chemo/radiotherapy
Examination for specific tumors
Specific examination and sampling of vasculature (renal, cerebral, and cardiac)
Formal neuropathologic examination of brain and spinal cord
Consider examination of eyeballs
Examination of the gastrointestinal tract
Histology to include tumors, vessels, gut, and bone marrow
Toxicological testing for anticonvulsants
Blood and tissue for possible cytogenetic/molecular evaluation if required

TABLE 4—*Summary of possible causes and mechanisms of death in neurofibromatosis types 1 and 2.*

1. Related
Tumors
Intracranial tumors
Epilepsy
Hemorrhage
Brainstem compression
Hydrocephalus
Peripheral neural tumors
Hemorrhage
Vagal inhibition
Airway compression
Blood vessel compression
Pheochromocytoma
Hypertensive crisis
Malignancy
Vascular
Hypertension
Stroke
Intratumoral hemorrhage
Cardiomegaly/arrhythmia
Fibromuscular dysplasia (vasculopathy)
Hypertension (renal artery stenosis)
Stroke
Myocardial ischemia
Peripheral gangrene
Hemothorax
Aneurysm (vasculopathy)
Soft tissue hemorrhage
Intracerebral hemorrhage
Hemothorax
Congenital anomalies
Cardiac
Hypertrophic cardiomyopathy
"Floppy" mitral valve
Coronary artery vasculopathy
Acute myocardial ischemia/infarction
Myocardial fibrosis
Congenital anomalies
Complications of pregnancy
Hypertension
Abortion
2. Unrelated
Other causes of natural and unnatural death

Mechanisms of Death

It has been shown that individuals with NF2 have a reduction in their lifespan with a mean age of death of 36 years and a mean actuarial survival of 62 years (54). This reduction in lifespan results from the complications of intracranial neoplasia. While sudden death may be related to critical brainstem compression and/or hydrocephalus, the clinical course leading to this event is usually protracted. Although it has been asserted that epilepsy and seizures are not common in NF2 (7), others have reported seizures as a presenting feature in 8% of cases (54). The risk of mortality increases with decreasing age at diagnosis and the presence of meningiomas (55). Features that may be associated with unexpected death in NF2 are summarized in Table 2 and autopsy considerations in both types 1 and 2 are listed in Table 3.

While most cases of neurofibromatosis will be diagnosed prior to death, it is always possible that an undiagnosed case may present *de novo* to autopsy. Accuracy of diagnosis is then critical, particularly given the inherited nature of 50% of cases. In addition, meticulous documentation of the features present will be required to help determine the particular manifestations of the disorder in the victim. The causes and mechanisms of death may vary greatly between cases and have been summarized in Table 4.

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