CASE REPORT

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Postmortem Diagnosis of Leukodystrophies

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ABSTRACT: Leukodystrophies are progressive disorders involving the development and maintenance of myelin in the central and peripheral nervous systems. Although relatively uncommon, leukodystrophic disorders may be undiagnosed or misdiagnosed during life, and may appear as ''sudden death.'' In such instances, these victims may be referred to a forensic pathologist. In general, leukodystrophies are inherited in an autosomal recessive manner so that proper postmortem diagnosis by the forensic pathologist is extremely important to the decedent's family for future family planning.

KEYWORDS: forensic science, forensic pathology, leukodystrophy, sudden death, inherited disorder, lysosomal disorder, progressive demyelination

Leukodystrophies are caused by a specific abnormality in the formation or maintenance of myelin in the central and peripheral nervous systems (1–3). In most cases, the disorders are inherited in an autosomal recessive manner (2,4). Manifestations of a leukodystrophy usually have their onset during infancy or childhood, although juvenile and adult cases are reported (1,2). Infants with a disorder are often mentally retarded and demonstrate progressive ataxia and paralysis with seizures, dementia, blindness, deafness, and rigidity (2). Adults are usually not as severely affected, and features may be limited to behavioral changes and psychosis. Victims often die within a few years of diagnosis, although some may live more than 20 years. The leukodystrophies include several varied disorders, including Alexander's disease, metachromatic leukodystrophy, Krabbe's disease (globoid cell leukodystrophy), adrenoleukodystrophy, Canavan's disease, and Pelizaeus-Merzbacher disease.

Since these disorders are rare, they may be undiagnosed or misdiagnosed during life. Although leukodystrophies are discussed in general reference texts, the possibility of presentation as ''mental impairment not otherwise specified, with sudden death'' is not discussed. Further, standard reference texts in forensic pathology do not discuss leukodystrophies. Therefore, the practicing forensic pathologist may have little knowledge of leukodystrophies. However, correct diagnosis of these disorders has profound implications for surviving family members, due to their hereditary nature. We present two individuals with leukodystrophies undiagnosed during life, and referred to the medical examiner's office as ''sudden death.'' These cases are presented to remind the forensic pathologist of the characteristics of leukodystrophies, and the importance of postmortem diagnosis of these inherited disorders.

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Case Reports

Case 1

A two-year-old girl with a clinical history of cerebral palsy was unexpectedly found dead in bed, without previous acute illness. The brain at postmortem examination weighed 850 g and showed diffuse, symmetric cerebral demyelination with subcortical sparing. The cerebral cortical convexities displayed a dysgenetic gyral pattern with symmetric relative enlargement of the frontal gyri bilaterally. The gyri displayed narrowing, with widened sulci. There was symmetric dilatation of the ventricular system. The adrenal glands were markedly diminished in size. Microscopic examination of the brain revealed diffuse, symmetric demyelination of the cerebral white matter with subcortical sparing. Cresyl violet stains and PAS with Luxol fast blue stains were negative for the spherical granular masses associated with metachromatic leukodystrophy. Chemical analysis of vitreous humour revealed: sodium 94 meq/L, potassium 10 meq/L, chloride 77 meq/L, urea nitrogen 21 mg/dL, creatinine 0.6 mg/dL. The immediate cause of death was attributed to electrolyte imbalance, arising as a consequence of cerebral leukodystrophy, not otherwise specified. The findings were most consistent with the autosomal recessive form of adrenoleukodystrophy.

Case 2

A nineteen-year-old girl experienced a ''sudden'' respiratory arrest following a two day history of nausea and vomiting. She had been developmentally normal until the fourth grade, when she experienced difficulty with gross and fine motor control. Prior to death, despite exhaustive medical evaluations, the only clinical diagnosis rendered was ''progressive neurologic deterioration, not otherwise specified.'' Postmortem examination of the brain after fixation revealed a weight of 950 g with severe cortical atrophy. There was generalized narrowing of the gyri and widening of the

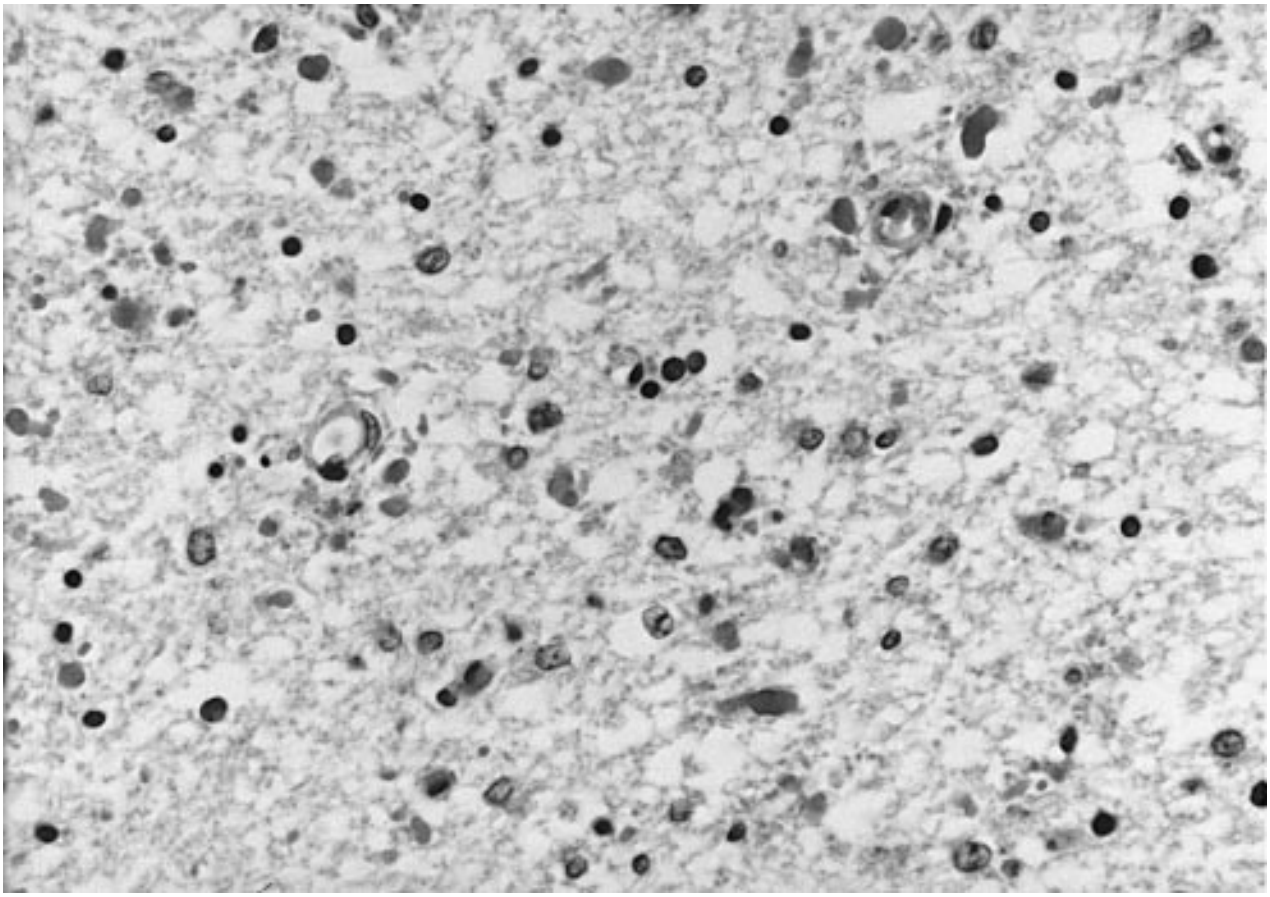

FIG. 1—*Numerous eosinophilic globules within the deep basal ganglia (hematoxylin and eosin: magnification ×400).*

sulci, as well as severe atrophy of the corpus callosum which measured 2 mm in thickness. Microscopic examination demonstrated diffuse demyelination involving the centrum semiovale, brainstem, corpora striata, and cerebellum. There was associated neuronal loss, and abundant eosinophilic globules (see Fig. 1). These findings were consistent with Alexander's disease. All other organs were essentially normal with the exception of the lungs, which displayed bilateral acute bronchopneumonia with micro-abscesses. The immediate cause of death was bronchopneumonia, arising as a complication of Alexander's disease.

Discussion

Leukodystrophies are progressive, degenerative disorders of the cerebral white matter which are usually transmitted in an autosomal recessive manner (1–6). They are caused by a deficiency in enzymes needed for the formation or maintenance of myelin (2,7). The microscopic features include a symmetric decrease of myelin staining, severe loss of axons, and diffuse fibrillary astrocytosis in the cerebrum and cerebellum (1). Characteristics of specific leukodystrophies are discussed in Table 1.

Alexander's disease is characterized by the diffuse extensive accumulation of irregular, elongated, hyaline structures called Rosenthal fibers within astrocytes coupled with demyelination and sometimes eosinophilic globules (2,8–13). The Rosenthal fiber formation is noted particularly in the subpial, perivascular, and subependymal zones (9,11–15). This rare progressive neurological disease is marked by symmetrical low density in the frontal white matter and the basal ganglia and enlargement of the frontal horns (6,9,11). The disease affects the entire central nervous system, including the brain stem, cerebellum, and spinal cord (6,15). It has been suggested that Alexander's disease may represent a genetically determined error in the metabolic processes involved in the chemical formation and maturation of myelin (8,12,15). Familial cases have been described (15).

Metachromatic leukodystrophy is a lysosomal storage disease, and the most common of the leukodystrophies. It is characterized by a deficiency of cerebroside sulfatase, commonly referred to as ''arylsulfatase A'' (1,16,17). Also a disease marked by progressive myelin breakdown, this deficiency causes galactosyl sulfatide deposits to accumulate in the central white matter, Schwann cells, and epithelial cells of the gallbladder, intrahepatic bile ducts, or renal tubules (1,4,16). The central nervous system displays bilateral, symmetrical white matter loss, with sparing of the subcortical ''U'' fibers. The accumulation of the galactosyl sulfatide deposits in the white matter causes metachromatic staining with certain dyes, such as Toluidine blue. This autosomal recessive disorder leads to a progressive impairment of motor function coupled with mental deterioration (4,16,18).

Krabbe's disease, also called globoid cell leukodystrophy or galactosylceramide lipidosis, results from an absence of galactoside β-galactosidase (1,2,4,17,19,20). It is also an autosomal recessive disorder. The deficiency of this enzyme causes an accumulation of galactocerebroside in the central white matter, with clusters of large multinucleated ''globoid'' cells (1,2,20). It has been suggested that these globoid cells are altered macrophages

TABLE 1—*Characteristics of leukodystrophies.*

DISEASE	INHERITANCE	SIGNS/SYMPTOMS	CNS/MORPHOLOGY
Alexander's Disease	Familial cases described	Large head, mental retardation spasticity	Extensive accumulation of Rosenthal fibers in white matter
Metachromatic Leukodystrophy	Autosomal recessive	Progressive motor and mental deterioration	Progressive myelin break down. Accumulation of galactosyl sulfatide deposits causing metachromatic staining. Sparing of subcortical "U" fibers
Krabbe's Disease	Autosomal recessive	Mental and motor developmental delays beginning around 3-6 months of age	Perivascular accumulation of multi-nucleated globoid cells within the white matter
Adreno-leukodystrophy	X-linked recessive or	X-linked mixed motor & sensory neuropathy beginning in 2nd decade. Eventual dementia. Adrenal insufficiency	Progressive demyelination of cerebral white matter.
	Autosomal recessive	Autosomal recessive-symptomatic at birth, with severe CNS impairment, seizures. Death in childhood. Adrenal insufficiency	Autosomal recessive form involves both gray & white matter
Canavan's Disease	Autosomal recessive	Symptoms beginning around 6 months of age. Psychomotor developmental delays	Spongy degeneration of the white matter, with Alzheimer Type II cells
Pelizaeus-Merzbacher Disease	X-linked	Pendular nystagmus, progressing to widespread CNS white matter dysfunction	Extensive demyelination with patches of spared areas, resulting in "tiger skin" or "leopard skin" appearance with myelin stains

containing the accumulated galactocerebroside in the central nervous system (2,4). Patients displaying this disorder are normal at birth, but develop symptoms around 3 to 6 months of age, including irritability, unexplained crying, stiffness of the limbs, and slowing of mental and motor development (5,20).

Adrenoleukodystrophy is characterized by progressive sudanophilic demyelination of cerebral white matter and adrenal insufficiency (1–3,5,21). It manifests as either an X-linked recessive disorder or as an autosomal recessive infantile form, and may occur in juveniles and adults as well. The X-linked form of adrenoleukodystrophy is a peroxisomal disorder, in that impaired function of the peroxisome prevents degradation of very long chain fatty acids in the brain and adrenals (22). Infants with the autosomal recessive form are symptomatic at birth and usually die within two years (5). They display severe central nervous system dysfunction, with deafness and seizures. These infants are incapable of walking or developing language. The infantile variant involves both cerebral gray and white matter.

Canavan's disease, also called spongiform leukodystrophy, is due to the deficiency of the enzyme aspartoacylase, which results in the accumulation of N-acetylaspartic acid (23–25). Also an autosomal recessive disorder, Canavan's disease often affects individuals of Jewish heritage (2,3,23–25). This disease is marked by spongy degeneration of white matter with astrocytic swelling and elongated mitochondria (3,24–26), and a proliferation of Alzheimer's type II astrocytes (15). Patients display severe cerebral edema that affects the deeper layers of the cortex and superficial layers of the white matter, followed by the sponginess spreading to the brainstem, cerebellum, and spinal cord (3). Canavan's disease may be distinguished from the other leukodystrophies by an increased N-acetylaspartic acid excretion in the urine of these patients (24,25).

Pelizaeus-Merzbacher disease, inherited as a sex-linked recessive disorder, is marked by widespread demyelination in the centrum ovale, cerebellum, and parts of the brain stem (2,3,5,27,28). Throughout the white matter, focal perivascular sudanophilic lipid

are present as perinuclear droplets (2,27,28). The primary pathological finding of this disease is the presence of ''myelin islands'' in demyelinated areas, giving a spotty, ''tiger-skin'' or ''leopard-skin'' appearance. The clinical features of this disorder appear early in life, but patients may live into their third decade or longer (2,3,5,27,28). Manifestations include difficulty with coordination and balance as well as impaired mental function.

Conclusions

Although the leukodystrophies are encountered rarely by forensic pathologists, it is important for forensic pathologists to be aware that these disorders can present as ''sudden death'' cases, and thus fall under the jurisdiction of the coroner/medical examiner. The two patients described herein were not diagnosed with a leukodystrophy during life, and were presented to the medical examiner's office as cases of ''sudden death.'' Since the leukodystrophies are generally inherited in an autosomal recessive manner, postmortem diagnosis of these disorders may have a strong impact on surviving family members. Recognition of such a case by the prosecting pathologist allows survivors to seek genetic counseling, and make informed family-planning decisions.

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