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The Spectrum of Neuropathologic Findings in Deaths Associated with Seizure Disorders

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ABSTRACT: The pathologic and neuropathologic findings in 90 autopsied cases of death associated with a seizure disorder or complication thereof were reviewed. Most (69%) of the deceased individuals were between 21 and 40 years of age; two thirds were male. In 58% of patients, no cause of death other than seizure disorder was found. The ultimate cause of death in those patients was assumed to be a cardiac arrhythmia or respiratory arrest. Drowning accounted for 19% of deaths, and 17% of patients died of other contributory causes such as suicide, exposure, or atherosclerotic coronary vascular disease. Aspiration was found in the remaining 6%. Tongue lacerations or bite marks were observed in only one third of cases. The brain was normal in approximately two thirds of cases, with no focus for the origination of seizure found on neuropathologic examination. In the remainder of cases, a variety of lesions was found, with cavitary lesions, contusions, and dural lesions being the most common ones.

KEYWORDS: pathology and biology, seizure disorders, neuropathology, postmortem examinations

Persons with epilepsy have shortened life spans compared with the rest of the population [*1-3*]. At least part of this may be due to a marked increase in the incidence of sudden death [*1-7*]. At autopsy, there are often insufficient morphologic findings to explain death.

Neuropathologic findings in patients with seizure disorders have been described in a few studies [*4-10*]. The percentage of detectable lesions varies from 11 to 63% in these different series. This study was designed to describe the spectrum of neuropathologic findings in normally functioning persons with established seizure disorders who died unexpectedly.

Methods

All deaths occurring in the state of New Mexico between 1980 and 1986 where seizure disorder was listed on the death certificate or report of death were reviewed. A total of 206 cases were so identified. In 94 of these cases, jurisdiction was terminated, or a death certificate was issued without autopsy. A total of 112 cases were autopsied at the Office of the Medical Investigator. We were interested in analyzing only those cases of normally function-

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ing persons with a well-documented history of seizures. Thus, we excluded cases where the seizures were poorly documented or were most likely due to the effects of drugs, alcohol, or alcohol withdrawal (11 cases). In addition, since severely mentally retarded or handicapped individuals often have seizures which are likely to be a consequence of their underlying disease process, these patients (11 cases) were also excluded. The records of the remaining 90 cases were reviewed to determine the neuropathologic findings and other contributing information. Tissue slides were reviewed where appropriate.

Results

The age distribution of the 90 patients was as follows: < 10 years of age, 4 cases; 11 to 20 years, 7 cases; 21 to 30 years, 34 cases; 31 to 40 years, 28 cases; 41 to 50 years, 11 cases; > 51 years, 6 cases. The majority of the patients (69%) were between 21 and 40 years of age. Sixty of the patients (66.7%) were male; thirty (33.3%) were female.

The causes of death are listed in Table 1. In almost 60% of the cases, no anatomic cause of death could be identified. These patients were signed out as deaths as a result of a seizure disorder. As will be discussed below, these deaths were most likely caused by a cardiac arrhythmia or respiratory arrest secondary to the seizure process. Drowning, most often in a bathtub or shower, was the most common accidental cause of death in individuals with seizures. In approximately 17% of patients, the seizures were felt to be a contributing cause of death. These patients died of a number of other causes, including suicide, exposure, and infections. Atherosclerotic coronary vascular disease was a surprisingly uncommon cause of death in these patients. Aspiration of food or other objects accounted for the deaths of six individuals.

The neuropathologic findings in the 90 patients in this series are displayed in Table 2. In the majority of cases, no central nervous system (CNS) finding was present by either gross or microscopic examination (no specific pathologic diagnosis [NSPD]). In those cases where an anatomic lesion was present, cavitary lesions, contusions, and dural lesions (subdural hematoma or dural adhesion) accounted for the largest number. Many of these could be compatible with previous trauma; not all patients, however, had a history of trauma. A total of 15 patients had a history of trauma that was noted on the death certificate or report of death; of these, 4 patients had unremarkable CNS examinations, 4 had dural lesions, 4 had cavitary lesions, and 3 had contusions. A variety of other processes, as listed in the table, made up the remainder of the cases. Fourteen patients had more than one lesion.

In many of these cases, pathologic findings were localized to a particular portion of the

TABLE 1—*Causes of death.*

Cause		Number
Seizure disorder		52
Drowning		17
bathtub or shower	12	
irrigation ditch	3	
pool	2	
Contributing cause		15
suicide	4	
exposure	4	
multiple injuries	1	
infection	3	
cardiomyopathy	1	
cardiac	2	
Aspiration		6

TABLE 2—*Neuropathologic findings.*

NSPD	57
Cavitary lesion	12
Contusions	7
Dural lesion	7
Tumor	6
arteriovenous malformation	(3)
subependymoma	(1)
meningioma	(1)
oligodendroglia hamartoma	(1)
Localized atrophy/hypoplasia	4
Hemiatrophy	2
Focal inflammatory infiltrate	2
Microcephaly	1
Cystocercosis	1
Multiple lesions	14

brain. Nine lesions were frontal, eight temporal, three lesions were in the basal ganglia, two lesions were occipital, and one lesion each was localized to the cerebellum and insula. Again, some patients had more than one lesion localized in more than one area. Localization of lesions within the brain may be important in the generation of seizure activity. Some regions, such as the hippocampus and motor cortex, have much lower thresholds for excitability than do other regions, such as frontal and occipital lobes [*11*].

Hippocampal sclerosis and cerebellar cortical atrophy are often found in patients with seizure disorders. The significance of these findings is debated in the neurologic and neuropathologic literature. As a result, cases where the only findings were hippocampal sclerosis or cerebellar cortical atrophy have been included in the NSPD category. Cerebellar cortical atrophy is an extremely nonspecific finding, since Purkinje cells undergo atrophy secondary to age, hypoxia, or exposure to common toxins such as alcohol. Hippocampal sclerosis is commonly described in patients with seizure disorders. Particularly affected is Sommer's section of Ammon's horn, the neurons of which seem to be selectively susceptible to hypoxia. In our material where the hippocampus was available for evaluation (60 cases), hippocampal sclerosis was identified in 15 cases. In 8 of these cases, it was the only finding, and in 7 cases, it was associated with other significant lesions.

Of the 52 patients who had no anatomic cause of death, only 15 patients had an identifiable central nervous system lesion. No nervous system lesion was found in 37 of these patients; 5 of these had hippocampal sclerosis.

Laceration or bruising of the tongue or surrounding oral mucosa is thought to be a common finding in patients dying of seizure disorders. These lesions were carefully searched for in each of our autopsied cases. However, only 24 patients (26.7%) had tongue or oral mucosa lesions. This included tongue lacerations found in 6 of the 17 individuals who drowned secondary to their seizure disorders.

Most patients with chronic, long-term seizure disorders take prescription anticonvulsive medication. Compliance is often a problem in these patients, and low or absent levels of anticonvulsants probably predispose these individuals to seizures which may be lethal. In our series, anticonvulsant levels were measured in 73 patients. Of these, 28 (38.4%) had negative levels, and 27 (37%) had subtherapeutic levels. Only 18 patients in our series (24.7%) had therapeutic levels of anticonvulsants. The most common drugs measured were phenobarbital and dilantin.

Discussion

Many patients with seizures would be expected to have a morphologic substrate for their disease. However, in series of autopsies on seizure patients where careful neuropathologic examinations have been performed, variable results have been reported. Freytag and Lindenberg, reporting on 294 deaths, found significant lesions in 63% [*4*]. The most common source of these lesions was old trauma, and 56% were known to abuse alcohol. Hirsch and Martin performed neuropathologic examinations on 19 patients with good clinical documentation of epilepsy; only 4 of these 19 patients (21%) had significant lesions [*5*]. Terrence found abnormalities in 4 of 37 patients (11%) with known seizures [*6*]. Bowerman et al. noted neuropathologic findings in three of their 11 cases (27%) [*7*]. Leestma et al. found lesions in 46 of 66 cases (70%) in their study; the most common finding was old contusions [*8*]. Eighteen percent of patients in his series were known abusers of alcohol. Margerison and Corsellis, studying patients with temporal lobe epilepsy, found structural or post-traumatic abnormalities in 20 of their 55 patients (36%) [*9*]. Finally, Copeland reported significant pathology in 47% in his 148 cases [*10*]. Twenty to thirty percent of these were thought to be related to the use of alcohol. Thus, our finding of significant pathology in 33 of 90 cases (37%) confirms previous observations that not all, but only a minority, of patients with seizures have demonstrable neuropathologic lesions.

The significance and prevalence of sclerosis of Ammon's horn also varies between series. Hippocampal sclerosis was seen in 6% of Leestma's cases [*8*], 14% of Freytag and Lindenberg's cases [*4*], and 65% of Margerison and Corsellis' cases [*9*]. We observed hippocampal sclerosis in 25% of our cases (15 of 60). Thus, although hypoxia as a result of seizure activity may cause neuronal loss in the hippocampus, it is by no means inevitable.

Copeland's study documented that tongue lacerations were present in 18% and absent in 23% of deceased individuals [*10*]. An additional study described oral or lingual lacerations in 44% of patients brought to an emergency room because of seizures [*12*]. Tongue lacerations were present in only 28% of our cases. Thus, although this finding is helpful when present, its absence does not exclude a seizure disorder.

Patients with a history of seizure disorders have long been known to have excess mortality over the normal population [*1-3*]. A significant portion of the patients die suddenly and unexpectedly [*1-7*]. The lack of an anatomic cause of death in patients with seizure disorders is a fairly common finding which can be troubling to forensic pathologists. Most authors think that these deaths result from autonomic dysfunction, which in turn causes a cardiac arrhythmia, cardiac arrest, or respiratory arrest [*5,11,13*]. Autonomic functions are controlled by cortical, limbic, hypothalamic and brainstem centers. If these areas are involved in or disturbed by the seizure activity, normal autonomic function may be disrupted. Experimental models of seizure activity in cats have been consistent with this hypothesis [*14,15*]. Conversely, increased autonomic activity may initiate seizures. Subtherapeutic levels of anticonvulsants, as been noted by previous authors and confirmed in this study, may contribute to the problem [*6,8,10*].

References

[*1*] Krohn, W., "Causes of Death Among Epileptics," *Epilepsia*, Vol. 4, 1963, pp. 315-321.

[*2*] Zielinski, J. J., "Epilepsy and Mortality Rate and Cause of Death," *Epilepsia*, Vol. 15, 1974, pp. 191-201.

[*3*] Hauser, W. A., Annegers, J. F., and Elveback, L. R., "Mortality in Patients with Epilepsy," *Epilepsia*, Vol. 21, No. 8, 1980, pp. 399-412.

[*4*] Freytag, E. and Lindenberg, R., "Medicolegal Autopsies on Epileptics," *Archives of Pathology*, Vol. 78, No. 9, 1964, pp. 274-286.

[*5*] Hirsch, C. S. and Martin, D. L., "Unexpected Death in Young Epileptics," *Neurology*, Vol. 21, No. 7, 1971, pp. 682-690.

[6] Terrence, C. F., Wisotzkey, H. M., and Perper, J. A., "Unexpected, Unexplained Death in Epileptic Patients," *Neurology*, Vol. 25, No. 6, 1975, pp. 594–598.
[7] Bowerman, D. L., Levisky, J. A., Urich, R. M., and Wittenberg, P. H., "Premature Deaths in Persons with Seizure Disorders—Subtherapeutic Levels of Anticonvulsant Drugs in Postmortem Blood Specimens," *Journal of Forensic Sciences*, Vol. 23, No. 3, July 1978, pp. 522–526.
[8] Leestma, J. E., Kalelkar, M. B., Teas, S. S., Jay, G. W., and Hughes, J. R., "Sudden Unexpected Death Associated with Seizures: Analysis of 66 Cases," *Epilepsia*, Vol. 25, No. 1, 1984, pp. 84–88.
[9] Margerison, J. H. and Corsellis, J. A. N., "Epilepsy and the Temporal Lobes," *Brain*, Vol. 89, No. 3, 1966, pp. 499–537.
[10] Copeland, A. R., "Seizure Disorders: The Dade County Experience from 1978 to 1982," *American Journal of Forensic Medicine and Pathology*, Vol. 5, No. 3, 1984, pp. 211–215.
[11] Jay, G. W. and Leestma, J. E., "Sudden Death in Epilepsy," *Acta Neurologica Scandinavica*, Vol. 63, Supplement 82, 1981, pp. 1–66.
[12] Roberge, R. J. and Maceira-Rodriquez, L., "Seizure-related Oral Lacerations: Incidence and Distribution," *Journal of the American Dental Association*, Vol. 111, No. 8, 1985, pp. 279–280.
[13] Wannamaker, B. B., "Autonomic Nervous System and Epilepsy," *Epilepsia*, Vol. 26, Supplement 1, 1985, pp. S31–S39.
[14] Lathers, C. M. and Schraeder, P. L., "Autonomic Dysfunction in Epilepsy: Characterization of Autonomic Cardiac Neural Discharge Associated with Pentylenetetrazol-Induced Epileptogenic Activity," *Epilepsia*, Vol. 23, No. 12, 1982, pp. 633–647.
[15] Schraeder, P. L. and Lathers, C. M., "Cardiac Neural Discharge and Epileptogenic Activity in the Cat: An Animal Model for Unexplained Death," *Life Sciences*, Vol. 32, No. 12, 1983, pp. 1371–1382.

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