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# Sudden Unexpected Death in Epilepsy

## Neuropathologic Findings

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Sudden unexpected death in epilepsy refers to sudden death of an individual with a clinical history of epilepsy, in whom a postmortem examination fails to uncover a gross anatomic, toxicologic, or environmental cause of death. Evidence of terminal seizure activity may not be present. One to two percent of natural deaths certified by the medicolegal death investigator are attributed to epilepsy. Detailed microscopic examination of the brain has increasingly afforded the identification of structural changes representative of epileptogenic foci. The authors present 70 cases of death attributed to sudden unexpected death in epilepsy. These cases were classified as follows: individuals who lacked a gross brain lesion, those who had a brain lesion demonstrable at autopsy, and those who lacked neuropathologic evaluation because of decomposition or because only an external examination was done. All of the subjects had a clinical history of seizures. The authors confirm that various microscopic findings, including neuronal clusters, increased perivascular oligodendroglia, gliosis, cystic gliotic lesions, decreased myelin, cerebellar Bergmann's gliosis, and folial atrophy, are present in a higher percentage of the brains of sudden unexpected death in epilepsy subjects than in the brains of age- and sex-matched control subjects.

**Key Words:** Epilepsy—Sudden unexpected death—Neuropathology.

Sudden unexpected death in epilepsy (SUDEP) refers to sudden death in a person with epilepsy in whom a demonstrable anatomic or toxicologic cause of death is not found after complete postmortem examination with scene investigation (1). Deaths resulting from a seizure occurring in hazardous settings resulting in fatal trauma, such as an epileptic seizure while the subject is in water or is driving a motor vehicle, deaths due to status epilepticus, and deaths resulting from fatal asphyxia due to obstruction of the airways by aspiration of gastric contents have been previously excluded from this definition. The reported occurrence of SUDEP is between 1 in 370 to 1 in 1,110 in the general epileptic population (2). Compared with the general population, the risk of sudden unexplained deaths is 24 times greater in the epileptic population (3).

Numerous risk factors have been suggested as significant in SUDEP, including male gender, young adulthood (20–40 years), intractable epilepsy, polytherapy with antiepileptic drugs, generalized tonic-clonic seizures, poor compliance with anticonvulsant medications, and alcohol abuse (2,3). In official medicolegal death investigations, most persons dying of SUDEP are found in bed, presumably having experienced an unwitnessed seizure.

The mechanism of unexpected death in persons with a history of epilepsy remains unclear. Numerous and varied hypotheses exist, including that autonomically mediated cardiac arrhythmia alone or in combination with central hypoventilation may prompt the release of endogenous opioids that suppress the respiratory drive (2,4). The "neurogenic" pulmonary edema often identified at autopsy suggests the theory of autonomic dysfunction with altered pulmonary vascular tone, cardiac dysfunction, or both. Sleep has also been proposed as a risk factor for SUDEP (5,6). The disorganized synchronization of brain neuroelectrical activity induced by sleep may predispose to increased epileptic discharges, which could induce convulsions and sudden death.

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Several studies of both gross and microscopic findings have described the neuropathologic findings in individuals with epilepsy. Gross neuropathologic findings in seizure victims are as follows: hippocampal Ammon's horn sclerosis; cerebral or cerebellar cysts; congenital malformations such as ectopic gray matter, microcephaly, and focal polymicrogyria; and benign or malignant tumors of the brain, either primary or metastatic (7,8). In a study by Kasper et al., numerous histopathologic findings were noted in neurosurgical specimens removed from patients with medically refractory temporal lobe epilepsy (9). These abnormalities included clustering of neurons throughout cortical layers II through VI, prominent perivascular clustering of oligodendroglia in the white matter, increased single heterotopic neurons in the white matter, and glioneuronal hamartomas. Cerebral microdysgenesis was also evident in seven of eight patients with primary generalized epilepsy in a study by Meencke and Janz (10).

This 5-year retrospective study is, to our knowledge, the first of its kind to review both the gross and the microscopic neuropathologic examinations in cases of SUDEP evaluated in a medical examiner's office, comparing them with age- and sex-matched nonepileptic control subjects. The focus of this study was to identify pertinent neuropathologic findings in epileptic persons who die unexpectedly. The brains of each SUDEP subject and each control subject were examined microscopically by a neuropathologist in a blinded review. Other factors investigated in the SUDEP subjects in this study include compliance with antiepileptic drugs, previous neurosurgical intervention, location of body on discovery, history of possible witnessed seizure before death, and other significant nonneuropathologic autopsy findings.

## MATERIALS AND METHODS

### Study Population

*SUDEP Subjects*

The population in this 5-year (1996–2000) retrospective study consisted of individuals with a clinical history of seizures and no anatomic or toxicologic cause of death revealed by postmortem examination performed either at the Office of the Chief Medical Examiner in Louisville, Kentucky, or the Office of the Associate Chief Medical Examiner in Frankfort, Kentucky. After gross examination of the brain by either a forensic pathologist or a consulting neuropathologist, the consultant microscopically evaluated representative brain regions. These study cases were divided into three distinct SUDEP categories: (1) Group 1: subjects with a clinical history of epilepsy; lack of a lethal systemic, cerebral anatomic, or toxicologic cause of death; and absence of gross brain lesions at autopsy; (2) Group 2: subjects with a clinical history of epilepsy, lack of a lethal anatomic or toxicologic cause of death, and presence of gross brain lesions at autopsy (macroscopic abnormalities included a high-grade glioma, varix, leptomeningeal cyst, cortical and/or cerebellar atrophy, severe cerebral edema, and a craniotomy); and (3) Group 3: subjects with a clinical history of epilepsy, lack of a lethal anatomic or toxicologic cause of death, and inability either to detect gross brain lesions or to retrieve a brain specimen for histologic analysis during autopsy as a result of severe decompositional changes. One subject in the SUDEP 3 category had a clinical history of seizures and human immunodeficiency virus; death was attributed to seizures, but only an external examination of the body and retrieval of toxicologic specimens were performed.

Several individuals who had a clinical history of seizures and/or a witnessed seizure before death were not included in this study for the following reasons: cerebral palsy due to global brain damage, age under 15 years, drowning, no clinical history of seizures but a single witnessed seizure ascribed to delirium tremens, implanted pacemaker and numerous cerebral infarcts, death due to aspiration associated with a seizure, clinical history of seizures but also coexistent severe liver failure, with death attributed to seizures.

*Control Subjects*

Individuals with no history of seizures and whose deaths were not seizure related were prospectively selected as age- and sex-matched control subjects. The postmortem examinations of these subjects were performed in 2000 and 2001 at the Office of the Chief Medical Examiner in Louisville, Kentucky. All brains were examined grossly and microscopically.

### Analytic Methods

*Sampling for Microscopy and Staining Methods*

Both formalin-fixed and nonfixed brains of the SUDEP and control subjects were examined grossly and cut at a thickness of 1.5 cm to evaluate coronal cortical, horizontal brainstem, and sagittal cerebellar sections. The selected brain sections were fixed in 10% buffered formalin and processed routinely, i.e., placed in paraffin, cut at 5.0 $\mu$m, and stained with hematoxylin and eosin. Even though standardized and selective sampling of the brains was not performed, great effort was made to retrieve the hippocampus and cerebellum in as many cases as possible.

### Statistical Analysis

A $\chi^2$ analysis and nonparametric binomial test were performed on the noncerebral findings and the histologic features in the microscopic evaluations of the brains to

**TABLE 1.** *Clinical features of sudden unexpected death in epilepsy (SUDEP) cases*

| Category | Sex | Age (y) | Alcoholism | Witnessed seizure | Death site |
|---|---|---|---|---|---|
| SUDEP 1 (32 subjects) | M: 13 (41%)<br>F: 19 (59%) | Range: 18–54<br>Mean: 32 | 2 (6%) | 2 (6%) | Home: 18 (56%)<br>Other site: 14 (44%)[a] |
| SUDEP 2 (32 subjects) | M: 22 (69%)<br>F: 10 (31%) | Range: 16–71<br>Mean: 40 | 11 (34%) | 6 (19%) | Home: 17 (53%)<br>Other site: 15 (47%) |
| SUDEP 3 (6 subjects) | M: 3 (50%)<br>F: 3 (50%) | Range: 26–71<br>Mean: 42 | 1 (17%) | 0 (0%) | Home: 5 (83%)<br>Other site: 1 (17%) |

[a] Death sites outside of the home included a hospital, a cell in custody, and outdoors.

examine whether there were statistically significant differences between the SUDEP and control groups.

## RESULTS

### Clinical Features of SUDEP subjects

This group consisted of 70 subjects who had a history of epilepsy without an anatomic or toxicologic cause of death as revealed by complete autopsy. The subjects were assigned to the aforementioned three main categories based on the presence or absence of gross brain abnormalities, or lack of brain examination because of other reasons. Thirty-two individuals who had no gross findings in their brains were assigned to the SUDEP 1 category. The sexes and ages of these subjects are shown in Table 1, which also shows other variables, such as history of alcoholism, a witnessed seizure before death, and death site. The antiepileptic drug status, in relation to monotherapy, polytherapy, or lack of antiepileptic drug use, is shown in Table 2; antiepileptic drug polytherapy included phenytoin (Dilantin), valproic acid (Depakote), carbamazepine (Tegretol), neurontin, and clonazepam (Klonopin). Table 2 also shows the postmortem toxicology of antiepileptic drugs with respect to subtherapeutic, therapeutic, or supratherapeutic levels of antiepileptic drugs, or a negative antiepileptic drug toxicology screen.

Thirty-two subjects in the SUDEP 2 category all had a grossly apparent brain abnormality. Table 1 shows the sexes and ages of these individuals as well as data pertaining to their use of alcohol, a witnessed seizure before death, and death site. Antiepileptic drug therapy and postmortem antiepileptic drug toxicology are summarized in Table 2.

Six (9%) individuals were in the SUDEP 3 category. Four subjects had brains that did not undergo gross or microscopic brain examinations secondary to advanced decompositional changes, and one autopsy consisted only of an external inspection of the body with toxicology specimen recovery. The ages and sexes of these subjects, as well as alcohol use status, witnessed seizure before death, and death site, are shown in Table 1. Table 2 denotes the antiepileptic drugs prescribed and postmortem antiepileptic drug toxicology.

### Control Subjects

Eleven age- and sex-matched control subjects having no seizure history were prospectively selected. A male and a female control subject was chosen for each decade of life corresponding to the SUDEP cases and included one male and female subject between ages 15 and 19 and in the 3rd, 4th, 5th, and 6th decades, and one male subject in the 8th decade. The causes of death included two resulting from multiple blunt force injuries sustained in a motor vehicle collision, two with ischemic heart disease, one with multiple sharp force injuries to multiple body surfaces, two resulting from drowning, two result-

**TABLE 2.** *Antiepileptic drug status of sudden unexpected death in epilepsy (SUDEP) cases*

| Category | Antiepileptic drugs | Postmortem AED toxicology[a] |
|---|---|---|
| SUDEP 1 (32 subjects) | Monotherapy: 16 (50%)<br>Polytherapy: 11 (34%)<br>None: 3 (9%)<br>Unknown: 2 (6%) | Subtherapeutic: 14 (44%)<br>Therapeutic: 7 (22%)<br>Supratherapeutic: 0 (0%)<br>Negative: 11 (34.5%) |
| SUDEP 2 (32 subjects) | Monotherapy: 17 (53%)<br>Polytherapy: 10 (31%)<br>None: 1 (3%)<br>Unknown: 4 (13%) | Subtherapeutic: 14 (44%)<br>Therapeutic: 4 (13%)<br>Supratherapeutic: 1 (3%)<br>Negative: 14 (44%) |
| SUDEP 3 (6 subjects) | Monotherapy: 3 (50%)<br>Polytherapy: 2 (33%)<br>None: 0 (0%)<br>Unknown: 1 (17%) | Subtherapeutic: 1 (17%)<br>Therapeutic: 2 (33%)<br>Supratherapeutic: 0 (0%)<br>Negative: 2 (33%)<br>Unknown: 1 (17%) |

[a] Two individuals in the SUDEP 1 category and one subject in the SUDEP 2 category were prescribed two antiepileptic drugs; postmortem toxicology revealed that one drug was in the subtherapeutic range and the other drug had therapeutic levels, thus reflected in both the subtherapeutic and therapeutic groups.

AED, antiepileptic drugs.

**TABLE 3.** *Noncerebral findings in subjects with sudden unexpected death in epilepsy (SUDEP) categories 1 and 2 and age- and sex-matched control subjects*

| Category | Gingival hyperplasia | Tongue/lip contusion | Petechiae[a] | Pulmonary edema/congestion |
|---|---|---|---|---|
| SUDEP 1 (32 subjects) | 3 (9%) | 14 (44%) | 14 (44%) | 29 (91%) |
| SUDEP 2 (32 subjects) | 5 (16%) | 12 (38%) | 14 (44%) | 23 (72%) |
| Controls (11 subjects) | 0 (0%) | 0 (0%) | 0 (0%) | 5 (45%) |

[a] Petechiae were seen on various areas of the body including conjunctiva, epiglottis, thymus, trachea, pleural surfaces, epicardium, and skin of the neck and chest.

ing from a drug overdose, one resulting from thromboembolism due to a deep venous thrombosis, and one with acute coronary thrombosis due to coronary atherosclerosis.

### Noncerebral Postmortem Findings in SUDEP and Control Subjects

In addition to the neuropathologic changes, several non—central nervous system findings, which may have been seizure related, were identified during postmortem examination. Table 3 shows the noncerebral findings of the subjects in the SUDEP 1 and 2 categories and the control subject, which include the following: gingival hyperplasia, tongue/lip contusion, cutaneous and visceral petechiae, and pulmonary edema or congestion.

### Macroscopic Examination of Brains of SUDEP and Control Subjects

Each brain of the subjects in the SUDEP 1 and 2 categories and the control subjects was compared. Neuropathologic findings were not grossly present in the cases in the SUDEP 1 category. Table 4 shows the gross findings in the subjects in the SUDEP 2 category, which included brain atrophy of cortical, hippocampal, or cerebellar areas; prior damage to the brain (Fig. 1), including gliosis, necrosis, cystic encephalomalacia, sclerosis, contusion, craniotomy site, or gunshot wound; venous hemangioma or leptomeningeal varix; and malignant glioma.

All of the 11 subjects (100%) in the control group had no brain abnormalities on gross examination.

### Microscopic Examination of the Brains of SUDEP and Control Subjects

Microscopic examinations were performed on the brains of 22 of 32 (69%) subjects in the SUDEP 1 category and 29 of 32 (90%) subjects in the SUDEP 2 category. In several cases, the brain was not routinely sampled at autopsy. Thus, 13 of the 64 (20%) subjects in the SUDEP 1 and 2 categories lacked brain tissue for histologic evaluation. The hippocampus was not sampled in an additional 3 cases (5%). Because the brain was collected prospectively in the 11 control subjects, the hippocampus was collected in every one. The hippocampus was a site of particular attention during microscopic neuropathologic examinations for documentation of the presence or absence of the following four specific findings, as shown in Table 5: neuronal clusters (Fig. 2), neuronal heterotopia (Fig. 3), oligodendroglial clusters (Fig. 3), and perivascular oligodendroglia (Fig. 4). As shown in Table 6, several other features were analyzed for their presence or absence in the brains of SUDEP and control subjects, including cerebral gliosis, a cystic gli-

**TABLE 4.** *Macroscopic findings in sudden unexpected death in epilepsy (SUDEP) category 2 cases (32 subjects)*

| Abnormal gross brain findings |
|---|
| Remote traumatic event: 19 (59%)[a] |
| Cortical and hippocampal atrophy: 9 (28%) |
| Cerebellar atrophy: 10 (31%) |
| Venous hemangioma: 2 (6%) |
| Leptomeningeal varix: 1 (3%) |
| Tumor (glioblastoma multiforme): 1 (3%) |

[a] Remote traumatic events demonstrated on gross brain evaluation included contusions, gliosis, necrosis, cystic encephalomalacia, gunshot wound, and previous craniotomy site.

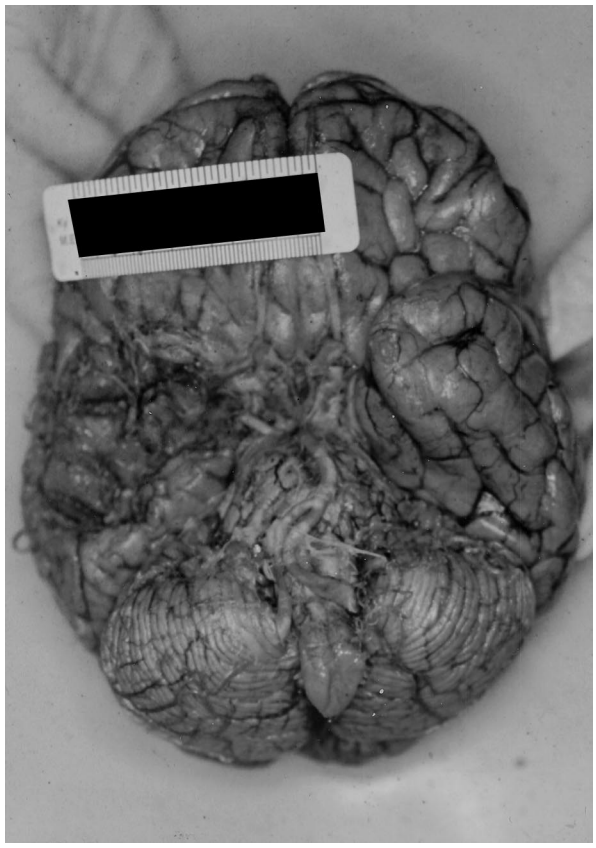

**FIG. 1.** Lesion in the temporal lobe on gross examination.

**TABLE 5.** *Histologic features in the hippocampus of sudden unexpected death in epilepsy (SUDEP) category 1 and 2 cases and age- and sex-matched control subjects*

| | Neuronal clusters | Neuronal heterotopia | Oligodendroglial clusters | Perivascular oligodendroglia |
|---|---|---|---|---|
| SUDEP 1 (21 subjects) | 3 (14%) | 21 (100%) | 20 (95%) | 9 (43%) |
| SUDEP 2 (27 subjects) | 4 (15%) | 24 (89%) | 19 (70%) | 4 (15%) |
| SUDEP 1/2 (48 subjects) | 7 (15%) | 45 (94%) | 39 (81%) | 13 (27%) |
| Controls (11 subjects) | 0 (0%) | 11 (100%) | 11 (100%) | 3 (27%) |

otic lesion, perivascular lymphocytes (Fig. 5), hemosiderin/hematoidin, decreased myelin, corpora amylacea, cerebellar Purkinje cell loss, Bergmann's gliosis (Fig. 6), and folial atrophy.

## DISCUSSION

Numerous studies have addressed specific microscopic features in the brain, either in surgical specimens from patients with medically refractory epilepsy or in postmortem specimens (8,9,11). To our knowledge, our study is the first comparative microscopic analysis of SUDEP brains with age- and sex-matched control subjects in a medical examiner setting. Frater et al. found microscopic neuronal heterotopia in surgical specimens in 59 (44%) of 133 epileptic patients (8). A neoplasm was identified in 37 (28%) of the cases. Our study shows similar findings to those in a study by Kasper et al., which histologically analyzed brain tissue excised for medically refractory epilepsy, as compared with tissue from control subjects (9). The study by Kasper et al. focused on the presence or absence of the following histologic features: marked clustering of neurons throughout cerebral cortical layers II through VI, marked perivascular clustering of oligodendroglia in the white matter, and single heterotopic neurons in the deep white matter. This group compared 47 epileptic patients with 29 control subjects. Neuronal clusters were present in 16 (34%) of the epileptic patients and 2 (10%) of the control subjects; heterotopic neurons in 47 (100%) of surgical patients and in 29 (100%) of control subjects, and perivascular clustering of oligodendroglia in 14 (30%) of epileptic patients and none in control subject.

Our study demonstrated a higher percentage of SUDEP cases having neuronal clusters, whereas the control group displayed both a higher percentage of heteropic neurons in white matter and of oligodendroglial clusters. The percentages of perivascular oligodendroglia were equal between the SUDEP and control groups. A $\chi^2$ Fisher's exact test was unable to be performed on the combined data from the SUDEP 1 and 2 categories versus the control group because of the extreme range of

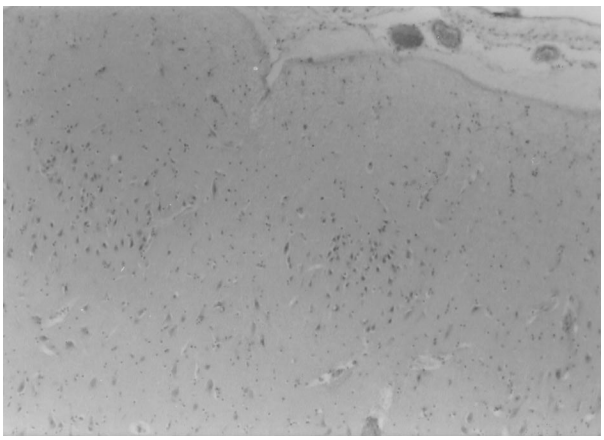

**FIG. 2.** Low-power view of neuronal clusters seen in the cortex (hematoxylin and eosin, ×50).

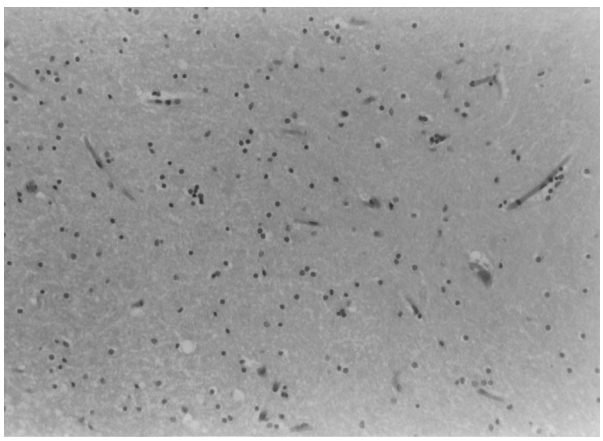

**FIG. 3.** High-power view of heterotopic neurons and oligodendroglial clusters seen in the cortex (hematoxylin and eosin, ×100).

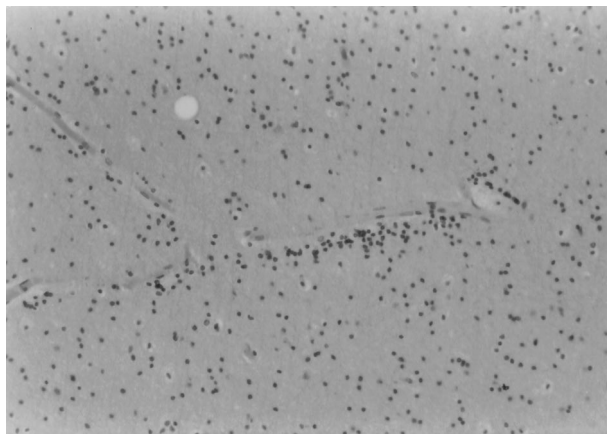

**FIG. 4.** High-power view of perivascular oligodendroglia seen in the cortex (hematoxylin and eosin, ×100).

**TABLE 6.** *Histologic features in the microscopic evaluations of brains of sudden unexpected death in epilepsy (SUDEP) category 1 and 2 cases and age- and sex-matched control subjects*

| | Gliosis | Cystic gliotic lesion | Perivascular lymphocytes | Hemosiderin/ hematoidin | Decreased myelin | Corpora amylacea | Purkinje cell loss[a] | Bergmann's gliosis and folial atrophy[a] |
|---|---|---|---|---|---|---|---|---|
| SUDEP 1 (22 subjects) | 5 (23%) | 0 (0%) | 10 (45%) | 9 (41%) | 11 (50%) | 6 (27%) | 6 (60%) | 0 (0%) |
| SUDEP 2 (29 subjects) | 14 (48%) | 10 (34%) | 4 (14%) | 12 (41%) | 22 (76%) | 6 (21%) | 8 (62%) | 6 (46%) |
| SUDEP 1/2 (51 subjects) | 19 (37%) | 10 (19%) | 14 (27%) | 21 (41%) | 33 (65%) | 12 (19%) | 14 (61%) | 6 (26%) |
| Controls (11 subjects) | 1 (9%) | 0 (0%) | 8 (73%) | 7 (64%) | 5 (45%) | 4 (36%) | 8 (73%) | 2 (18%) |

[a] The cerebellum was evaluated microscopically in 10 of the 32 (31%) SUDEP #1 cases, 13 of the 32 (41%) SUDEP #2 cases, and in all (100%) of the eleven age- and sex-matched control cases.

percentages (0% and 100%) as well as the equality of the percentages. When the category of SUDEP was divided into SUDEP 1 and SUDEP 2 categories, a statistically significant difference ($P < 0.05$) was seen in the number of oligodendroglial clusters between the SUDEP and control group. Both the study by Kasper et al. (9) and the current study showed a greater percentage of neuronal clusters in the seizure subjects than in the control subjects. Because the study by Kasper et al. did not separate oligodendroglial clusters from perivascular oligodendroglia in its analysis, this portion of the histologic examination cannot be compared.

A nonparametric binomial test was performed on the data of the microscopic cerebral findings from the SUDEP and control subjects. The percentages of gliosis ($P = 0.1$) and Bergmann's gliosis and folial atrophy ($P < 0.005$) of the SUDEP group were significantly higher than in the control group. By contrast, the percentages of perivascular lymphocytes ($P < 0.05$) and corpora amylacea ($P < 0.001$) of the control subjects were significantly greater than in the seizure subjects. No statistically significant findings were associated with the hemosiderin/hematoidin, the decreased myelin, and the Purkinje cell loss ($P > 0.05$).

In the study by Leestma et al. (12) addressing the neuropathology of SUDEP in a medical examiner setting, no anatomic findings of the brain were seen in 30% of the cases. Old traumatic lesions including contusions, subdural hematomas, and a prior craniotomy were seen in 40% of cases, and a brain tumor was demonstrated in 5% (12). Our study of 64 cases in the SUDEP 1 and 2 categories uncovered no anatomic findings in the brain in 50% of the cases. Old traumatic lesions, including gliosis, necrosis, contusion, cystic encephalomalacia, gunshot wound, and a remote craniotomy site, were present in 30% of the cases. A brain tumor was seen grossly in 2% of the cases, and cerebral or cerebellar atrophy was seen in 23%.

Other features at autopsy besides the neuropathologic changes may be related to terminal seizure activity, antiepileptic drug side effects, or both. The agonal terminal seizure event prior to death may account for the tongue/lip contusions and petechiae. Gingival hyperplasia is a common side effect of phenytoin use. In the previously cited prospective study by Leestma et al., pulmonary edema and congestion were noted in 42 of 52 (81%) cases (2). Our study demonstrated a higher percentage of pulmonary edema in the seizure subjects than in the control subjects. A $\chi^2$ Fisher's exact test performed on the findings of pulmonary edema showed no significant difference ($P > 0.05$) between the SUDEP and control groups.

Epilepsy is attributable to neurologic dysfunction effected by abnormal electrochemical activity of the brain and manifested by recurrent, paroxysmal disturbances

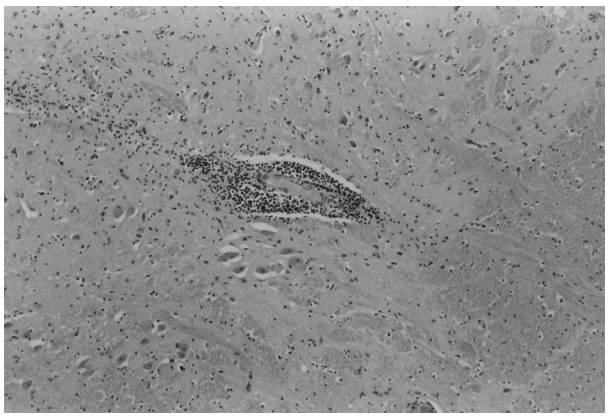

**FIG. 5.** High-power view of perivascular lymphocytes seen in the cortex (hematoxylin and eosin, ×100).

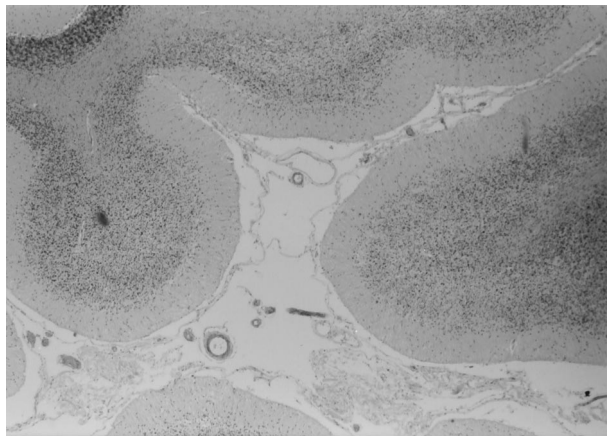

**FIG. 6.** Low-power view of Bergmann's gliosis seen in the cerebellum (hematoxylin and eosin, ×50).

(13). Approximately 2 million people in the United States have epilepsy, with 100,000 new cases diagnosed annually in the United States (14). It may be either acquired or idiopathic. The acquired form results from neurologic injury, structural brain abnormalities, or a variety of medical diseases. The idiopathic form occurs in individuals without a history of neurologic insult and no clinical evidence of neurologic dysfunction, measured by physical examination and diagnostic tests such as electroencephalography, computed tomography, and magnetic resonance imaging of the brain. The goal of antiepileptic drug therapy is to treat the patient, not the plasma drug concentration. In this manner, the condition of some patients may be well controlled in the subtherapeutic, therapeutic, or supratherapeutic range of antiepileptic drug. Alteration of the dosage of the medication is based clinically on the occurrence of side effects or efficacy (14).

The majority of SUDEP subjects in this study had been prescribed anti-epileptic drugs. Polytherapy with antiepileptic drugs where seizures may be poorly controlled by monotherapy is an indication of poor seizure control, and regarded as a risk factor for SUDEP (15). The risk of SUDEP increases with the number of antiepileptic drugs taken concomitantly, in fact the risk rises tenfold when patients were taking three antiepileptic drugs, versus monotherapy (15). This study supports the literature showing increased risk of SUDEP with antiepileptic polypharmacy and toxicologic evidence for antiepileptic drug noncompliance (2,12).

Our study correlates with previous literature about alcoholic men in the 20-year to 40-year age range being at risk for SUDEP (2,4,6,12). Women are more likely to be in SUDEP group 1, whereas more men are in the SUDEP 2 category. This finding may be due to the greater male predominance of brain trauma: injuries sustained in Vietnam, gunshot wounds, and physical assaults. The higher percentage of known alcoholism in the SUDEP 2 category likely correlates with other SUDEP 2 category data, such as traumatic head injury and a greater number of male subjects. Finally, our findings also agree with previous literature describing most SUDEP cases as unwitnessed seizures, most individuals being found dead at their residences (6,11).

This study serves to remind forensic pathologists that a subset of well-recognized microscopic neuropathologic findings can be seen in the brains of epileptic subjects whose deaths have been attributed to SUDEP. Because of the retrospective nature of the study, several inherent limitations were present, particularly including the lack of routine and thorough sampling of the brains of SUDEP subjects for microscopic neuropathologic evaluation. Medical examiners should consider examining all brains of decedents with a history of epilepsy and should sample specific areas in those epileptic subjects in whom no anatomic or potential toxicologic cause for death are found. Sections that are helpful include the hippocampi, amygdala, lateral temporal lobe, and superior, lateral, and inferior frontal lobes. Routine examination of the brain includes sampling of the basal ganglia, the mammillary bodies, cerebellum including the vermis and dentate nucleus, midbrain, upper pons, medulla at the area postrema, and the hypothalamus. Our conclusions reinforce the observation that microscopic examination of a grossly normal brain from an individual with a history of a seizure disorder may yield lesions statistically associated with epilepsy. Thus, when careful gross examination of the brain is performed and specific areas of the brain are consistently examined microscopically, neuropathologic study is more likely to uncover these lesions and confirm others associated with known head trauma. Cerebellar abnormalities (e.g., folial sclerosis, atrophy) may be difficult to appreciate grossly but can be easily documented microscopically. Whether cerebellar atrophy indicates repeated episodes of brain edema associated with seizures, or is a result of specific antiepileptic drug therapy, has never been resolved. Special stains can be helpful in poorly fixed brain material and when changes such as gliosis or demyelination are mild but diffuse; they include glial fibrillary acidic protein immunostains for astrogliosis, synaptophysin immunostains for neurons, periodic acid Schiff with luxol fast blue for corpora amylacea and myelin, and Masson trichrome for fibrosis. With more extensive sampling of the brain and with the aid of certain histologic stains, a limited focus protocol can be created to offer forensic pathologists a more reliable way to confirm SUDEP.

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