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Mortality in Captive Baboons with Seizures: A New Model for SUDEP?

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Summary

As the baboon is a model of primary generalized epilepsy, we were interested in mortality of captive animals with a history of witnessed seizures. Causes of natural death were investigated in 46 seizure baboons (SZ) and 78 nonepileptic controls (CTL), all of which underwent a complete pathological examination at the Southwest Foundation for Biomedical Research (SFBR) in San Antonio. SZ animals died at a younger age than the control baboons ($p<0.001$). Almost all epileptic baboons that died suddenly without an apparent cause (SZ-UKN), had pulmonary congestion or edema without evidence of trauma, systemic illness or heart disease, compared to 9 (12%) controls ($p<0.001$), most of which demonstrated evidence of a concurrent illness. Serosanguinous bronchial secretions were found in 15 (58%) SZ-UKN baboons, but only in 3 (4%) controls ($p<0.001$). Chronic multifocal fibrotic changes in myocardium were noted in only 3 (12%) of SZ-UKN baboons and one control baboon. Based upon these results, untreated seizures appear to reduce the life expectancy of captive baboons. Sudden unexpected death in epilepsy (SUDEP) may be a common cause of natural death in epileptic baboons.

Keywords

Papio; Baboon; Mortality; Epilepsy; SUDEP

Epilepsy is associated with increased mortality in humans. Population-based studies showed that people with epilepsy have increased mortality associated with cerebrovascular diseases, neoplastic disorders, suicide and pneumonia, compared to the general population (Lhatoo and Sanders, 2005). This increase can be, in large part, attributed to ischemia and tumors triggering seizures. Mortality is also increased in relation to seizure activity, either in the form of accidents

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or trauma, status epilepticus or sudden unexpected death in epilepsy (SUDEP). SUDEP is a definite or highly probable cause of death if the patient with epilepsy dies unexpectedly without any obvious cause of death while in a reasonable state of health (Earnest et al., 1992; Lhatoo and Sanders, 2005; Langan et al., 2005). A definitive diagnosis requires pathological evaluation that excludes other causes of death. Autopsies in SUDEP victims typically demonstrate pulmonary and visceral congestion, cerebral edema, multifocal interstitial fibrosis and signs of recent seizures, such as bruising or tongue bites (Earnest et al., 1992; Kloster and Engelskjøn, 1999). SUDEP accounts for 5–30% of deaths in people with epilepsy (Nilsson et al., 1999), making it a major cause of death, particularly in 20–40 year old patients with chronic, medically refractory epilepsy (Lhatoo and Sanders, 2005).

Baboons have idiopathic generalized epilepsy electroclinically, with sporadic generalized tonic-clonic seizures and myoclonic seizures (Szabó et al., 2005). The Southwest Foundation for Biomedical Research (SFBR) in San Antonio housed up to 4,000 baboons, with records on more than 1,500 animals that belonged to a single pedigree (Williams et al., 2005). Although most of the epileptic baboons are euthanized for chronic diseases, debilitation or colony maintenance purposes, some of the baboons die spontaneously in their cages. As the prevalence of seizures is 20% in the pedigree, it some natural deaths should occur due to seizures, even SUDEP. In order to investigate the mortality in this pedigree, a database was searched for natural deaths.

The primary goal of this study was to evaluate the cause of death in SZ baboons by a retrospective survey of necropsy results. The secondary goal was to compare historical and pathological findings between epileptic animals with (SZ-KN) or without (SZ-UKN) a known cause of death and nonepileptic control (CTL) baboons.

Methods

The Computerized Animal Management Program (CAMP) is used to enter, query, and process data on vital events, genealogic relationships, animal locations, routine clinical exams, laboratory tests, experimental procedures, treatments, as well as IACUC assignments and committee records at the SFBR. Daily observations of animals are entered directly by the veterinary staff using a Palm OS device, which is subsequently used to transfer data directly into the Primate Records Database. These records are reviewed daily by veterinary staff to insure uniform descriptions of observations and procedures. Classification of SZ and CTL animals was verified using a retrospective case detection survey of the Primate Records Database. Sixty-five SZ baboons with witnessed seizures succumbed to natural deaths between 1988 and 2004, compared to 79 CTL baboons.

Pathological examination was performed in 78 (98%) of the CTL baboons and in 46 (71%) SZ baboons by a single certified veterinary pathologist (GBH). Autopsies are performed to evaluate the cause of death or experimentally induced changes. Standard operating procedures include standardized forms which are used to enter accession number, animal identification number, date of birth, date of death, location of death, species, body weight, charge number, date of necropsy, type and date of death, special procedures, gross description and diagnoses, submitting technician and person to receive the report. A standardized form is also used to designate a tissue harvest and cassette location for 27 tissues. The complete gross necropsy is performed, involving the removal of individual organs, which, after gross examination, are opened or “bread sliced”. Tissues routinely taken for histologic evaluation include the lungs and hilar lymph nodes, heart, left ventricle, spleen, kidneys, liver/gall bladder, thyroid/parathyroid glands, adrenal glands, mesenteric lymph nodes, stomach with esophagus, colon (5 cm from cecum), pancreas/duodenum, axillary lymph nodes, midbrain (thalamus/midbrain), pituitary, ovaries/testicles, urinary bladder, uterus/prostate, skeletal muscles, salivary glands,

and thymus. Additional histological samples are taken of lesions identified by gross examination.

Based upon the pathological examination, SZ animals were categorized as having a known cause of death (SZ-KN) or without a known cause (SZ-UKN). Twenty-six SZ-UKN animals were compared to 20 SZ-KN and 78 CTL animals for gender, age at death and pathological findings (two-tailed *t*-test or chi-square, $\alpha < 0.05$). Historical factors, such as the duration of epilepsy or quantity of lifetime seizures were compared between SZ-UNK and SZ-KN groups.

Results

The SZ (UKN and KN) animals expired at a significantly earlier age (mean 5.6, and SD 5.1, years) than CTL (mean 12.8, and SD 5.0, years; $t(122)=7.71$, $p<0.001$, two-tailed). Despite the predominance of males in the SZ groups, gender differences were not statistically significant.

Among the SZ groups that underwent pathological examination, there were no significant differences with respect to age at death, gender, duration of epilepsy, or number of lifetime seizures (Table 1). With respect to pathological findings, pulmonary congestion or edema was found in 25 (96%) of the SZ-UNK cases, which was significantly increased compared to the CTL ($\chi^2(1, N=104)=63.45, p<0.001$) and SZ-KN animals ($\chi^2(1, N=46)=38.22$, $p<0.001$). Bloody, frothy sputum was found in 15 (58%) of SZ-UNK cases compared to 3 (4%) in the CTL baboons ($\chi^2(1, N=104)=39.50$, $p<0.001$) and none of the SZ-KN animals ($\chi^2(1, N=46)=17.12, p<0.001$). Chronic multifocal myocardial fiber degeneration and fibrosis was noted in three (12%) SZ-UKN animals compared to one CTL baboon. Causes of the death in the CTL and SZ (KN) animals are listed in Table 2.

Discussion

This retrospective case detection survey identified causes of natural deaths in a captive pedigreed colony of baboons at the Southwest Foundation for Biomedical Research (SFBR) in San Antonio. As most animals with chronic disease are euthanized in order to minimize suffering and because of constraints of treatment, the animals that succumb to natural death are relatively infrequent. Because of the high prevalence of seizures in this pedigree (Williams et al., 2005; Szabó et al., 2005), we were interested in comparing the mortality and causes of natural death between animals with a history of witnessed seizures to those without seizures in a group of baboons that underwent a complete pathological examination.

Epileptic (SZ) baboons died at a significantly younger age than control (CTL) animals without a history of witnessed seizures. SZ baboons died in adolescence or young adulthood, while CTL baboons died predominantly in adulthood. There were no significant gender differences between the groups, although males were proportionally more common among epileptic baboons. Epileptic baboons with a known cause of death (SZ-KN) died slightly earlier than those without a known cause of death (SZ-UKN), predominantly from infection (60%) and trauma (20%). While CTL baboons died from a variety of causes at a significantly older age than the SZ group, they also succumbed to mainly infections (37%). It will be important to investigate whether there is any interaction of infection and epilepsy that drives mortality in the SZ-KN group.

The SZ-UKN baboons had more frequent seizures and a longer duration of epilepsy than the SZ-KN cases, though these differences were not statistically significant. The main reason for these differences may have been the longer life expectancy of the SZ-UKN animals. Although the SZ-UKN animals died suddenly and unexpectedly, their longer life expectancy compared to SZ-KN animals was probably due to their relatively good state of health. Autopsies in the SZ-UKN baboons revealed pulmonary edema, serosanguinous bronchial secretions, and

chronic multiregional fibrotic changes in the myocardium, which are commonly reported in humans succumbing to SUDEP (Earnest et al., 1992; Kloster and Engelskjøn, 1999). These findings were significantly less common in SZ-KN and CTL groups, suggesting a specific pathophysiology in the SZ-UKN group.

Similar to SUDEP patients, it is unclear whether pulmonary failure in the SZ-UKN group was "neurogenic" or related to a cardiac arrhythmia (Terrence et al., 1981; Earnest et al., 1992; Leung et al., 2006). While pulmonary edema was found in almost all of the baboons, none of them exhibited intracranial pathology or edema. Cardiac pathology was also relatively infrequent among SZ-UKN animals, occurring in 12% compared to a prevalence of 11–40% in humans (Earnest et al., 1992; Kloster and Engelskjøn, 1999; Condrea et al., 2005). While SUDEP is associated with cardiac arrhythmias in some patients (Leung et al., 2006), the risk for cardiac arrhythmias in epileptic baboons is unknown. There is a need for the prolonged cerebral and cardiac electrophysiological monitoring of unsedated SZ baboons in order to demonstrate the potential for ictal or interictal arrhythmias.

In summary, this study evaluated the causes of mortality in a captive baboon pedigree. While the deaths were not witnessed, thorough pathological examination identified a subgroup of epileptic baboons (SZ-UKN) that died suddenly and unexpectedly, in a good state of health, with pulmonary edema as the most prevalent finding on autopsy. The male predominance and younger age of SZ-UKN group compared to controls, the history of witnessed and chronic generalized tonic-clonic seizures, and the pathological findings in the SZ-UKN baboons are consistent with human studies of SUDEP (Earnest et al., 1992; Nilsson et al., 1999; Langan et al., 2005). This may present the first natural model of SUDEP described in a nonhuman primate. As baboons have idiopathic generalized epilepsy, SUDEP data in this untreated population may help to determine the risk factors for mortality in related epilepsy syndromes in humans. Because of its phylogenetic similarities to humans, the baboon offers a potential animal model to evaluate genetic factors and pathophysiology underlying SUDEP.

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Table 1

Demographic and Historical Factors

Groups	Control (CTL) Animals	Seizure (SZ) Animals	
		KN	UKN
Number	78	20	26
Sex	M=35 (45%) F=43 (55%)	M=12 (60%) F=8 (40%)	M=15 (58%) F=11 (42%)
Mean Age at Death (SD)	12.8 (5.0) years	4.7(5.8) years	6.3 (4.4) years
Mean Age of Onset Of Epilepsy (SD)	NA	3.3 (3.7) years	4.3 (3.4) years
Mean Epilepsy Duration (SD)	NA	1.0(1.2) years	2.0 (2.7) years
Total Number of Seizures (SD)	NA	1.8 (1.4)	7.4 (14.0)
Pathology available Serosanguinous Bronchial Secretions Pulmonary Edema/Congestion	3 (4%) 9 (12%)	0 1 (5%)	15 (58%) 25(96%)

Legend: SD standard deviation, M(ale), F(emale), KN(own) or UKN(own) cause of death.

Table 2

Causes of Death in Control and SZ-KN animals

	Controls (N=78)	SZ-KN (N=20)
Cardiopulmonary	18*	1
Infection	19	12
Gastrointestinal	13*	0
Trauma	10	4
Other	18	3

Legend:

* seven control animals succumbed to congestive heart failure due to a chronic viral encephalomyocarditis and three to infectious gastroenteritis, SZ-KN seizure animals with a known cause of death, *Other* includes control animals that died from cancer (2), coagulopathies (1), diabetes (1), hypo- or hyperthermia (7), iatrogenic causes (4), pregnancy related complications (2), kidney disease (1), and SZ-KN animals that died from pregnancy related complications (1), hypothermia (1) and an eroded esophagus (1).