Seizures in East-bound Visitors to Hawaii

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Anecdotal observations by emergency physicians at Straub Clinic and Hospital suggest that first-time seizures are common in Japanese tourists visiting Hawaii. Because such patients seemed to present in the evening of their day of arrival, some physicians have attributed these seizures to sleep deprivation based primarily upon clinical impressions. However, there has been no previous review of these cases to confirm the impression that these seizures have a relatively benign cause. This retrospective study aims to identify the role of sleep deprivation as a potential factor in seizures within this population.

Introduction

Sleep deprivation lowers one's seizure threshold[1,2] and may be a cause of "idiopathic" seizures. However, many emergency physicians may only infrequently see patients whose seizures are attributable to sleep deprivation. Emergency physicians at Straub Clinic and Hospital have seen seizures occurring somewhat commonly in visiting Japanese tourists, usually on the day of the visitor's arrival in Honolulu. In this clinical setting, sleep deprivation appears the likely precipitating factor in these seizures, but no study has described the relationship of seizures and sleep deprivation in this population or any similar population of travelers.

Most travelers are familiar with jet lag occurring from travel through multiple time zones. Eastward travel is generally more stressful than westward travel. Various studies have demonstrated greater impairments of human performance[3,4] and greater disruptions of sleep cycles with eastward travel compared to westward travel.

Most East-bound transoceanic flights depart in the evening and arrive in the morning. Throughout this night, already made shorter by crossing multiple time zones in an easterly direction, these travelers endure several stresses which interfere with normal sleep. These stresses include: sitting in a nearly upright position, noise, unfamiliar surroundings, in-flight movies, in-flight meal and beverage service, alcohol consumed during the flight, and alteration of light-dark cycles. The result is sleep deprivation for most east-bound travelers as most were awake throughout the day of departure and most are active throughout their day of arrival. By the evening of their day of arrival in Honolulu, many of these travelers have been awake for 30-36 hours continuously.

Straub Clinic and Hospital serves as the primary hospital for Waikiki, a heavily visited tourist destination for many travelers from the Far East (especially Japan). Hawaii saw over 2.8 million east-bound arrivals in 1996. Of these, over 2.1 million (75%) were Japanese visitors with a mean length of stay of 5.78 days.[5]

Vacationing Japanese travelers tend to concentrate in Honolulu, by virtue of the geography of the Pacific Basin. Visitors to Honolulu tend to concentrate in Waikiki, by virtue of the fame and the availability of hotel rooms in Waikiki. Waikiki visitors with acute medical problems tend to concentrate at Straub Clinic and Hospital, by virtue of Straub's proximity to Waikiki and ambulance policies requiring transport to the nearest available hospital. Straub Clinic and Hospital, therefore, is in a unique position to study this patient population.

Mainland visitors to Hawaii are more difficult to study on their eastward return trips as they scatter quickly across North America when they return home. Likewise, trans-Atlantic travelers scatter throughout Europe, scatter further throughout the countries they visit, and further scatter to various medical facilities within those countries when an acute medical condition arises. These eastbound travelers are, therefore, nearly impossible to study collectively once they present for medical care. Honolulu, therefore, is a focal point where East-bound travelers concentrate in a manner scarcely seen in other parts of the world.

Methods

We reviewed the Emergency Department registration log for 16 non-consecutive months in 1994, 1995 and 1996 to identify a series of adult patients presenting with a chief complaint of seizure. Inclusion criteria were: East-bound travelers, age 16-65 years, witnessed tonic-clonic seizure, and temperature less than 38 degrees Celsius. Exclusion criteria were: residents of Hawaii, fever on presentation (> 38 degrees Celsius), history of head trauma in previous 2 weeks (if known).

Review of the available ED logs for December 1994, January-December 1995 and April-June 1996 revealed 154 visits for seizure by 148 individuals (6 patients with more than one visit). Of these, 16

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Table 1.—Summary of East-Bound Visitors to Hawaii with Seizures

Patient	*Age (years)*	*Sex*	*Registration Time (HST)*	*Prior Seizures*	*Medications*	*Drug levels (Valp: 50-100)*	*CT Scan*
1	26	M	1840				Negative
2	19	F	2321				Negative
3	24	F	1650				Negative
4	23	F	1952	Yes ("fatigue")			
5	23	F	2148	Yes	Valproic acid	Valp=10.8	
6	23	F	2136	Yes	Valproic acid	Valp=40.6	
7	27	F	2115		Theophylline, Aspirin	Theo=15.0	Negative
8	28	M	1005	Yes			
9	18	F	1544	Yes ("lack of sleep")			
10	17	F	2233				Negative
11	18	M	2247				Negative
12	22	F	1534	Yes	Valproic acid	Valp=83.9	
13	22	F	0734	Yes	Valproic acid	Valp=32.0	
14	28	F	2130	Yes	Valproic acid, Carbamazepine	not done	
15	25	F	0839		Insulin		
	Mean = 23	12 of 15 F	Mean = 1751	8 with prior seizures	5 on Valproic acid 1 also on Carbamazepine	1 of 5 in Rx range for Valp	6 of 6 Negative

records met the inclusion criteria for further review, and 15 of these 16 records were available for review. Data collected from these records included nationality, age, gender, history of previous seizures, antiepileptic medication, results of non-contrast computed tomography (CT) of the head (if done), and time of registration. Most interviews of patients took place with the assistance of an interpreter.

Results

Table 1 includes the data among the 15 records evaluated. One additional record meeting the review criteria was unavailable.

Mean age was 23 years (range 17-28) among reviewed records. Three were male and 13 were female. All patients were Japanese. Registration time in the ED (with seizures presumably occurring shortly before) peaked in the early evening with a mean registration time of 17:51 hours. Eight of the 15 patients (53%) presented with a seizure occurring on the day of arrival in Hawaii, and eleven (73%) presented within the first 48 hours after arrival. Three records did not mention the interval from arrival to seizure.

Eight patients had a prior history of seizures; of these two gave a history of "fatigue" or "lack of sleep" with their prior seizures. Five patients were taking antiepileptic medication. Four were taking valproic acid, and one was taking both valproic acid and carbamazepine (but admitted non-compliance with her regimen). Only one patient had a serum concentration of valproic acid in the therapeutic range.

No patient reported either recent or remote history of head trauma. Six patients with first-time seizures underwent non-contrast CT scans during the E.D. visit. None showed any acute neurosurgical pathology.

Patient 7 had a prior medical history of pulmonary hypertension and was taking aspirin, theophylline, and several other medications. Her theophylline level was 15.0 mcg/ml, a level at which seizures are uncommon. Her arterial blood gas on 100% O2 showed pH 6.73, pCO2 29, pO2 449. Her measured bicarbonate level was 5. No salicylate level was available, but salicylate toxicity could explain both the seizure and her acid-base abnormalities.

Patient 15 had Type I diabetes mellitus but no prior seizure history. Her seizure occurred in the morning of her second day in Honolulu (registration at 0839 hrs) after taking insulin but before eating. Her initial blood glucose measured 59 mg/dl, and she appeared neurologically normal after paramedic administration of 50% dextrose.

Discussion

The mean time of registration was 1751 (5:51 p.m.) HST, which corresponds to 2151 (9:51 p.m.) in Japan. One might speculate that this reflects a threshold of sleep deprivation for seizures to occur in these recently arrived east-bound travelers. An alternate explanation would be that the peak occurs in the evening because these visitors are more likely to be in Waikiki (and therefore in Straub's catchment area) in the evening while spending the daytime elsewhere on the island nearer other hospitals.

The lack of any abnormal CT scans suggests the relatively benign nature of seizures occurring in young, otherwise healthy people in the setting of sleep deprivation. While emergent CT is not mandatory, neuroimaging remains part of the standard evaluation of a first-time seizure, either during the E.D. visit or in close follow-up.[6] The problems of difficulty in assuring adequate follow-up in travelers make emergent CT attractive to the clinician.

With 4 out of 5 patients on medication presenting with either subtherapeutic drug levels, non-compliance with medication contributes to the seizures in the patients with known prior seizure disorder. However, sleep deprivation appears to be an exacerbating factor in these seizures as well. Alterations in sleep cycles can change the effectiveness of anticonvulsants.[7-9] Also, the abrupt change in time zone may challenge patients' ability to maintain optimum dosing intervals of their medication.

While our inclusion criteria included age up to 65 years, no patient in our series was over 30 years of age. The significance of this is

unclear, but it possibly represents a behavioral difference in younger adults who may be more likely to "burn the candle at both ends" (e.g. working on the day of the flight to Hawaii, staying awake during much of the flight, and trying to meet an ambitious activity schedule on the day of arrival). Other alternative explanations could be either a change in sleep requirements or a change in seizure threshold with increasing age. Another explanation could be that older adults with seizure disorders more carefully maintain their dosing schedules of their anticonvulsants or simply travel less than younger patients.

It is difficult to calculate a useful expected number of seizures in this population of travelers for comparison to the observed number. Assuming a lifetime seizure risk of approximately 5 percent[10] distributed evenly across a life span of exactly 75 years, the expected incidence of seizures on any given day would be approximately 0.00018 percent. Using the population of over 2.1 million east-bound visitors annually, this translates into a crude estimate of 5.1 seizures occurring the first two days of any visit during the study period (11 observed) and 15 seizures at any time during an average visit (15 observed). Since data collection for this study occurred in only one Emergency Department, any patients presenting at other hospitals would represent excess seizures above the expected number. However, because both the observed and expected numbers are small, and because the assumptions underlying the calculation of the expected number are tenous, no useful statistical inference is possible.

The only other study of seizures in travelers is a retrospective study done in children visiting Orlando, Florida.[11] The Florida study found that seizures accounted for about 70% of their neurologic admission of out-of-state patients. Out of 36 seizure admissions, 16 were for acute febrile seizures, 13 for first-time seizures (all with normal CT scans), and 7 with prior history of seizure.

A study of acute psychiatric emergencies in visitors to Hawaii demonstrated an asymmetry between east-bound and west-bound travelers; east-bound travelers tended to present with ma-

nia while west-bound travelers tended to present with depression.[12] Any relationship of these observations to seizures in travelers is open to speculation. However, they do suggest a difference in CNS activity or function depending upon the direction of travel.

This retrospective review of a case series has multiple limitations. The sample size is small, so no statistical inferences are possible, especially with no control population. Without the prospective use of a standard questionnaire, the study relies upon the information deemed relevant by the clinician at the time of evaluation. Therefore, we lack adequate and consistent information on the activities in the 24 hours preceding the apparent seizure including how many hours the patients actually slept, how much alcohol and caffeine they consumed compared to their usual habits, and history of remote or recent head trauma. We also have no data on similar patients who presented to other area hospitals. Although Straub is the closest hospital to Waikiki, The Queen's Medical Center and other hospitals are somewhat nearby and may receive similar patients who arrive during times of ambulance diversion or whose seizures occur elsewhere on the island. The diagnosis of seizure in these patients generally rested upon the description of family, friends, bystanders, or paramedics; the combination of a lay person's concept of a seizure and cultural/language barriers in obtaining history creates some degree of uncertainty in the diagnosis. A future prospective study should include a uniform series of questions in a survey written in both Japanese and English and should involve the participation of other area hospitals.

Perhaps these seizures may be preventable either by educating the traveling public, both arriving visitors from the Orient and visitors returning to the Mainland, on how to change their habits when flying (possibly by taking medication to improve sleep on the flight) or lobbying for change in how airlines treat passengers on long east-bound flights. The U.S. Air Force uses short-acting benzodiazepines for aircrews who must rapidly shift their circadian rhythms to accommodate the demands of rapid deployments or night missions.[13] However, benzodiazepines are controlled substances requiring a physician's prescription. Inexpensive over-the-counter medications such as diphenhydramine are safe and effective in promoting sleep and could be useful in this setting. Various scientific and lay articles have touted the benefits of melatonin in the amelioration of jet-lag.[14,15] However, the effectiveness remains unproven, and animal studies have yielded conflicting data on the effect of melatonin on seizure threshold.[16,17]

Hotels could change their policies to permit early registration for newly arrived east-bound travelers in order to allow them to nap early on the day of arrival. One major hotel chain has recently begun an new advertising campaign indicating that they can now accept check-ins as early as 9 a.m. However, the Hawaiian hotel industry may have difficulty accommodating two million early check-ins per year without considerable additional cost to prevent a relatively small number of seizures.

Conclusions

Sleep deprivation and medication non-compliance each appear to have a role in the seizures seen in these young adults. Disruption of normal sleep during east-bound trans-oceanic flight plausibly contributes to these seizures in most of these young adults, both those with known prior seizure disorder and those who were in apparently good general health.

This pilot study raises questions suitable for future study with surveys to provide better data on patient habits, activities, time of arrival in Hawaii, recent use of alcohol and medications, etc. Ideally such a study would involve the participation of other hospitals on Oahu and the Neighbor Islands in order to include data from patients who may seize outside of the Waikiki area and to assess more accurately the magnitude of the problem.

As new flights bring more Japanese visitors directly to the Neighbor Islands, other physicians on Maui and the Big Island may see this clinical problem more frequently.

References

1. Van Sweden B: Sleep and the temporal lobe. *Acta Neurol Belg* 1996 Mar; 96(1):19-30.
2. Aguglia U, Gambardella A, Le Piane E, et al: Chlorpromazine versus sleep deprivation in activation of EEG in adult-onset partial epilepsy. *J Neurol* 1994; 241(10):605-610.
3. Recht LD, Lew RA, Schwartz WJ: Baseball teams beaten by jet lag. Nature 1995; 377: 583.
4. Jehue R, Street D, Huizenga R: Effect of time zone and game time changes on team performance: National Football League. *Med Sci Sports Exerc* 1992; 25: 127-31.
5. Hawaii Convention and Visitors Bureau, Honolulu, HI
6. American College of Emergency Physicians: Clinical policy for the initial approach to patient presenting with a chief complaint of seizure who are not in status epilepticus. *Ann Emerg Med* 1997;29:706-724.
7. Shouse MN, da Silva AM, Sammaritano M: Circadian rhythm, sleep, and epilepsy. *J Clin Neurophysiol* 1996; 13(1):32-50.
8. Bourgeois B: The relationship between sleep and epilepsy in children. *Semin Pediatr Neurol* 1996; 3(1):29-35.
9. Bazil CW, Walczak TS: Effects of sleep and sleep stage on epileptic and nonepilectic seizures. *Epilepsia* 1997; 38(1) 56-62.
10. Osborn HH, Dillon D: Treatment of the noncompliant seizure patient. *Emergency Medicine* 1996. Suppl.: 22-25.
11. Farrell MM, Pollack MA: Mickey Mouse neurology: Neurological disorders in children visiting Central Florida. *J Florida Med Assoc* 1990; 77(6):600-601.
12. Young DM: Psychiatric morbidity in travelers to Honolulu, Hawaii. *Compr Psychiatry* 1995; 36(3): 224-8.
13. Ferrer CF, Bisson RU, French J: Circadian rhythm desynchronosis in military deployments: a review of current strategies. *Aviat Space Environ Med* 1995; 66(6) 571-8.
14. Claustrat B, Brun J, David M, Sassolas G, Chazot G: Melatonin and jet lag: confirmatory result using a simplified protocol. *Biol Psychiatry* 1992; 32: 705-11.
15. Petrie K, Dawson AG, Thompson L, Brook R: A double-blind trial of melatonin as a treatment for jet lag in international cabin crew. *Biol Psychiatry* 1993; 33: 526-30.
16. Yehuda S, Mostofsky DI: Circadian effects of beta-endorphin, melatonin, DSIP, and amphetamine on pentylenetetrazol-induced seizures. *Peptides* 1993; 14(2): 203-5.
17. Champney TH, Hanneman WH, Legare ME, Appel K: Acute and chronic effects of melatonin as an anticonvulsant in male gerbils. *J Pineal Res* 1996; 20(2): 79-83.