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Epilepsy and common comorbidities: improving the outpatient epilepsy encounter

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ABSTRACT – Epilepsy is a chronic disorder that has been associated with other specific health problems. Evidence from recent clinical and basic investigations indicates that aspects of cerebral dysfunction associated with a lowered seizure threshold may also predispose toward other disorders such as depression, cognitive impairment, sleep disorders, and migraine. Similarly, certain types of brain injury may also increase the risk of adverse antiepileptic drug (AED) effects. For example, a history of febrile seizures is associated with a three fold increase in the occurrence of negative psychiatric effects of two newer AEDs. Poor fitness and obesity are also reported at higher rates in epilepsy. Some comorbid conditions in epilepsy, such a depression and anxiety, may have a greater influence on subjective health status than does seizure rate. Management strategies employed in the outpatient clinic to maximize overall health outcomes should include screening and treatment for the commonly coexistent conditions in persons with epilepsy.

Keywords: epilepsy, depression, cognitive dysfunction, sleep disorders, migraine, antiepileptic drug

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Epilepsy is a complex, chronic disorder that interacts with many aspects of human function. Psychological, social, and biological aspects of health have appropriately been the focus on many studies of persons with epilepsy. Results of clinical and basic investigations during the past decade have elucidated the occurrence and impact of several comorbid conditions commonly associated with epilepsy. Although the literature on comorbid disorders in epilepsy is extensive, this paper attempts to efficiently review the salient data on the impact of reduced fitness, depression and anxiety, sleep dysregulation, and headache on health status in epilepsy.

Health care considerations in epilepsy

Health is defined by the World Health Organization as ″a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity″ (Preamble to the Constitution of the World Health Organization 1946). The evolution of this comprehensive construct of health within the medical science community led the leadership of the Agency for Health Care Policy and Research to emphasize that ″outcomes research- the study of the end results of care that takes patients' experiences, preferences, and values

into account- is intended to provide scientific evidence relating to decisions made by all who participate in health care" (Clancy 1998). During the past decade health outcomes researchers have developed reliable and valid measures of function, well-being, and patient preference for use in persons with epilepsy (Baker 1998). Numerous subsequent clinical investigations have evaluated the complex interactions of epilepsy with various aspects of health, and the role of coexistent disorders is becoming better formulated and clinically useful (Gilliam 2001).

The translation of advances in knowledge of comorbid conditions in epilepsy into improved health substantially depends on the quality of the interaction between the clinician and patient. Growing pressures to decrease clinic visit duration and perform more administrative duties may impair delivery of optimal care. These considerations require that the outpatient clinic visit be well organized, and specifically target the most common problems in epilepsy that have the greatest impact on health status, as outlined in the table. Systematically utilizing reliable and valid screening instruments to aid efficient diagnosis of common coexisting disorders may be the most effective methodology to improve overall health outcomes.

Physical fitness

The fitness levels of persons with epilepsy as a group have been studied by several investigators (Arida 2003, Nakken 1990). Steinhoff *et al.* (1996) evaluated 35 adults with epilepsy and 36 controls using physical parameters such as body mass index and body composition and standardized tests of aerobic and muscle strength endurance and physical flexibility. Control subjects participated in regular sports significantly more frequently than the epilepsy sample ($p = 0.005$). Epilepsy subjects demonstrated significant differences of aerobic endurance ($p < 0.001$), muscle strength endurance ($p < 0.001$), and physical flexibility ($p < 0.001$) in favor of the control subjects. Also, the body mass index was significantly higher in patients ($p = 0.03$).

Another study of 44 adults patients with at least one seizure per month found that they were only half as active physically as the average Norwegian population of comparable age and sex (Bjorholt 1990). As predicted by the decreased activity, maximum oxygen uptake was considerably lower (75-80%), and the decrease observed in aerobic capacity with increasing age was more pronounced than that of the average population. The authors concluded that "prescription of adapted physical activity is an important means of improving quality of life" (Bjorholt 1990).

An interesting study of the association of 133 adults with epilepsy in a tertiary care center found lower levels of depression among patients who exercised regularly (Roth 1994). Statistical analyses showed direct effects of exercise and stressful life experience on depression. These effects were independent of each other, and independent of the influence of other predictor variables, such as seizure frequency, age, and gender. The results suggest a significant association of poor fitness with depression in persons with epilepsy.

Improved physical fitness has been associated with decreased seizures in a small Norwegian study (Eriksen 1994). Fifteen women with pharmacologically intractable epilepsy were given physical exercise (aerobic dancing with strength training and stretching) for 60 min, twice weekly, for 15 weeks. Medication doses were kept as constant as possible. Self-reported seizure frequency was significantly reduced during the intervention period. The exercise also led to reduced level of subjective health complaints, such as muscle pains, sleep problems, and fatigue. The clinical observation of seizure reduction after initiating an exercise regimen is supported by studies of certain rodent models of epilepsy (Arida 2004).

Evidence from recent clinical studies indicates that hormonal and bone health is reduced not only in women with epilepsy, but also children and men (Pack 2005, Sheth 2004, Pack 2004). Although bone fragility in persons with epilepsy is likely related to multiple factors, decreased activity and subsequent reduced physical fitness is likely a significant influence. Furthermore, epilepsy increases the risk of bone fracture (Huopio 1900; Souverein 2005), which subsequently may lead to decreased activity and fitness. The impact of hormonal and bone health changes on quality of life in epilepsy has not been systematically studied, but the connection seems apparent and remains an important area for further research.

Sleep dysfunction

The association of aspects of epilepsy and sleep has been recognized for many decades, but only in recent years have the consequences and neurobiological factors been systematically investigated (Bazil 2004, Autret 1999, Bazil 2003, Malow 1996, Vaughn 2004, Mendez 2001, Radtke 2001). Although sleep deprivation may lower the seizure threshold, this relationship is not well understood and may not occur in all seizure types (Malow 2002). Specific aspects of sleep may be associated with the occurrence of epileptiform EEG activity or seizures (Malow 1998), and seizures (especially nocturnal) can adversely affect sleep architecture (Bazil 2000). Daytime sleepiness in epilepsy may be due most commonly to an underlying sleep disorder than to type or number of antiepileptic drug or seizure frequency (Malow 1997).

In a recent series, 39 candidates for epilepsy surgery without a history of obstructive sleep apnea (OSA) received a polysomnogram as part of a research protocol examining the relationship of interictal epileptiform discharges to sleep state (Malow 2000). One-third of the

subjects had OSA as defined by accepted standards. Five subjects (13%) had moderate to severe OSA. Subjects with OSA were more likely to be older, male, and more likely to have seizures during sleep than those without OSA ($p < 0.05$). Seizure frequency per month, the number or type of antiepileptic drugs (AED) prescribed, the localization of seizures (temporal versus extratemporal) were not statistically different between the two groups. The authors concluded that OSA is common in patients with refractory epilepsy.

A recent investigation of children with idiopathic generalized epilepsy found unexpected results that suggest potentially clinically significant sleep disturbances in this population (Maganti 2005). Children between the ages of 5 and 18 years with well controlled primary generalized epilepsy, as well as age-and gender-matched healthy controls, underwent two consecutive nights of nocturnal polysomnography. Children with epilepsy had longer stage 1 sleep percentage (7.19 ± 3.2 *versus* 4.8 ± 3.5; $p = 0.05$) and latency to rapid-eye-movement (REM) sleep (123.5 ± 40.1 *versus* 101.75 ± 24.3; $p = 0.018$) compared with controls. There was a trend toward worsened scores on standardized measures of attention and behavior in patients with more abnormal sleep architecture.

A large study of 486 adult epilepsy patients and 492 controls found that the subjects with partial epilepsy had a highly significant, twofold higher prevalence of sleep disturbance compared with controls (38.6 *versus*. 18.0%; $p < 0.0001$) (De Weerd 2004). Most sleep-disorder subscales showed significant abnormalities in respondents with epilepsy, compared with controls. The presence of a sleep disturbance in respondents with epilepsy was associated with the greatest impairment in quality of life based on SF-36 scores.

Although sleep disorders may require additional effort to diagnose in the busy outpatient epilepsy clinic setting, the prevalence and adverse effect on subjective health status supports the use of systematic screening with a valid and reliable instrument *(table 1)*. Recently published recommendations for evaluation and treatment may aid neurological management of sleep problems in epilepsy patients:

The most important aspect of treating sleep disorders, especially sleep apnea, is the recognition of the problem.

Table 1. Components of the outpatient epilepsy encounter that should be included in every clinic visit.

• Seizure rate and severity assessment
• Screen for adverse AED effects
• Assess physical fitness activity
• Screen for depression and anxiety
• Review symptoms of endocrine dysfunction
• Review sleep hygiene
• Assess any other patient or family concerns

« In a busy clinical practice, symptoms of sleep disorders are frequently overlooked or mistaken. Whenever sleep disruption or excessive daytime somnolence is potentially problematic, the patient should be referred to a sleep specialist and, if indicated, diagnostic testing performed (usually polysomnography with or without multiple sleep latency tests). The author also recommends that all patients receive basic counseling about sleep hygiene, because its principles are often helpful to patients in general. Even in the absence of a sleep disorder, the choice of an anticonvulsant can be partly tailored to the sleep needs of the patient, with alerting drugs (lamotrigine and felbamate) dosed early in the day and relatively sedating agents (phenobarbital and phenytoin) dosed later or at bedtime » (Bazil 2004).

Depression and anxiety

Most prior published investigations of the prevalence of depression in epilepsy have found increased rates compared to the general population (Mendez 1986, Jacoby 1996, Lambert 1999, Kanner 2003, Ettinger 2004, Hermann 2000). Although sample bias from tertiary care centers with more severe epilepsy disorders may explain a component of the increased rate, and techniques for measuring depressive symptoms have varied, the studies using structured psychiatric diagnostic interviews in samples of consecutive patients in epilepsy clinics demonstrate a prevalence of significant depression of up to 55% (Jacoby 1996). Suicide is reported to be over 10% of all deaths in persons with epilepsy, compared with 1% in the general population (Jones 2003).

Ettinger *et al.* (2004) recently utilized the data collected through the National Family Opinion to study depression and quality of life in persons with epilepsy, asthma, and healthy controls. The response rate for the survey was approximately 50% in each group, with a total of 1532 responses. Patients with epilepsy were significantly more likely to score in the depressed range on the Center for Epidemiological Studies Depression Scale (CES-D) (37%), than were those with asthma (28%) or healthy subjects (12%). Although nearly half of the group with epilepsy had not had a seizure during the past year, their mean scores on the Short Form-36 scales for role limitations, emotional well-being, and social well-being were significantly worse than those measured in the asthma group. None of the scales was lower for asthma.

Beghi *et al.* (2002) compared depression severity across samples of patients with epilepsy, type I diabetes mellitus, and community controls. Fifty-five patients with idiopathic or cryptogenic epilepsy were compared with age and sex matched subjects with type I diabetes or persons donating blood in the local medical clinic. Epilepsy subjects with any structural brain abnormality were excluded

from the study, and only 37% reported a seizure within the past year, suggesting that the sample represented the less severe aspect of the spectrum of epileptic disorders. Although reliable and valid measures of frustration, aggressiveness, and apathy were not different between groups, patients with depression had significantly higher mean Beck Depression Inventory (BDI) scores. Thirty-four percent of epilepsy patients scored in the depressed range compared with 27% of type I diabetes patients and 7% of blood donors.

Two recent studies demonstrated that a history of febrile seizures in early childhood was one of the strongest predictors of an adverse psychiatric reaction to topiramate or levetiracetam (Mula 2003a, Mula 2003b). Patients with childhood febrile seizures were three times more likely to have a mood disorder, psychosis, or anxiety after initiating the antiepileptic drug. Potential mechanisms for permanent limbic system injury that might predispose to psychiatric side effects were elucidated in study of long term (into adulthood) hippocampal dysfunction following hyperthermic seizures in rat pups at a specific developmental stage (Chen 1999).

Perrine *et al.* (1995) evaluated 257 epilepsy patients in a multicenter prospective study designed to evaluate the association of neuropsychological function and health-related quality of life. The neuropsychological variables included mood, verbal memory, psychomotor function, visuospatial function, language, and cognitive inhibition. The mood factor had the highest correlations with scales of the Quality of Life in Epilepsy Inventory-89 (r = -0.20 to r = -0.73 with the 17 subscales) and was the strongest predictor of quality of life in regression analyses. Nearly one half of the variance in overall quality of life was explained by the mood factor ($p < 0.0001$). A subsequent study by Johnson *et al.* (2004) found that anxiety may have similarly strong adverse effect on quality of life, and both depression and anxiety seem to have more negative effects than specific epilepsy factors.

Multiple subsequent investigations of epilepsy outpatients, presurgical candidates, and postsurgical patients have demonstrated similarly strong associations with depression and worsened subjective health assessment (Boylan 2004, Gilliam 1999, Lehrner 1999, Hermann 2000). Furthermore, Cramer *et al.* (2004) found that health care utilization was significantly increased in epilepsy patients with depression compared with a non-depressed epilepsy sample; depressed patients had more than twice as many non-psychiatric office visits and emergency room visits. Although only one randomized controlled trial has evaluated treatment efficacy for depression in epilepsy (Robertson 1985, Gilliam 2004c), current recommendations are to utilize standard treatments for non-neurological depression and anxiety in persons with epilepsy and major mood disorders (Barry 2000, Gilliam 2002).

Migraine

Migraine and epilepsy are both disorders characterized by paroxysmal, transient alterations of neurologic function, and a link between the two has been recognized for decades. Not infrequently, one disorder is mistaken for the other, as there may be substantial overlap in clinical symptoms and signs. Perhaps more significantly, these two conditions often coexist in the same patients.

Numerous studies over the years have demonstrated the association between migraine and epilepsy. Andermann and Andermann summarized thirteen such studies, noting an epilepsy prevalence ranging from 1 to 17% (median 5.9%) in patients with migraine. (Andermann 1987). Conversely, in a summary of four studies, they noted a migraine prevalence ranging from 8 to 15% in patients with epilepsy. More recently, Ottman and Lipton systematically studied a large population of 1948 adult epilepsy patients in the Epilepsy Family Study of Columbia University (Ottman 1994). They found the cumulative incidence of migraine to be 24% in probands with epilepsy, 23% in relatives with epilepsy, and 12% in relatives without epilepsy. The rate ratio for migraine was 2.4 (95% C.I.) in both probands and relatives with epilepsy compared to relatives without epilepsy. Of note, the increased migraine risk was found to be independent of seizure type, etiology of epilepsy, age at onset, or family history of epilepsy.

Marks and Ehrenberg (1993) similarly found that 20% of a series of 395 adult epilepsy patients suffered from a migraine syndrome. While migraines and epileptic seizures most often had no temporal association with one another, these authors found that 3% of patients experienced seizures during or immediately following a migraine aura. Certain childhood epilepsy syndromes may have an even stronger association with migraine. In particular, in Childhood Epilepsy with Occipital Paroxysms, migraine-type headaches follow seizures in about one-third of patients (Gastaut 1987).

As in epilepsy and other chronic neurological disorders, overall quality of life has been found to be significantly reduced in patients with uncontrolled migraine headaches (Bussone 2004, Lipton 2000). Lipton and colleagues looked at health related quality of life, as measured by the Medical Outcomes Study Short Form 36-Item Health Survey (SF-36), in a population-based study comparing 200 patients with migraine and a matched control population (Lipton 2003). They found significantly lower scores in 8 of the 9 domains of the SF-36 and in the overall Physical Component and Mental Component Summary scores in the migraine patients. Moreover, those that were more disabled, as defined by number of lost work days, had significantly lower overall health related quality of life scores. Despite the known association between migraine and epilepsy, and the known effects on quality of life in each individual disorder, there are no studies assessing these outcomes in relation to the comorbid conditions.

While a relationship between migraine and epilepsy is recognizable, the mechanisms of association remain unclear. Ottman and Lipton hypothesized that the comorbidity occurs due to a shared genetic susceptibility, but found that relatives of probands with epilepsy did not have an increased risk of migraine, and that relatives of probands with migraine did not have an increased risk of epilepsy (Ottman 1996). These findings were inconsistent with a shared genetic susceptibility. Almost certainly, the causes of comorbidity are multifactorial, with both environmental and genetic factors playing important roles.

Given the known effects on overall health, recognition of migraine syndromes in patients with epilepsy is critical, in order to optimize overall health outcomes. In particular, in these patients, we may be able to take advantage of the dual beneficial effects of certain anticonvulsant medications. Both Valproate (Silberstein 1999, Hering 1992) and Topiramate (Silberstein 2004) have been shown in prospective trials to be effective in migraine prophylaxis, and each has received an FDA indication for this use. Gabapentin (Mathew 2001) has also shown benefit, as did Zonisamide (Drake 2004) in a small open label trial. Lamotrigine (Steiner 1997, D'Andrea 1999) has shown mixed results, and VNS Therapy (Mauskop 2005) was recently reported to be effective in a small number of patients with chronic refractory migraine.

Conclusions

Although epilepsy is a complex disorder that interacts with many aspects of a person's health, a well organized and efficient approach to the outpatient clinic encounter can readily address most significant health considerations. Systematic assessment of physical fitness activities, sleep hygiene, depression, anxiety, headache, and adverse medication effects (Gilliam 2004a) using reliable and valid instruments (Gilliam 2004b) ought to assist delivery of optimal care. Efforts should be made at every clinic visit to screen for common comorbidities that have been demonstrated to have significant adverse health effects in persons with epilepsy. □

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