Interictal Epileptiform Discharges in Persons Without A History of Seizures: What Do They Mean?

Elson L. So

Abstract: Interictal epileptiform discharge (IED) is rarely observed in healthy volunteers without a history of seizures, but higher rates of occurrence are reported in children than in adults. Higher rates are also observed among neurologic inpatients and outpatients without a seizure history, but the risk of subsequent unprovoked seizures or epilepsy is low in healthy volunteers and patients. An exception is the patients with autism spectrum disorders, attention deficit/hyperactivity disorder, or cerebral palsy, who are predisposed to epilepsy development. However, it is currently unclear whether epilepsy risk is higher for patients with incidentally detected IED than for the patients without IED. Hospitalized patients with IED but no prior seizures often have underlying acute or progressive brain disorders. Although they have increased risk of acute seizures, the risk for subsequent unprovoked seizures or epilepsy is unknown and requires assessment on an individual basis. For patients who have psychogenic spells but no seizure history, the rate of IED detection is low, similar to that of healthy volunteers. The association between IED and transitory cognitive impairment has not been established in nonepileptic persons. Evidence thus far does not suggest that routine EEG screening of pilot candidates reduces risk of flight-related accidents.

Key Words: EEG, Epilepsy, Interictal epileptiform discharges, Seizures.

(J Clin Neurophysiol 2010;27: 229–238)

The best known types of interictal epileptiform discharge (IED) are the spike and sharp wave, either of which can occur with or without a subsequent slow wave. Spikes have been defined as “a transient clearly distinguished from the background activity, with pointed peak at conventional paper speeds and a duration from 20 to under 70 milliseconds, i.e., 1/50–1/14 seconds, approximately. Main component is generally negative [compared] to other areas” (International Federation of Societies for Electroencephalography and Clinical Neurophysiology, 1983) (Fig. 1). A sharp wave discharge differs from a spike only in its longer duration, with a range of 70 to 200 milliseconds (Fig. 2). It should be considered a variation of spike activity; as such, both have the same clinical significance. More importantly, descriptions of sharp wave discharge as an IED should be distinguished from those of normal background activity, which uses terminology such as “sharply contoured waves” and “sharp transients.”

Spike and sharp wave discharges are more commonly focal in distribution, but they can also be generalized, either as independently appearing waveforms or as components of complexes of different waves. Examples of the latter are generalized, atypical, spike-and-slow-wave discharges (Fig. 3) and, uncommonly, 3-Hz spike-and-wave discharges.

Detection of IED in the clinical practice is invaluable for diagnosing epilepsy, classifying seizure type, and localizing the seizure focus. However, IED are also encountered in persons with no seizure history. The detection of IED in such persons raises questions regarding the probability of future seizures and whether that probability justifies treatment with antiepileptic drugs (AED) or restriction of activities such as driving, flying aircraft, or playing sports. The objective of this article is to review the prevalence of IED in persons without a seizure history and to discuss the implications of IED detection in these persons.

NONSEIZURE SETTINGS IN WHICH IEDs MAY BE IDENTIFIED

EEG has endured the rapid advances in brain imaging technology because of its unique role in evaluating abnormal brain function, its wide availability, and relatively low cost. Therefore, EEG is regularly used in many clinical practice situations other than evaluation of epileptic seizure disorders. The yield of EEG in some of these conditions is arguable, but EEG is still commonly performed in these scenarios.

All too often, the question of an unrecognized seizure disorder is raised as the indication for performing EEG (Williams et al., 2002). For children, inattention, unsatisfactory school performance, or behavioral disorders often lead to neurologic evaluation that includes EEG. This course of action is not totally unfounded. Children with epilepsy have a 2.5-fold higher risk of attention deficit/hyperactivity disorder (ADHD) than children without epilepsy (Hesdorffer et al., 2004). The increased risk of ADHD is antecedent to epilepsy onset; therefore, the ADHD risk cannot be attributed to seizure episodes or AED treatment.

EEG is also used as a screening test for aircraft pilot candidates. The advent of clinical EEG in the late 1930s coincided with the rise in deployment of military aircraft during World War II. The next decades saw the establishment and expansion of civilian air travel. With these developments, both civilian and military authorities assumed that EEG would be a good screening test to help with pilot selection.

Syncopal and psychogenic events frequently are encountered in clinical practice, especially in neurologic practice. Up to 30% of patients undergoing spell evaluation receive the diagnosis of psychogenic spells (Lancman et al., 2001). With or without simultaneous video-recording, EEG is regularly conducted to evaluate syncope and psychogenic spells. EEG and video features of these conditions have been well characterized (Brenner, 1997; French, 1995), but limitations in the reliability between video-EEG reviewers for psychogenic spells have been reported (Benbadis et al., 2009). The observation of IED always raises concern of misdiagnosis in a patient who otherwise has evidence only of psychogenic spells (Iriarte et al., 2003).

Standard EEG is no longer routinely required before initiating electroconvulsive therapy. The risk of a prolonged seizure that is induced during the first electroconvulsive therapy session is only 1% to 2%, and prolonged seizures are usually shorter than 3 minutes.
Whittaker et al., 2007). Nonetheless, a history of episodic behavioral dysfunction or behavioral change after electroconvulsive therapy has warranted EEG recording.

An established indication for EEG is the evaluation of traumatic and nontraumatic encephalopathy (Kaplan, 2006; Young, 2007). EEG provides diagnostic and prognostic information for different types of obtundation or coma (Young, 2000). The increasing use of EEG monitoring in patients with encephalopathies and coma is due to the observation that subclinical seizures or status epilepticus are not uncommon in these patients (Jirsch and Hirsch, 2007). Some centers have implemented routine EEG monitoring of critically ill patients.

A recent critical review of the literature described numerous studies of EEG in the evaluation of dementia (Jelic and Kowalski, 2009). Although the usefulness of routine EEG in patients with dementia has not been convincingly established, patients with Alzheimer disease and other dementias have a sixfold higher risk of unprovoked seizures than the general population (Hesdorffer et al., 1996). Consequently, EEG is still performed to assess episodic behavioral changes in patients with dementia. Also, the usefulness of clinical and quantitative EEG in differentiating between various types of dementia continues to be investigated (Gawel et al., 2009; Pijnenburg et al., 2008; Schreiter Gasser et al., 2008).

FIGURE 1. EEG Tracing in a Laplacian montage. The arrow denotes a left temporal spike. The interval between grid lines represents 1 second. The patient was a 78-year-old woman. EEG was performed to help evaluate a 5-year history of episodic visions of serrated wheel-like phenomena, with alternating areas of dark and light that would enlarge slowly and migrate inferiorly in her visual field. The visual experience was followed more recently by head or eye pain. The patient recalled that an EEG, performed when she was 50 years old, had shown abnormalities on the left side of her head. She was advised to initiate antiepileptic drug treatment at that time, but she declined the advice.

FIGURE 2. EEG tracing. The arrow denotes a right temporal sharp wave. The interval between grid lines represents 200 milliseconds. The patient was a 24-year-old man with easily provoked outbursts of anger.

(Whittaker et al., 2007). Nonetheless, a history of episodic behavioral dysfunction or behavioral change after electroconvulsive therapy has warranted EEG recording.

An established indication for EEG is the evaluation of traumatic and nontraumatic encephalopathy (Kaplan, 2006; Young, 2007). EEG provides diagnostic and prognostic information for different types of obtundation or coma (Young, 2000). The increasing use of EEG monitoring in patients with encephalopathies and coma is due to the observation that subclinical seizures or status epilepticus are not uncommon in these patients (Jirsch and Hirsch, 2007). Some centers have implemented routine EEG monitoring of critically ill patients.

(Whittaker et al., 2007). Nonetheless, a history of episodic behavioral dysfunction or behavioral change after electroconvulsive therapy has warranted EEG recording.

An established indication for EEG is the evaluation of traumatic and nontraumatic encephalopathy (Kaplan, 2006; Young, 2007). EEG provides diagnostic and prognostic information for different types of obtundation or coma (Young, 2000). The increasing use of EEG monitoring in patients with encephalopathies and coma is due to the observation that subclinical seizures or status epilepticus are not uncommon in these patients (Jirsch and Hirsch, 2007). Some centers have implemented routine EEG monitoring of critically ill patients.
The standard protocol of polysomnogram review is not ideal for detection of IED because of limited scalp coverage of the recording and the compressed time scale of EEG display. However, given that nocturnal seizures are often in the differential diagnosis of parasomnias and other sleep-related events (Bazil, 2004; Nobili, 2007), a montage of full-head EEG recordings has been selectively used in polysomnographic recordings for patients with nocturnal paroxysmal events. The longer duration of EEG recording in polysomnograms, especially of sleep activity, is considered an advantage over routine EEG recordings for detecting IED.

**TYPES OF IED STUDIES IN PERSONS WITHOUT A SEIZURE HISTORY**

IED have been detected in various groups of persons without a seizure history and in different settings. A review of the literature in 2001 showed that these persons with IED range from young children to adults (Table 1) (Sam and So, 2001). In 1940s, clinical application of EEG was just beginning, two decades after its discovery by Hans Berger. Clinicians and investigators needed to assess the specificity of IED for clinical disorders. Therefore, many EEG studies were subsequently performed in healthy volunteers for the purpose of determining the prevalence of IED in the general population. Some studies assessed only children (Brandt and Brandt, 1955; Brandt et al., 1961; Cavazzuti et al., 1980; Corbin and Bickford, 1955; Doose et al., 1968; Eeg-Olofsson et al., 1971; Herrlin, 1954; Okubo et al., 1985, 1993), whereas others confined the study population to adults (Gibbs et al., 1943; Jabbari et al., 2000; Kooi et al., 1964).

In addition to healthy children and adult volunteers, two particular cohorts of persons without a seizure history were also studied with EEG for IED: neurologic patients and aircrew candidates. In the first group, inpatients and outpatients were studied, mostly in an attempt to gauge the specificity of IED for seizure disorders and to assess the prognosis for seizure occurrence in those who had brain injury (Bridgers, 1987; Doose et al., 1968; Iida et al., 1985; Sam and So, 2001; Zivin and Marsan, 1968). As mentioned earlier, EEG routinely was used to screen military and civilian aircrew candidates, but fewer countries now use EEG for this purpose.

**PREVALENCE OF IED IN PERSONS WITHOUT A SEIZURE HISTORY**

The prevalence of IED in persons without a seizure history must be assessed according to patient age and health status. Also, a distinction should be made between IED that are spontaneous and those that are activated by photic stimulation or hyperventilation. A review of the literature shows that the prevalence rates of spontaneous IED in healthy children volunteers vary from 0% to 5.6% (Table 1) (Brandt and Brandt, 1955; Cavazzuti et al., 1980; Corbin and Bickford, 1955; Doose et al., 1968; Eeg-Olofsson et al., 1971; Herrlin, 1954; Okubo et al., 1993; Sam and So, 2001). Similarly, the
### TABLE 1. Summary of Studies of IED of Persons Without Epilepsy

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Patient</th>
<th>No. Patients</th>
<th>Basal Transients</th>
<th>EEG Recording State</th>
<th>Duration of Follow-Up</th>
<th>Seizure Development (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unspecified Wake and Drowsy</td>
<td>Not done</td>
<td>Not done</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Photic Stimulation</td>
<td>Not done</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hyperventilation</td>
<td>NA</td>
<td>0.8</td>
</tr>
<tr>
<td>Gibbs et al. (1943)</td>
<td>Volunteers, ≥20 years</td>
<td>1,000</td>
<td>Not excluded</td>
<td>0.4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Williams (1944)</td>
<td>Healthy aircrew</td>
<td>241</td>
<td>Not excluded</td>
<td>0.8</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Buchthal and Lennox (1953)</td>
<td>Predominantly male air force applicants</td>
<td>682</td>
<td>Not excluded</td>
<td>NA</td>
<td>2.6</td>
<td>—</td>
</tr>
<tr>
<td>Herrlin (1954)</td>
<td>Nonepileptic children</td>
<td>70</td>
<td>Not excluded</td>
<td>NA</td>
<td>0</td>
<td>Not done</td>
</tr>
<tr>
<td>Brandt and Brandt (1955)</td>
<td>Healthy children, &lt;5 years</td>
<td>135</td>
<td>Not excluded</td>
<td>0.7</td>
<td>Not done</td>
<td>Not done</td>
</tr>
<tr>
<td>Corbin and Bickford (1955)</td>
<td>Healthy children, 1–10 years</td>
<td>71</td>
<td>Not excluded</td>
<td>NA</td>
<td>5.6</td>
<td>Not done</td>
</tr>
<tr>
<td>Larsson and Weden (1958)</td>
<td>Control subjects, ≥7 years</td>
<td>120</td>
<td>Not excluded</td>
<td>0.8</td>
<td>Not done</td>
<td>Not done</td>
</tr>
<tr>
<td>Kooi et al. (1964)</td>
<td>Predominantly male volunteers, 26–81 years</td>
<td>218</td>
<td>Not excluded</td>
<td>—</td>
<td>6.6</td>
<td>—</td>
</tr>
<tr>
<td>Bennett (1967)</td>
<td>Predominantly male aviators</td>
<td>1,332</td>
<td>Not excluded</td>
<td>0.6</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Doose et al. (1968)</td>
<td>Neurologically healthy children</td>
<td>118</td>
<td>Not excluded</td>
<td>0.8</td>
<td>—</td>
<td>Not done</td>
</tr>
<tr>
<td>Zivin and Marsan (1968)</td>
<td>Inpatients in tertiary care</td>
<td>6,497</td>
<td>Not excluded</td>
<td>2.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Eeg-Olofsson et al. (1971)</td>
<td>Healthy children, 1–15 years</td>
<td>743</td>
<td>Excluded 14 and 6 positive spikes</td>
<td>NA</td>
<td>1.9</td>
<td>8.1&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cavazzuti et al. (1980)</td>
<td>Neurologically healthy children, 6–13 years</td>
<td>3,726</td>
<td>Excluded 14 and 6 positive spikes, high-voltage non-epileptiform synchronous activities, and “excessive sensitivity” to hyperventilation</td>
<td>—</td>
<td>3.5</td>
<td>Not done</td>
</tr>
<tr>
<td>Iida et al. (1985)</td>
<td>Nonepileptic outpatients</td>
<td>10,473</td>
<td>Not excluded</td>
<td>8.1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Bridgers (1987)</td>
<td>Nonepileptic psychiatric inpatients, 11–85 years</td>
<td>3,143</td>
<td>Excluded</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Gregory et al. (1993)</td>
<td>Aircrew trainees, 17–25 years</td>
<td>13,658</td>
<td>Excluded 6-Hz spike-wave and positive spikes</td>
<td>0.2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Okubo et al. (1993)</td>
<td>Healthy children, 6–12 years</td>
<td>1,057</td>
<td>Excluded, except small sharp spikes</td>
<td>5.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Jabbari et al. (2000)</td>
<td>Healthy male volunteers, 18–45 years</td>
<td>100</td>
<td>Excluded</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sam and So (2001)</td>
<td>Community outpatients and inpatients</td>
<td>521</td>
<td>Excluded</td>
<td>—</td>
<td>10.5</td>
<td>1.2</td>
</tr>
</tbody>
</table>
rates of spontaneous IED in healthy adult volunteers vary from 0% to 6.6% (Gibbs et al., 1943; Jabbari et al., 2000; Kooi et al., 1964). The prevalence rates of spontaneous IED reported in patient groups are overall higher than those of healthy volunteers. The rates in groups of inpatients and outpatients (or both) range from 2% to 12% (Bridgers, 1987; Iida et al., 1985; Sam and So, 2001; Zivin and Marsan, 1968). The higher prevalence rates observed in patients is expected because these nonepileptic patients would still have had some neurologic complaint or condition to warrant referral for EEG. In one study, nearly three-fourths of nonepileptic patients with IED had acute or progressive brain disorders (Sam and So, 2001).

Shelley et al. (2008) recently conducted a review of the extensive literature on EEG in nonepileptic patients with psychiatric disorders and in children with neurobehavioral disorders. EEG abnormalities had been observed in up to 50% to 70% of patients with psychiatric and neurobehavioral disorders, but many of the abnormal EEG findings were not epileptiform. They included slowing of the background, which could be due to drowsiness, concomitant nonepileptic cerebral disorders, or medication effects. One retrospective study reported that 60% of patients with autism spectrum disorders (but no prior seizures or EEG abnormality) had IED detected by 24-hour ambulatory digital EEG (Chez et al., 2006). The majority of the IED (55%) were temporal in location. The EEG normalized in approximately 47% of a subgroup of patients who received valproic acid, with another 17% showing EEG improvement. The remarkably high IED rate of 60% may be partly explained by the high association between autism and epilepsy, with nearly 40% of autistic persons reported to have epilepsy (Danielsson et al., 2005). The other explanation for the high IED rate detected in the study is that the EEG performed were 24-hour, prolonged, ambulatory recordings (a routine EEG procedure typically records for an hour or less). The authors of the study had commented that their yield of IED detected with 24-hour, ambulatory recording was twice that detected with routine EEG.

Definite epileptiform abnormalities have been reported in 30% of children with ADHD but no prior seizures (Hughes et al., 2000). Most of the IED detected were focal at the occipital or temporal regions. Other EEG studies of nonepileptic ADHD children showed lower IED rates of 5% to 15% (Hemmer et al., 2001; Holtmann et al., 2003; Richer et al., 2002). The value of EEG and the implications of IED in this subgroup of patients remain uncertain (Richer et al., 2002).

Many studies omitted or did not mention photic stimulation or hyperventilation procedures (Sam and So, 2001). The prevalence of photoparoxysmal response (PPR) ranges from 2.0% to 8.9% (Verrotti et al., 2004). Higher rates may include nonepileptiform abnormalities such as EEG slowing (Eeg-Olofsson et al., 1971). The risk of seizure occurrence after incidentally recorded PPR is very small. A study of 33 nonepileptic persons with PPR showed that none had seizures during an average follow-up duration of 9 years (So et al., 1993). However, this favorable finding is most likely age dependent. PPR in many persons is due to an autosomal, inherited trait that has age-dependent penetrance (Waltz and Stephani, 2000). In that study, seizure onset of the patients with PPR and epilepsy occurred at an average age of 9 years, whereas PPR was recorded incidentally in nonepileptic persons at an average age of 17 years. Therefore, incidentally recorded PPR in the first decade of life (or soon after) may still be associated with seizure risk, although the risk is generally believed to be small (Verrotti et al., 2004).

PPR discharge that exceeds the end of photic stimulation initially was thought to be associated with a higher seizure risk than when the entire discharge was confined to the stimulation period (Reilly and Peters, 1973). Findings of two later studies failed to support this notion (Jayakar and Chiappa, 1990; So et al., 1993). In fact, the waveform appearance of PPR in persons without seizures is indistinguishable from the PPR in persons with epilepsy (So et al., 1993).

Two studies reported rare IED activation by hyperventilation, affecting only 0.3% of persons without a seizure history (Buchthal and Lennox, 1953; Eeg-Olofsson et al., 1971). One study reported an unusually high rate of 8% activation by hyperventilation (Eeg-Olofsson et al., 1971). However, the high rate also included non-epileptiform abnormalities.

LIMITATIONS OF IED PREVALENCE STUDIES IN PERSONS WITHOUT A SEIZURE HISTORY

Although it can be said that IED prevalence in persons without a seizure history is generally low, the prevalence rates among studies vary by as much as eightfold. The wide variation suggests differences in EEG recording techniques and differences in the subjects studied. Few studies specifically excluded benign transients that resemble IED (Cavazzuti et al., 1980; Eeg-Olofsson et al., 1971; Gregory et al., 1993; Jabbari et al., 2000; Okubo et al., 1993; Sam and So, 2001; Shelley et al., 2008). Only one or two types of benign transients were specifically excluded in some of the studies. Many types of benign transients are frequently mistaken for epileptiform discharges (Benbadis, 2007); wicket waves are probably the patterns most frequently interpreted as epileptiform sharp waves (Fig. 4) (Benbadis, 2007; Krauss et al., 2005). Even nonspecific fluctuations of the background EEG could be mistaken for epileptiform discharges. Benbadis and Lin (2008) reported a series of 34 nonepileptic patients with background EEG fluctuations that were misinterpreted as temporal sharp waves (n = 30), frontal sharp waves (n = 2), and generalized sharp waves (n = 2).

Early EEG studies of IED in persons without a seizure history were very limited in terms of the recording duration and the number of recording electrodes. Studies were as short as 10 minutes or were obtained using only three scalp electrodes (Bennett, 1967; Gibbs et al., 1943). One study was conducted using EEG samples from awake activity only (Brandt and Brandt, 1955). Activation procedures such as hyperventilation and photic stimulation were not consistently conducted across studies during the EEG procedure (Sam and So, 2001). Many of the early EEG studies were also performed before the establishment of diagnostic criteria that defined specific clinical entities, especially for psychiatric, cognitive, and behavioral disorders.

The type of study population strongly influences the rate of EEG detection of IED. The reported rates increase from healthy adult and children volunteers (up to 6%), to nonepileptic and non-predisposed patients (up to 12%), to nonepileptic but predisposed patients (up to 60%). Moreover, retrospective studies are most likely to be influenced by referral or selection bias, when patients with seizure risks are more frequently referred for EEG procedures. This probability was underscored by authors who reported a very high IED rate of 60% in their patients with autism spectrum disorders (Chez et al., 2006).

A type of IED that has not been reported in persons without a seizure history is temporal intermittent rhythmic delta activity (TIRDA) (Fig. 5) (Reiher et al., 1989). This type of IED was not widely recognized until the past decade. It is currently unclear whether TIRDA occurs in persons without a seizure history. If future studies of TIRDA should determine that it does not occur in persons without seizures, TIRDA may be designated as a more specific correlate of seizure history than other types of IED.

RISK OF SEIZURES SUBSEQUENT TO IED DETECTION IN PERSONS WITHOUT A SEIZURE HISTORY

The important issue raised by incidentally recorded IED is how to determine the risk of subsequent epileptic seizure occur-
Anxiety. had a history of panic attacks and from her surroundings. She also longed spells of feeling distant from her surroundings. She also had a history of panic attacks and anxiety.

ence. Few studies have reported rates of seizure occurrence after IED observation. Differences in seizure occurrence rates seem to be influenced by the populations being studied. The highest seizure rate reported was 14%, but the study involved a referral hospital and patients who were more likely to have cerebral disorders than subjects from other studies (Zivin and Marsan, 1968). In contrast, a study of nonseizure outpatients and inpatients in a nonreferral community population showed a much lower rate for provoked seizures (6.3%) and no unprovoked seizures or epilepsy (Sam and So, 2001). Of note, that study specifically asked whether seizure occurrence was provoked or unprovoked. Provoked seizures are due to acute structural or functional disturbance of the brain (e.g., stroke, head trauma, and electrolyte imbalance), whereas acute cerebral disturbance is absent in unprovoked seizures. The distinction between provoked and unprovoked seizure occurrence has important therapeutic and prognostic implications (So, 2006). Compared with persons who had an unprovoked seizure occurrence, persons with provoked seizures are five times less likely to subsequently experience unprovoked seizures (Hesdorffer et al., 2009). Moreover, the acute factors that underlie provoked seizure occurrence are often remediable. Therefore, chronic AED therapy is generally not necessary for provoked seizure occurrences (So, 2006).

Compared with nonseizure patients, healthy volunteers generally have lower rates for seizures after IED detection. Among healthy volunteers, children have higher seizure occurrence rates than adults (approximately 6% versus 2%) (Cavazzuti et al., 1980; Gregory et al., 1993; Iida et al., 1985; Okubo et al., 1993). The reason for the difference in the seizure occurrence rates is not clear. Duration of follow-up may be a reason, but the “survival phenomenon” may also contribute to the difference (i.e., IED hypothetically develop early in life in all subjects, and the risk of seizure occurrence may be higher in the first few years after IED development). The types of IED observed in healthy children volunteers may also be different from IED observed in healthy adult volunteers.

Unfortunately, no information is available regarding the rate of subsequent seizure development in nonseizure patients who are reported to have high IED rates (Shelley et al., 2008). With rare exceptions, the studies are retrospective, and many patients were empirically treated with AED.

IED DETECTION IN AIRCREW CANDIDATES

Pilot applicants make up the largest group of aircrew and traffic controller candidates who have been evaluated with EEG. A review of the literature shows that the rate of IED in these candidates ranges from 0.5% to 5.0% (Table 2) (Hendriksen and Elderson, 2001; Sam and So, 2001). The high rate of 5.0% is clearly an outlier (Buchhal and Lennox, 1953), considering that most studies reported rates of approximately 1% or less, and a few reported rates of 2.0% to 2.5% at the highest. The unusually high rate of 5% is almost certainly because of the administration of a convulsant, pentylentetrazol, to subjects in the study.

Information regarding seizure occurrence after IED detection in aircrews is sparse. Follow-up is rarely performed for aircrew candidates who fail medical screening tests because of IED detection. Nevertheless, one report indicated that 1 in 20 aircrew candidates with IED subsequently had a seizure disorder develop during 10 years of follow-up (Robin et al., 1978). One review estimated a 25% probability of an aircrew candidate with IED subsequently having seizures (Hendriksen and Elderson, 2001). However, this high rate of seizure development could be due to selection bias in the type of patients whose follow-up information was available. Small sample sizes in many studies also reduce the reliability of the estimates of subsequent seizure rate.

Although only 1% or less of all aviation accidents is due to sudden incapacitation of the pilot (Hendriksen and Elderson, 2001), an epileptic seizure event is the most common medical disorder that causes sudden incapacitation because of loss of consciousness. This is likely the reason that EEG is used by many countries to scrutinize pilot candidates for risk of epileptic seizures. The crash rate because of pilot error is reportedly fourfold higher in pilots with abnormal EEG findings than in those with normal findings (Lennox-Buchthal et al., 1960). However, the association between EEG abnormalities and higher crash rates was not corroborated by results of a later study (Weber, 2002). The case-control study showed that serial EEG findings from 33 pilots killed in crashes were not different from 66 matched control pilots. In his review of publications on EEG as a screening tool in pilot applicants, Zifkin (2005) concluded that no evidence suggested that the practice reduced risk of flight-related
accidents. The low IED detection rate of 0.5% to 2.5% among young, healthy aircrew candidates and the low rate of subsequent seizure occurrences question the cost-effectiveness of routine EEG screening for qualifying aircrew candidates. Furthermore, aviation medical experts often disagree when interpreting EEG for pilot candidate assessment (Zifkin et al., 2005). The use of EEG as a screening tool in pilot candidates has been abandoned in the United States, Canada, and Australia, but it continues in many countries in Europe and Asia.

IED IN PATIENTS WITH PSYCHOGENIC SPELLS

Epileptic seizures are often included in the differential diagnosis when evaluating patients with psychogenic spells, and the converse is also true. Among all patients evaluated at referral epilepsy programs, the proportion with psychogenic spells is reportedly as high as 30% (Lancman et al., 2001). Moreover, at least 10% of patients with epilepsy have concomitant psychogenic spells (Lesser et al., 1983). Therefore, the detection of IED greatly influences the diagnosis and treatment of patients with suspected psychogenic spells. Ten percent of patients with psychogenic spells have been reported to have IED (Lesser, 1985). The proportion is even higher (26%) among elderly patients undergoing prolonged video-EEG monitoring (McBride et al., 2002). However, an exceptionally rigorous study that used multiple EEG reviewers who were blinded to clinical data showed that the rate of IED detection in patients with psychogenic spells is very low (2%), about the same as the rate in healthy control subjects (Reuber et al., 2002).

ARE IED REALLY CLINICALLY SILENT?

Generally, IED are considered to be clinically silent. However, several studies have shown that IED occurrence is associated with a transient alteration of behavior or mental performance (Aarts

FIGURE 5. A, EEG tracing. The arrow denotes temporal intermittent rhythmic delta activity on the right side. The interval between grid lines represents 1 second. B, Magnetic resonance image. Marked, diffuse atrophy is apparent. The patient was a 56-year-old woman who presented with a 5-year history of progressive memory loss and fainting spells.
impairing cognition. A double-blind, placebo-controlled study of suspicion that IED has the potential of disrupting behavior and prevention of IED. The reason for the treatment is the treatment of persons with reduced IED (Holmes and Lenck-Santini, 2006).

DOES AED TREATMENT OF IED HAVE A ROLE IN PERSONS WITHOUT SEIZURES?

Clinicians generally adhere to the principle of “treating the patient, not the EEG.” Nonetheless, AED treatment of persons without a seizure history is considered for two reasons: (1) to prevent future seizure occurrence and (2) to improve behavior and cognition. Theoretically, partial blockade of N-methyl-D-aspartate receptors could potentially reduce long-term risks of seizure development (Staley and Dudek, 2006). Still, AED treatment for seizure prevention has not been pursued clinically because of the overall low risk of epilepsy development in nonseizure patients with IED and because of the frequent absence of IED on follow-up EEG, especially in children. Besides, experience with AED treatment to prevent the development of epilepsy in patients with brain trauma suggests that long-term compliance with AED intake is poor when the aim of treatment is prevention of epilepsy development (compliance is better for those seeking to control active epilepsy) (Temkin et al., 1990).

In contrast, persons with and without epilepsy have been treated with AED for the purpose of improving behavior or cognition through suppression of IED. The reason for the treatment is the suspicion that IED has the potential of disrupting behavior and impairing cognition. A double-blind, placebo-controlled study of children with epilepsy treated with lamotrigine showed that reduction in IED was associated with improved global ratings of behavior (Pressler et al., 2005). Although seizure improvement could have accounted for the behavioral improvement, patients reportedly did not have significant changes in seizure frequency during the study period. Cognitive decline in the number of epileptic syndromes with frequent IED, generally termed “epileptic encephalopathies,” can sometimes be improved or arrested if AED treatment is associated with reduced IED (Holmes and Lenck-Santini, 2006).

Studies of AED effects on persons without epilepsy, which included IED, cognition, and behavior, consisted of only small numbers of patients. Although AED treatment could reportedly normalize EEG in persons with autism but no seizure history (Chez et al, 2006), no evidence suggests that EEG improvement is accompanied by cognitive or behavioral improvement (Binnie, 2003; Shelley et al., 2008). Also, IED are infrequent in many persons without seizures, and the effect of infrequent IED on baseline cognition or behavior is questionable. Moreover, many AED do not predictably suppress IED, especially focal IED. Also, the potential adverse effects on cognitive and behavioral function by AED treatment are well known.

COMMENTS

Currently, no evidence supports AED treatment of incidentally detected IED in persons without seizures, either for the prevention of subsequent epilepsy or for improving behavior or cognition. Moreover, if IED is detected in persons without seizure history, they often occur infrequently on the EEG recording and may not be observed in subsequent recordings.

The prognostic significance of IED in patients without a history of seizures deserves further study, particularly for patients with conditions such as cerebral palsy, autism spectrum disorder, or ADHD, which predispose them to epilepsy development (Boutros, 2009; Shelley and Trimble, 2009). However, the shortcomings of earlier studies of IED in persons without a seizure history should be avoided. EEG must be performed and reviewed using a standardized protocol that specifies the different types of epileptiform and non-epileptiform abnormalities. Reviews of the EEG recordings should lead to a reduction in unnecessary AED treatment and a better understanding of the role of IED in epilepsy development.

TABLE 2. Incidence of Abnormal and Epileptiform EEGs and Follow-Up Results in Pilot Groups

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Abnormal EEG</th>
<th>Epileptiform EEG</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lachaud et al. (1971)</td>
<td>French pilot candidates, 18–22 years</td>
<td>152/2,700 (5.6%)</td>
<td>73/2,700 (2.7%)</td>
<td>—</td>
</tr>
<tr>
<td>LeTourneau and Merren (1973)</td>
<td>Naval aviation students, 19–29 years</td>
<td>38/28,658 (0.1%)</td>
<td>21/28,658 (0.1%)</td>
<td>1 of 31 with an abnormal EEG located had a seizure in 11 years of follow-up</td>
</tr>
<tr>
<td>Oberholz (1976)</td>
<td>German AF candidates, 17–57 years</td>
<td>61/973 (6.3%)</td>
<td>13/973 (1.3%)</td>
<td>—</td>
</tr>
<tr>
<td>Maulsby et al. (1976)</td>
<td>French AF pilots and other crew members</td>
<td>2,050/10,000 (20.5%)</td>
<td>250/10,000 (2.5%)</td>
<td>No seizures after 4–10 years</td>
</tr>
<tr>
<td>Robin et al. (1978)</td>
<td>US AF male aviators, 18–55 years</td>
<td>166/7,760 (2.1%)</td>
<td>76/7,760 (1.0%)</td>
<td>1 of 20 had a seizure during 10 years of follow-up</td>
</tr>
<tr>
<td>Everett and Akhavi (1982)</td>
<td>US AF Academy cadets, fourth year</td>
<td>85/2,947 (2.9%)</td>
<td>14/2,947 (0.5%)</td>
<td>No seizures after 10–15 years</td>
</tr>
<tr>
<td>Trojaborg (1992)</td>
<td>Royal Danish AF male candidates, 17–28 years</td>
<td>142/5,893 (2.4%)</td>
<td>Mainly paroxysmal (≤2.4%)</td>
<td>Four applicants had a seizure during EEG recording</td>
</tr>
<tr>
<td>Gregory et al. (1993)</td>
<td>Royal AF (United Kingdom) candidates, 17–25 years</td>
<td>—</td>
<td>69/13,658 (0.5%)</td>
<td>1 of 38 had a seizure during 5–29 years of follow-up</td>
</tr>
<tr>
<td>Ribeiro (1994)</td>
<td>AF pilot applicants and other crew applicants</td>
<td>92/2,015 (4.6%)</td>
<td>38/2,015 (1.9%)</td>
<td>One with a normal initial EEG had a seizure during 15 years of follow-up</td>
</tr>
</tbody>
</table>

Adapted from Hendriksen and Elderon (2001) with permission. AF, air force.
be performed while blinded to clinical findings, and IED should be quantitated. The value of AED treatment must be assessed with a randomized, double-blind, controlled trial with a large enough sample size to reasonably expect meaningful results.

REFERENCES


Benbadis SR. Errors in EEGs and the misdiagnosis of epilepsy: importance, causes, consequences, and proposed remedies. Epilepsy Behav. 2007;11:257–262.


Reilly EL, Peters JF. Relationship of some varieties of electroencephalographic patterns...


