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The value of provocation methods in patients suspected of having non-epileptic seizures

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Non-epileptic seizures (NES) are reported in 18–23% of patients referred to comprehensive epilepsy centres. Non-epileptic seizures may also be present in 5–20% of the patients who are diagonised as having refractory seizures. Because of their prevalence, financial and psychosocial outcomes cannot be ignored and accurate diagnosis is of the utmost importance. Various methods of seizure induction have been developed with the aim of differentiating epileptic from non-epileptic seizures. However, recording the attacks by video-EEG monitoring is the gold standard. In our outpatient EEG laboratory we try to induce seizures with verbal suggestion or IV saline infusion in patients who are referred by a clinician with the diagnosis of probable non-epileptic seizures. In this study we investigated the results of 72 patients who were referred between January 1992–June 1996. Non-epileptic seizures were observed in 52 (72.2%) patients. Thirteen of these patients still had risk factors for epilepsy. We could not decide whether all of their previous attacks were non-epileptic because 10–30% of the patients with NES also have epileptic seizures. For a more accurate diagnosis it was decided that these 13 patients, together with the 20 patients who did not have seizures with induction, needed video-EEG monitoring. Thirty-nine patients who had NES and no risk factors for epilepsy were thought to have pure non-epileptic seizures. We claim that not all patients suspected of having NES need long-term video-EEG monitoring and almost half (54.2%) of the cases can be eliminated by seizure induction with some provocative techniques.

Key words: non-epileptic seizures; induction; video-EEG monitoring.

INTRODUCTION

Non-epileptic seizures (NES) are reported in 18–23% of patients referred to comprehensive epilepsy centres[1–4]. Several of the previous studies performed so far indicate that 5–20% of the patients who are referred with the diagnosis of refractory seizures actually have non-epileptic seizures[5–11]. The wrong diagnosis of epilepsy in these patients may be troublesome. Sometimes they are subjected to repeated hospitalizations, unnecessary medications and drug toxicity, loss of work, loss of driving privileges and strain on inter-personal relationships, all contributing to overall disability.

Distinguishing between non-epileptic and epileptic seizures can be one of the most challenging tasks facing the clinician. Whenever bizarre ictal behaviours (different from those seen in true epileptic seizures), attacks with a long duration or seizures with new presentations are reported, non-epileptic seizures should be suspected. Moreover, negative neuroradiological and EEG investigations in these patients are further, though not definite, evidence for the diagnosis of non-epileptic seizures. In some centres long-term video-EEG monitoring is used to detect clinical seizures and accompanying ictal EEG changes simultaneously to confirm the diagnosis[7–10, 12–18]. However, this method is expensive, time consuming and not routinely available.

In our outpatient EEG laboratory we use provocation techniques (verbal suggestion or intravenous saline infusion) to induce seizures whenever the referring physician suspects the presence of non-epileptic seizures. In this study we tried to identify the value of this method in inducing non-epileptic seizures and find out the percentage of patients who would not need long-term video-EEG monitoring for a definitive diagnosis.

MATERIALS AND METHODS

Induction tests were performed on the patients who were referred to the EEG laboratory of our hospital with the diagnosis of probable non-epileptic seizures between January 1992–June 1996. The tests were carried out according to a standardized protocol by one

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of the authors. The need to record a seizure and the steps of the procedure were explained to all the patients. Following routine EEG recording, patients were told to relax and lie still with their eyes closed. Either verbal suggestion or 5 ml of intravenous saline solution were used to induce seizures. The patients were told that they were going to have a seizure within a few minutes time. Response to verbal stimuli, muscle tone, pupillary light reflexes and plantar reflexes were noted whenever patients had a seizure. All patients were given two words during the seizure and were later asked to recall them. Post-ictal confusion was noted when present. Whenever possible, a witness of the previous seizures was allowed to watch the procedure to indicate any differences or similarities between the attacks. The diagnosis of non-epileptic seizures was confirmed by: (a) the presence of bilateral motor and/or sensory phenomena and/or change in the apparent level of consciousness; (b) absence of ictal epileptiform activity and post-ictal slowing. When one or more of the following criteria were present it was decided that the patients needed long-term video-EEG monitoring: (1) no seizure after induction; (2) epileptiform activity in previous inter-ictal EEGs; (3) abnormal cranial CT and/or MRI; (4) the absence of a witness during induction; (5) a seizure pattern different from those in the previous attacks. Information concerning the onset of seizures, previous inter-ictal EEGs, neuroradiological investigations, use of antiepileptic drugs (AED) was obtained from patient files, EEG forms and cards. Psychiatric evaluations were noted in patients who were referred to a psychiatrist.

RESULTS

Induction with IV saline or verbal suggestion was applied to 72 patients (50 female, 22 male) suspected of having non-epileptic seizures by the referring clinician. Fifty-two patients (72.2%) (Group I) had non-epileptic seizures while 20 (27.8%) (Group II) did not. Clinical characteristics, inter-ictal EEGs and neuroradiological investigations of both groups are shown in Tables 1 and 2, respectively.

The duration of non-epileptic seizures was 30–540 seconds (average 160 seconds) ($n = 48$). Seizures tended to recur within short intervals in one patient. As far as the ictal characteristics were concerned, eyes were closed in all of the patients. Thirty-five patients were unresponsive to verbal stimuli. Tonic–clonic movements of extremities were observed in 29 patients. Vocalization was observed in 10 and side-to-side head movements in seven patients. Sixteen patients recalled the two words.

Twenty-eight (53.8%) patients in Group I and 15 (75%) patients in Group II were on antiepileptic medication. Twenty-four patients in Group I were referred to a psychiatrist and 17 (70.8%) of them were diagnosed with depression or conversion reaction, whereas in Group II eight patients were referred and 5 (62.5%) were diagnosed as having depression or a conversion reaction. It was interesting to note that most of these patients refused a follow up by a psychiatrist.

Table 1: The clinical characteristics of the patients.

Patient characteristics	Group I ($n = 52$)	Group II ($n = 20$)
Age	16–53 (av. 31.2)	18–56 (av. 30.4)
Age at onset of seizures	10–49 (av. 24.3)	7–45 (av. 21.9)
Gender		
Female	38 (73%)	12 (60%)
Male	14 (27%)	8 (40%)

Table 2: Inter-ictal EEGs and neuroradiological findings.

Laboratory investigations		Group I ($n = 52$)	Group II ($n = 20$)
Inter-ictal EEGs	Number of EEGs	1–6 (av. 2.4)	1–9 (av. 3)
	E	3 (5.9%)	3 (15%)
	NP	17 (30%)	8 (40%)
	N	32 (61.5%)	9 (45%)
CT and/or MRI	*n*	31	13
	P	5 (16.1%)[a]	2 (15.4%)[b]
	N	26 (83.9%)	11 (84.6%)

E, epileptic abnormality; NP, non-specific paroxysmal; N, normal; P, pathological. [a]Left temporal focal atrophy; right temporal arachnoid cyst; hypodense area in frontal lobe; dilated left insular cistern; cerebral atrophy. [b]Left mesial temporal sclerosis; right temporal arachnoid cyst.

In Group I, all EEGs and neuroradiological investigations were normal in 39 (75%) patients. The induced attacks were similar to the previous ones. However, in 13 (25%) patients one or more of the above criteria were detected, so it was not possible to say that all of their attacks were non-epileptic as it is known that 10–30% of patients with non-epileptic seizures may also have true epileptic seizures[6, 19, 20]. A true epileptic seizure was observed in one of these patients after he was hospitalized with the diagnosis of neurosyphilis. The characteristics of these 13 patients are shown in Table 3. The characteristics of the 20 patients who did not have seizures with induction are summarized in Table 4. Four of these patients were hospitalized for other reasons and true epileptic seizures were observed in all. Non-epileptic seizures were observed in another patient during hospitalization.

DISCUSSION

Non-epileptic seizures are episodes of altered movement, emotion, sensation or experience which have purely emotional causes, but are similar to those due to epilepsy. This similarity may at times be so confus-

Table 3: The clinical characteristics of the 13 patients who had non-epileptic seizures and risk factors for true epileptic attacks.

Number of patients	Inter-ictal EEGs	Neuro-radiological investigations	Antiepileptic drug consumption	Similarity between attacks
2	N	N	+	D
1	N	N	−	U
1	N	—	−	U
1	N	P	−	S
1	NP	P	+	U
2	NP	P	+	S
1	NP	—	+	U
1	NP	—	−	U
1	E	N	+	S
1	E	P	+	S
1	E	—	−	S

N, normal; NP, non-specific paroxysmal; E, epileptic; P, pathological; D, different; S, similar; U, unknown.

ing that it is hard to decide whether an attack is non-epileptic or epileptic. The coexistence of non-epileptic and epileptic episodes in the same patient causes more difficulties. Because the cost of NES misdiagnosed as epilepsy can be extremely high, from both a financial and a psychosocial standpoint, the value of accurate diagnosis of NES cannot be underestimated.

Table 4: The clinical characteristics of the 20 patients who did not have seizures with induction.

Number of patients	Inter-ictal EEGs	Neuroradiological investigations	Antiepileptic drug consumption
4	N	N	+
1	N	N	−
1	N	P	+
3	N	—	−
6	NP	N	+
2	NP	—	+
1	E	P	+
1	E	—	+
1	E	—	−

N, normal; NP, non-specific paraxysmal; E, epileptic; P, pathological.

For several years, physicians have tried to differentiate the two entities based solely on patient characteristics and ictal behaviours. Most of the studies performed so far indicate that NES are more common in females[7, 21–25], have a later age of onset[16, 22] and the duration of a single episode is usually much longer than that of an epileptic seizure, although overlap exists[5, 7, 18, 26]. Ictal behaviours on the other hand are much more heterogeneous and there is controversy in the literature about the presence and relative frequency of certain ictal characteristics[5, 8, 10, 27, 28]. In our study, 73% of the patients who had NES with induction were females. The mean age of onset was 24.3 years (range 10–49 years). Mean duration of the episodes was 160 seconds (range 30–540 seconds). Our findings were consistent with those of the literature. The most common ictal phenomenon observed in our patients was unresponsiveness (67.3%) with or without motor manifestations, as has been described by some authors[23, 26]. Eyes were closed in all of our patients. Eye manifestations in NES have been reported to include eye blinking, staring, fluttering, unilateral tonic–clonic movement or none[7, 26, 29], with no manifestation being the commonest (82–88%).

Although significant differences in the occurrence of certain ictal characteristics do exist between non-epileptic and epileptic attacks, there is still a risk of misdiagnosis because none of these features are pathognomonic. Misdiagnosis on the other hand may also be due to the similarity between non-epileptic and epileptic seizures, especially when they are complex partial seizures of frontal lobe origin[30]. Besides ictal characteristics, a wide variety of additional means to distinguish the two disorders (post-ictal serum prolactin and creatin kinase levels etc.) including some aggressive methods have been described[31–35]. However, the best way to diagnose NES is to observe a typical attack which should be accompanied by ictal and post-ictal EEG recordings. This is accomplished using video-EEG monitoring in most epilepsy centres[7–10, 12–15, 18]. Various methods of seizure induction have also been developed as an aid to diagnosis of NES[5, 9, 14, 36, 37]. They can also be used during monitoring to facilitate the occurrence of attacks. In our study we used either verbal suggestion or IV saline infusion to induce seizures in 72 patients, who were thought to have NES either exclusively or in addition to epileptic seizures by the referring physician. Fifty-two (72.2%) patients developed NES while 20 (27.8%) did not. For 13 (25%) patients who had NES with induction, it was difficult to decide whether all of their previous attacks were non-epileptic or not (Table 3). Five of these patients had no witnesses of the previous attacks before those during the provocative tests. The induced attacks were different from the previous ones in two patients who had normal inter-ictal EEGs and neuroradiological investigations but used antiepileptic medication. It is unknown whether their previous attacks were epileptic or not. According to Luther *et al.*, 20% of patients with NES may have multiple seizures of differing clinical types[14]. On the other hand, it has been claimed that in some people with epilepsy, a large anticonvulsant dosage and ensuing CNS toxicity may facilitate NES[38]. In six patients, the induced attacks were similar to the previous ones. However, all of these patients had risk factors for epilepsy. A true epileptic attack was observed in one of these patients after he was hospitalized for neurosyphilis.

We could not induce seizures with the above-mentioned provocative techniques in 20 (27.8%) patients (Table 4). Although it suggests a diagnosis of epileptic seizures[39], lack of seizure induction does not exclude the presence of NES. Several studies have indicated that 9.4–22.6% of patients with a confirmed

diagnosis of NES do not have seizures with induction[23, 36, 40], so false negative results can be obtained. Most of the patients (16, 80%) in Group II had risk factors for genuine epilepsy. However, several studies in the literature suggest that 40–74% of patients with NES alone may have inter-ictal EEG abnormalities[16, 22, 41] and in complicated cases the presence of cerebral pathology cannot be relied upon to decide if patients' seizures are epileptic or not[22]. Patients with pure NES may erroneously be treated with anticonvulsant drugs[26]. Therefore, it is difficult to decide if patients in this group have pure epileptic, pure non-epileptic or epileptic and non-epileptic seizures together. When hospitalized for other reasons, epileptic seizures were observed in four and non-epileptic seizures in one of these patients.

Thirty-nine patients who had attacks similar to the previous ones with induction lacked risk factors for epilepsy. No ictal or post-ictal EEG changes to suggest the diagnosis of epilepsy were detected. Supplementary motor seizures or complex partial seizures of frontal lobe origin may have ictal abnormalities undetectable by scalp electrodes. However, the risk of inducing epileptic seizures with provocative methods in these particular types of seizure is probably so small (or not present at all) that it can be ignored.

As indicated by most authors, the best way to diagnose NES is to record several attacks (spontaneous or induced) with simultaneous EEG changes, which is best accomplished by long-term video-EEG monitoring. But this is an expensive method which is not always available. We claim that video-EEG monitoring need not be performed in all patients who are suspected of having NES. According to the results of this study almost half (54.2%) of the cases can be eliminated through some methods of induction.

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