Startle provoked epileptic seizures: features in 19 patients

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Abstract

***Objectives*—To define the clinical characteristics of a group of patients with startle provoked epileptic seizures (SPES).**

***Methods*—Nineteen patients were identified during the course of a larger study of clinical seizure patterns. A witnessed seizure account was obtained in all patients; interictal EEG in 18, video-EEG-telemetry in eight, CT in 18, and high resolution MRI in eight.**

***Results*—The onset of SPES was in childhood or adolescence in 14 of 19 patients. It was preceded by exclusively spontaneous seizures in nine patients and SPES had been replaced by exclusively spontaneous seizures in two patients. Sudden noise was the main triggering stimulus and somatosensory and visual stimuli were also effective in some patients. The clinical seizure pattern involved asymmetric tonic posturing in 16 of 19 patients. Focal neurological signs were present in nine patients, mental retardation in six, and 10 were clinically normal. Ictal scalp EEG showed a clear seizure discharge in only one patient with a tonic seizure pattern; over the lateral frontal electrodes contralateral to the posturing limbs. Brain CT showed a porencephalic cyst in three patients, focal frontal atrophy in one, and generalised atrophy in one. Brain MRI was undertaken in five normal subjects and three neurologically impaired patients, six with normal CT. It showed a porencephalic cyst in one patient. In six patients, there were dysplastic lesions. They affected the lateral premotor cortex in three patients and the perisylvian cortex in three patients, one with bilateral perisylvian abnormality.**

***Conclusions*—SPES are more frequent than is generally appreciated. They may be transient and occur relatively commonly without fixed deficit, by contrast with previous reports. The imaging abnormalities identified in those without diffuse cerebral damage suggest that SPES are often due to occult congenital lesions and that the lateral premotor and perisylvian cortices are important in this phenomenon.**

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A major issue in the understanding of seizure mechanisms lies in the factors determining the transition from interictal state to seizure and those controlling termination of seizure activity. For most patients, the occurrence of epileptic seizures is sporadic and unforeseeable. In about 5% of patients, however, specific triggers for the epilepsy have been identified,[1] the commonest being photosensitivity. These cases provide an opportunity to explore factors involved in generation of seizures. Some patients have seizures precipitated by startle stimuli, which are known as "startle provoked epileptic seizures" (SPES). The stimuli can be sensory stimuli of various modalities, most commonly noise, but only in a specific context; the same stimulus that triggers a seizure if unexpected, will have no effect if the patient is forewarned. We have found 65 previously reported cases of SPES[1–7]; they are usually considered rare.[8] The patients described mostly had severe epilepsy, often associated with moderate to severe fixed neurological handicaps, representing diffuse neurological damage. The purpose of this paper is to present the clinical and investigational findings of a further 19 patients. Only some of the current series were affected by fixed neurological deficit, others had no neurological signs and were of normal intelligence. The second group affords the opportunity of trying to localise the region responsible for startle sensitivity without the confounding factor of widespread damage that is often associated with fixed neurological deficit.

Methods

PATIENT SELECTION

Nineteen patients with SPES were identified during the course of a larger study of 252 patients, investigating the clinical features of frontal and temporal lobe epilepsies. In that study,[9] potential cases were identified by retrospective selection and ongoing surveillance of hospital records. The criterion for inclusion was evidence of frontal or temporal lobe partial seizure onset as defined by: (1) a demonstrable structural lesion on CT or MRI; (2) an ictal EEG recording suggesting electrographic focal seizure onset; (3) an interictal EEG showing localised paroxysmal spike activity; (4) ictal clinical features suggestive of focal epileptic activity according to current concepts.[10]

PATIENTS' SEIZURE DESCRIPTIONS

All patients were interviewed using a specially designed questionnaire. An open section was

used to collect details of the sequence of seizure manifestations, followed by a closed questionnaire to ensure completeness and to define the timing characteristics of the seizure—for example, seizure frequency and diurnal variation. In all cases the patient's subjective account and an objective account were obtained; from an eye witness only in 11 patients and also from video-EEG-telemetry in eight. Patients with SPES had seizures occurring consistently, but not necessarily exclusively, immediately after an unexpected sensory stimulus but not if the same stimulus was anticipated. In 17 of 19 patients a history of startle sensitivity was elicited spontaneously in the open section of the questionnaire. In all patients verification of the history was sought from an observer; the frequency, consistency, and spontaneous reporting of SPES left little doubt that the phenomenon was genuine, even in those in whom it was not seen on video-EEG-telemetry.

EEG ANALYSIS

A median of two EEGs was available for each patient. For the eight patients who had undergone video-EEG-telemetry, additional long periods of interictal recording were available. The locations of up to the first 100 spikes were assessed on available interictal EEGs for each patient. These included all available spikes in 17 patients. Other EEG manifestations were assessed qualitatively. Spikes were defined according to conventional criteria[11] and classified according to location. Video-EEG-telemery recordings were made with 24 channel EEG and computerised recordings, using the standard 10–20 system. Ictal scalp EEGs were available for nine of the 19 patients, eight with simultaneous video recording.

NEUROIMAGING

Abnormalities on CT were localised using a template technique[12 13] based on the atlas of Talairach *et al.*[14] Abnormalities on MRI were localised directly from anatomical landmarks visible on the scan. Eight patients underwent high resolution MRI, including six with normal CT. A 1·5 Tesla Signa machine (GE Medical systems, Milwaulkee, Wisconsin) was used and standard axial and sagittal series obtained with T2 and T1 weighting. In addition, a series of 124 contiguous, 1·5 mm, proton density, coronal sequences was obtained with techniques described previously,[15] allowing reformatting in any plane for optimal visualisation of structural abnormalities.

Results

CLINICAL CHARACTERISTICS

Nineteen patients were identified with SPES, 7·5% of the whole series. A congenital aetiology was postulated for 11 patients; on the basis of retardation or neurological signs since birth in six, and purely from the dysplastic nature of the imaging abnormalities in five. In one patient, severe meningitis in the first few months of life was thought to be the cause and in another SPES were seen after treatment for a pineal tumour at the age of 10. Table 1 shows the clinical characteristics and results of interictal EEG and neuroimaging. Table 2 shows the clinical seizure characteristics and ictal EEG. Patients were divided into two groups; patients 1–9 had fixed neurological deficits and patients 10–19 had no fixed deficit. There was no evidence that patients with clinical signs had a different pattern of epilepsy in terms of age of onset, seizure frequency, severity, or response to treatment.

The onset of startle sensitivity was in childhood or adolescence in 14 patients, but in five patients not until adult life. Nine patients had had seizures unrelated to startle stimuli for some years before startle sensitivity developed; in one patient, epilepsy started at the age of one year but startle sensitivity only supervened in association with an exacerbation of her epilepsy and a change in her seizure pattern at the age of 25. In five patients the seizure pattern preceding the onset of startle sensitivity was similar to that seen subsequently, except that seizures were spontaneous. In four patients development of sensitivity to startle was associated with new ictal manifestations. Pathological startle response had disappeared by the time of interview in two patients and it occurred, therefore, during only part of the course of many patients' epilepsy history. In all except one patient, identical seizures could occur spontaneously or be precipitated by startle at different times; the proportion of spontaneous versus triggered attacks varied widely between patients. The other patient was one of six who reported a second seizure type that was never induced by startle. Thus in no patient were seizures exclusively associated with startle stimuli.

SEIZURE CHARACTERISTICS (TABLE 2)

Seizures tended to occur with high frequency; all patients had, at some point, experienced more than one seizure in a day and 10 had had more than 10 a day. Seizures were usually brief, only four patients reporting habitual SPES lasting more than one minute. In 16 patients the seizures evolved into tonic motor activity, which was focal in 14. Five had a focal somatosensory onset before tonic posturing, but in the others there were no earlier specific symptoms. Three patients had very different seizure patterns; absence with no focal features; generalised tonic clonic with no focal features, and complex absence with giggling, then behavioural automatisms. These were all patients without fixed deficit. Clinical seizure patterns were otherwise similar in the two groups.

All patients' seizures could be triggered by sudden, unexpected noise, but other sensory modalities were more variable in their effect. Six could have a seizure triggered by somatosensory stimuli—for example, an unexpected tap on the shoulder or by catching a paretic foot. Visual stimuli such as sudden movement in the visual field were reported to be effective in three patients, but they were less reproducible in their effect than sudden noise. No patient reported a seizure in response to taste or smell.

Table 1 Clinical characteristics of patients with SPES

Case	Age at interview	Age at onset of epilepsy	Age at onset of startle response	Intelligence (full scale IQ or estimate)	Clinical signs	Interictal EEG spikes	Features of CT/MRI	Appearance of high resolution MRI	Aetiology
1	14	7	7	Mild retardation	Left hemiparesis	Rare right parietotemporal	Right frontal atrophy	N/A	Abscess age 5 months
2	20	1	3·5	74	Left hemiparesis	None	Right frontoparietal porencephalic cyst	N/A	Congenital
3	20	8	8	91	Left hemiparesis	None	Right frontocentral porencephalic cyst	N/A	Congenital
4	7	3·5	7	Moderate retardation	Right hemiparesis	N/A	N/A	Left frontopartietal porencephalic cyst	Congenital
5	31	12	12	75	Left hemiparesis	None	Right frontopartietal porencephalic cyst	N/A	Congenital
6	24	16	18	Moderate retardation	Bitemporal visual field defect	Bifrontal	Generalised atrophy	N/A	Pinealoma age 1
7	42	11	Uncertain	80	Pseudobulbar palsy	None	Normal	Bilateral opercular microgyria	Congenital
8	34	6·5	Uncertain	Low average	Left Babinski response	None	Normal	Right lateral frontal cortical thickening	Congenital
9	55	44	44	93	Bilateral optic atrophy from congenital rubella	None	Normal	Normal	Possible congenital
10	13	11	11	91	None	None	Mild hemiatrophy	Mild hemiatrophy with marked perisylvian atrophy	Congenital
11	58	14	14	High average	None	Occasional bifrontal	Normal	Normal	Unknown
12	20	2 months	Uncertain	85	None	Widespread	Normal	Right perisylvian atrophy and dysplasia	Congenital
13	31	2·5	Uncertain	High average	None	Rare right frontotemporal	Normal	Right lateral frontal migration defect	Congenital
14	31	1	25	84	None	Bifrontal	Normal	Right frontal migration defect	Congenital
15	18	7	13	Low average	None	Left temporal and bifrontal spikes	Normal	N/A	Unknown
16	50	20	33	84	None	Rare centrotemporal	Normal	N/A	Unknown
17	29	19	23	88	None	None	Normal	N/A	Unknown
18	45	7	17	84	None	Bifrontal	Normal	N/A	Unknown
19	53	13	22	Average	None	Bitemporal	Normal	N/A	Unknown

N/A = Not available.

Table 2 Seizure characteristics of patients with SPES

Case	Average seizure frequency	Maximum number in 1 day	Tendency to cluster	Diurnal variation	Clinical pattern of startle provoked seizures	Seizure duration	Postictal recovery time	Ictal EEG features
1	1/day	3	−	No pattern	Focal tonic	10–30 s	< 10 s	N/A
2	1–4/day	400	+	Most nocturnal	Focal tonic	30–60 s	30–60 s	N/A
3	7–12/y	2	−	No pattern	Focal somatosensory then focal tonic	2–5 min	5–20 min	N/A
4	> 10/day	20	−	Only waking	Generalised tonic	10–30 s	1–5 min	N/A
5	1–4/day	12	−	Only waking	Focal somatosensory then focal tonic	< 10 s	30–60 s	N/A
6	5–10/day	40	+	Most waking	Generalised tonic	30–60 s	1–5 min	N/A
7	1–4/mth	10	+	No pattern	Focal tonic	30 s	10–30 s	Single widespread slow wave at onset
8	> 10/day	100	−	Most nocturnal	Focal somatosensory then focal tonic	10–30 s	30–60 s	Muscle artefact
9	1–4/day	30	−	No pattern	Generalised tonic	30–60 s	10–30 s	Muscle artefact
10	1–4/day	6	−	No pattern	Focal tonic	10–30 s	10 s	Muscle artefact
11	1–6/y	100	+	Only waking	Focal tonic	10–30 s	< 10 s	Left frontal 16 Hz
12	1–4/day	6	−	Only waking	Focal somatosensory then focal tonic	10–30 s	10–30 s	Muscle artefact
13	5–10/day	75	−	No pattern	Epigastric then focal tonic	10–30 s	< 10 s	Muscle artefact
14	1–4/day	4	−	Most day	Generalised tonic	10–30 s	30–60 s	N/A
15	> 10/day	80	+	Only waking	Absence	< 10 s	< 10 s	Generalised spike and wave
16	7–12/y	20	+	No pattern	Absence with automatisms and laughter	1–2 min	2–5 min	N/A
17	1–4/day	6	−	Most waking	Epigastric sensation then focal tonic	10–30 s	10–30 s	Muscle artefact
18	7–12/y	4	+	Most waking	Generalised tonic clonic	2–5 min	20–60 min	N/A
19	1–6/y	8	+	Most nocturnal	Focal somatosensory then focal tonic	30–60 s	5–10 min	N/A

N/A = Not available.

Seizures were generally refractory to medical treatment; patients had received a median of four antiepileptic drugs and only four patients reported a moderate benefit from any of the agents received. In two patients this was clobazam, in one clonazepam, and in one carbamazepine.

EEG CHARACTERISTICS (TABLE 1)

Interictal scalp EEG was available in 18 patients. It showed spikes in only 10 and slow wave abnormalities in 12. It was normal in five. In patients with neurological signs, interictal spikes were identified in two and were bifrontal and parietotemporal. In the four patients with hemiparesis and porencephalic cysts, slow waves were generalised or widespread over one hemisphere. In three other patients with abnormal signs there were slow waves and these were pericentral, bifrontal, and generalised. Eight patients with no fixed deficit had spikes, more than in the clinically abnormal group. This may reflect selection bias, as patients without gross lesions on neuroimaging more often underwent video-EEG-telemetry with long periods of interictal EEG recording. Sites of spikes varied considerably within patients and between patients, involv-

ing frontal, central, and temporal regions and usually they were not highly localised. There were slow waves in five patients with no signs; generalised in one, bifrontal in one, and localised in three. Two patients with the most pronounced slow wave abnormalities had dysplastic lesions on MRI but the slow waves seemed to be more diffuse than the scan abnormality.

An ictal scalp EEG recording was available in nine patients, six patients in the group with no signs. The ictal EEG onset was obscured by artefact in seven patients. In one patient there was clear 12–16 Hz activity at the left mid-frontal electrode (F3) at the onset of the seizure, contralateral to the direction of head turning and to the predominant side of posturing. In patient 15, an absence was recorded fortuitously on routine EEG and was accompanied by a generalised spike and wave discharge, phase reversing at the mid-frontal electrodes. She reported similar seizures in response to startle and a second seizure type suggesting a focal onset that occurred less often. These seizures started with staring, pallor, and dysphasia, followed by a Jacksonian spread of tingling from her left hand and then she would turn her head to the right and occasionally rotate in circles for up to two minutes. Her interictal EEG showed occasional focal left anterior temporal and bifrontal spikes and this, combined with the clinical seizure pattern, suggested a localisation related epilepsy, despite the generalised EEG discharge recorded during her absence. In two patients, in whom there was no clear ictal onset of scalp EEG, there were postictal changes; unilateral, pericentral slow waves in one patient and widespread slowing in the other.

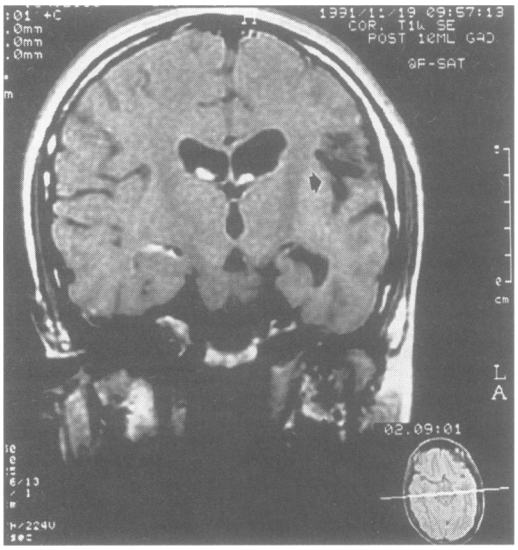

Figure 1 MRI of unilateral perisylvian atrophy in patient 10.

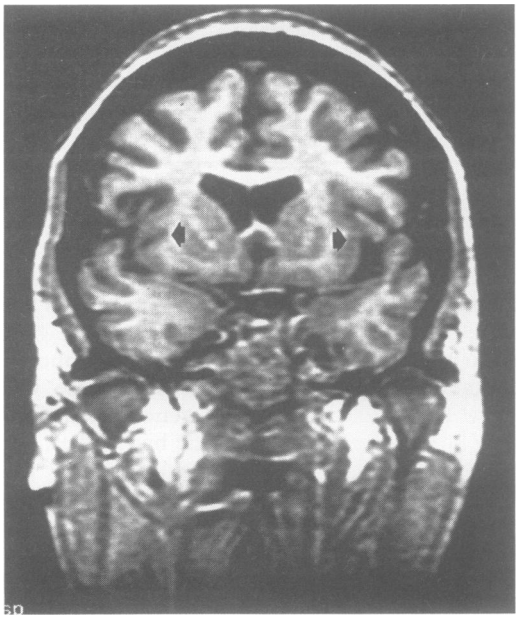

Figure 2 MRI of bilateral perisylvian atrophy in patient 7 with opercular syndrome.

IMAGING CHARACTERISTICS (TABLE 1)

In all patients with a hemiparesis, a porencephalic cyst or pronounced focal atrophy was seen in the contralateral hemisphere. In one patient with only reflex asymmetry, one with bilateral optic atrophy, and one with pseudobulbar palsy, CT was normal. One patient with no clinical deficit had mild hemiatrophy on CT; in all the others with no signs, CT was normal.

High resolution MRI was performed on six patients with normal CT, and in the patient with mild hemiatrophy on CT. Five of these had no signs, one an extensor plantar response, and one pseudobulbar palsy. Abnormalities on MRI were seen in six patients and seemed to fall into two overlapping patterns, both consistent with a dysplastic aetiology. In three patients there was perisylvian atrophy associated with thickening of the perisylvian grey matter. This was predominantly anterior and unilateral in two patients (fig 1), with maximal involvement of the frontal component of the perisylvian region. In the other it was bilateral, with narrowing of the perisylvian region (fig 2), in association with pseudobulbar palsy, and closely resembles the bilateral opercular pattern previously described on MRI[16] and pathologically.[17] The second pattern, frontal dysplasia, was seen in three patients. In two of these there was subcortical nodular heterotopia in association with cortical dysplasia. In the first patient (fig 3) the cortex overlying heterotopia appeared as normal on MRI but pathological examination confirmed the presence of focal cortical dysplasia. After resection of the abnormal region and adjacent cortex this patient has had one seizure in two years of follow up, having previously had several seizures a day. In the second patient, there was a similar but more severe appearance on MRI, this time associated with thickening of the lateral and mesial frontal cortices. The third patient had just thickening of the lateral frontal cortex, without heterotopia. There was no pathological verification in these patients.

The anatomical localisation of abnormal tissue remains difficult because of the wide extent of atrophy in some patients and the difficulty in defining the limits of cortical dysplasia. In the patients with unilateral perisylvian disease and those with porencephalic cysts, the maximal involvement seemed to be frontopari-

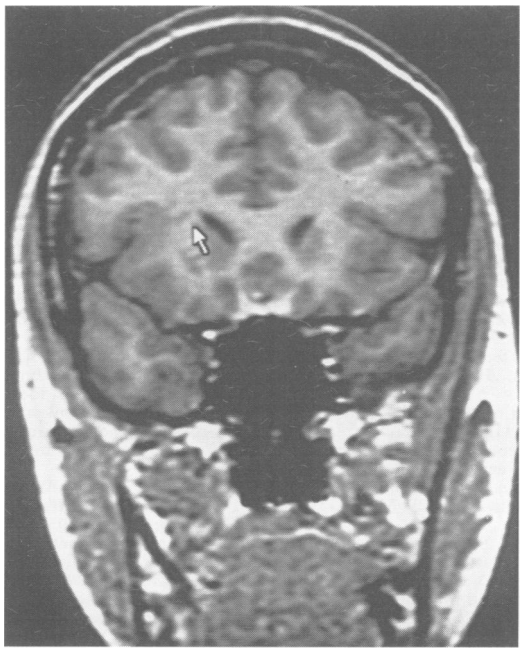

Figure 3 MRI of lateral frontal dysplasia in patient 13.

etal. In the opercular syndrome involvement was extensive and probably included all three lobes. In the four patients in whom the lesion was restricted to one lobe this was always frontal and never temporal.

Discussion

The selection methods in this series favoured patients with frontal lobe epilepsy and this may have contributed to the high frequency of SPES—7·5%. Frontal lobe epilepsy is, however, common in the general epilepsy population.[18] Moreover, our findings show that SPES are relatively common without fixed deficit (10 of 19 of our patients compared with only five of 65 patients reported previously) and the frequency is probably underestimated.[8] It is possible to miss SPES because they are a transient phenomenon in a patient's seizure history, as illustrated both in this and most previous studies.[2-4 6 7 19 20] Although typically starting in childhood, SPES may not occur until adult life, even if associated with a congenital MRI abnormality. The clinical ictal features of previously reported patients were similar—56 of 65 with a tonic seizure onset. Seizures are most consistently triggered by noise in all studies and other modalities seem to be less effective, but this may merely reflect the relative potency of noise to cause startle in normal people. The refractoriness of these seizures to medical treatment is well recognised and our uncontrolled results are similar to others in finding benzodiazepines of some benefit.[21]

No patients reported had previously undergone MRI. Brain MRI was not available in every patient with negative CT in this study, but the similarity of clinical and ictal features, in those with and without MRI, suggests that this was not a major source of bias. The identification of dysplastic lesions in six of seven patients in whom it was undertaken means that this type of pathology is likely to be important. It is consistent with the increasing recognition of cortical dysplasia as an important cause of partial epilepsies.[22] This represents a move away from previous views, in which SPES were commonly attributed to perinatal insult and in which the commonest abnormalities on CT were porencephalic cysts and centrotemporal hypodensity, consistent with the findings in our subgroup with a fixed deficit. Porencephaly, underlying some of the more severely affected patients' epilepsy, is also thought to have a dysplastic basis.[22]

Scalp EEG is recognised to have limited value in SPES. The ictal EEG often shows just a vertex spike, which may represent muscle artefact, rather than abnormal cortical activity.[8] Patients with Down's syndrome may be a distinct subgroup, as they more often have absence seizures and spike-and-wave on the EEG.[19] Our patient with absences did not, however, have Down's syndrome.

Our data showed the brunt of frontal lobe pathology to be lateral frontal but previous patients have shown lesions mainly in the mesial frontal lobes on CT, especially the supplementary motor area. All the previously reported patients with CT had fixed deficits and the imaging modality was less sensitive, unable to detect subtle dysplasia. This difference in location of lesion may be explained by the results of the only intracranial EEG study in SPES. Although seizure discharges were most commonly seen arising from the mesial frontal lobes, it was rare for them not to involve both mesial and lateral frontal structures, making it difficult to discern a pure mesial frontal or pure lateral frontal seizure type.[2]

There is no current measure of startle sensitivity in these patients, except the generation of seizures. Because seizures almost invariably occur both with and without startle sensitivity, the two components are dissociable and their neurological substrates may also, therefore, be spatially separated. We speculate that the junction of polymodal sensory connections and limbic inputs may provide the substrate for this response selective for unexpected stimuli in various modalities. Cortical regions that might fulfil these criteria include the perisylvian region, SMA, and especially lateral premotor cortex, which is involved in the sensory guidance of movement.[23-26] The phenomenon seems to be due to a variable abnormality superimposed on a fixed defect, as the underlying lesion is usually congenital and yet the effect is transient in the patient's history.

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