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Video-EEG evidence of lateralized clinical features in primary generalized epilepsy with tonic-clonic seizures

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ABSTRACT – *Background :* Whether cortical or subcortical structures, specifically the thalamus, play the dominant role in generating primary generalized seizures has been the subject of long debate. Most experimental data implicate a hyperexcitable cortical generator of spike-and-wave activity, with the thalamus quickly recruited to sustain the generalized oscillations through a reverberating thalamocortical network. However, there is little clinical evidence to support the cortical generator hypothesis. We present video-EEG recordings of generalized tonic-clonic seizures in three patients with proven primary generalized epilepsy (PGE), all of whom showed a consistent pattern of lateralized seizure onset compatible with a focal frontal lobe generator. *Methods :* Among 300 patients referred for video-EEG monitoring for intractable epilepsy, three were found to have PGE with tonic-clonic convulsions. All had a positive family history for epilepsy and no other epilepsy risk factors. Epilepsy onset was during adolescence (2/3) or childhood (1/3). Patients were taking 1-4 antiepileptic drugs (AEDs) at admission, none of which was valproic acid. *Results :* Interictal EEG showed very active, bilaterally synchronous generalized spike-and-wave or polyspike-and-wave discharges between 2.5-4.5 Hz, maximal over the midfrontal structures symetrically in all patients. Ictal EEG showed generalized rhythmic activity without lateralization at seizure onset. Surprisingly, in all 6 recorded tonic-clonic seizures there was a sustained (10-15 seconds), stereotyped, clinical lateralization at onset, which took the form of a tonic "fencing posture" in one patient (two seizures) and forced head/eye/torso version in two patients (four seizures). Two patients became seizure-free shortly after switching to valproate monotherapy. One patient refused valproate but has improved more than 90 % with a change in AEDs to lamotrigine and phenobarbital (follow-up in all patients > 18 months). *Conclusions :* Tonic-clonic seizures are presumed to be generalized from onset in patients with PGE. However, video-EEG monitoring in these patients is rarely performed and the actual clinical features of the seizures may be underappreciated. The demonstration of sustained lateralization at onset in our patients, with features clinically indistinguishable from focal onset frontal lobe seizures, is compatible with the hypothesis of a focal region of cortical hyperexcitability situated in the frontal lobes of some patients with PGE. Whether this cortical generator is autonomous or "triggered" by ascending, possibly normal, thalamocortical volleys is unresolved. [Published with video sequences].

KEY WORDS: clinical semiology, juvenile myoclonic epilepsy, lateralization, primary generalized epilepsy

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Primary generalized epilepsy (PGE; also idiopathic) is characterized by seizures showing bilaterally synchronous, generalized spike-and-wave activity recorded by electro-encephalography (EEG) with clinical manifestations including some, or all of, absences, myoclonic absences and/or myoclonic jerks, and generalized tonic-clonic seizures. Whether the cerebral cortex or subcortical structures, specifically the thalamus, plays the dominant role in generating these seizures has been the subject of long debate. Thalamic onset of generalized seizures was originally hypothesized, supported by experimental animal models of epilepsy and some human studies, and provided the initial evidence that primary generalized seizures were the product of bilateral reciprocal connections between specific thalamic nuclei and a hyperexcitable cortex. There is now mounting evidence to support a focal cortical generator as the initiator of cortical hyperexcitability and generalized seizures [1, 2]. Reverberating cortico-thalamo-cortical circuits, through thalamic structures that have a propensity for rhythmic oscillations, allow for maintenance of spike-and-wave activity and propagation of the seizure in a generalized fashion. However, evidence for the exact nature and localization of a focal cortical generator is lacking.

Very few patients with PGE undergo video-EEG monitoring, likely given the usual clarity of clinical diagnosis and generally excellent response to monotherapy with valproic acid, and the clinical features of generalized tonic-clonic seizures in PGE are typically based on historical information alone. Whether these seizures truly have a generalized onset or a focal onset that rapidly secondarily generalizes is therefore not clear. Some reports in the literature have provided evidence to support a focal clinical onset in some patients with PGE [3-5]. We report three patients who underwent video-EEG monitoring whose ultimate diagnosis was PGE based on clinical and EEG criteria; interestingly all six recorded generalized tonic-clonic seizures commenced with definite lateralizing features.

Methods and patients

From 300 patients referred to the Epilepsy Monitoring Unit (EMU) at the Toronto Western Hospital, University of Toronto, for continuous video-EEG investigation of refractory epilepsy, three patients were found to have PGE with tonic-clonic convulsions. Interictal and ictal EEG recordings and the corresponding video sequences were reviewed.

Patient 1. J.L. presented at 19 years of age with a five-year history of seizures, including generalized tonic-clonic seizures and brief episodes of staring with occasional bilateral, symmetric myoclonic jerks. He is the product of a normal pregnancy and delivery, and early development was normal. From the history there is no account of febrile or childhood seizures; there is a strong family history of epilepsy. Previous investigations included normal magnetic resonance imaging (MRI) of the brain and routine EEG reported to show brief episodes of spike-and-wave activity with a possible left frontal predominance. Formal neuropsychological testing revealed a superior intellect and no lateralizing abnormalities. He had been treated with carbamazepine monotherapy for five years with modest seizure control. On admission to the EMU, J.L. was having 4-6 generalized tonic-clonic seizures per year, with increased frequency during periods of stress, and daily morning myoclonic jerks and myoclonic absences.

Patient 2. S.W. is a 47 year-old woman, whose seizure disorder commenced during early childhood, consisting of generalized tonic-clonic seizures and occasional staring spells. Her mother had rubella during pregnancy, and S.W. was born with significant hearing deficits requiring hearing aids. There is a questionable family history of epilepsy in a sister. S.W. was treated with phenytoin and phenobarbital over many years and had a brief trial of valproic acid, which reportedly caused significant moodiness and resulted in its discontinuation. Eventually, she was switched to carbamazepine prior to being monitored in the EMU. She was having 10-20 generalized tonic-clonic seizures per year and up to 2-3 staring spells per day. During her hospital admission, a brain MRI revealed some non-specific white matter changes suggestive of microangiopathic disease but was otherwise normal. Neuropsychological testing revealed no lateralizing abnormalities.

Patient 3. M.M. is a 34 year-old woman with a 19-year history of generalized tonic-clonic seizures. She also had other 'spells' consisting of subjective dizziness and a sensation of choking, peri-orbital swelling, and limb shaking lasting for 30-40 minutes. Over many years she had been tried on multiple AEDs, and was taking carbamazepine, phenobarbital, topiramate, and clobazam on admission to the EMU. She was having up to one to two generalized seizures and several other "spells" weekly. In hospital, brain MRI was normal and neuropsychological testing showed above average intellect and no lateralizing deficits.

Results

Interictal EEG showed very active bilaterally synchronous generalized spike-and-wave or polyspike-and-slow wave discharges between 2.5-4.5 Hz, maximal over the mid-frontal structures symmetrically in all patients with no evidence of lateralized focality *(figures 1, 2, and 3)*. Coherence analyses [6] of the spike-and-wave activity showed no hemispheric time leads (data not shown). Recorded clinical seizures in these three patients all demonstrated definite, sustained (10-15 seconds), lateralized clinical features at onset.

Patient 1. Video-EEG revealed one generalized tonic-clonic seizure, the culmination of increasingly frequent,

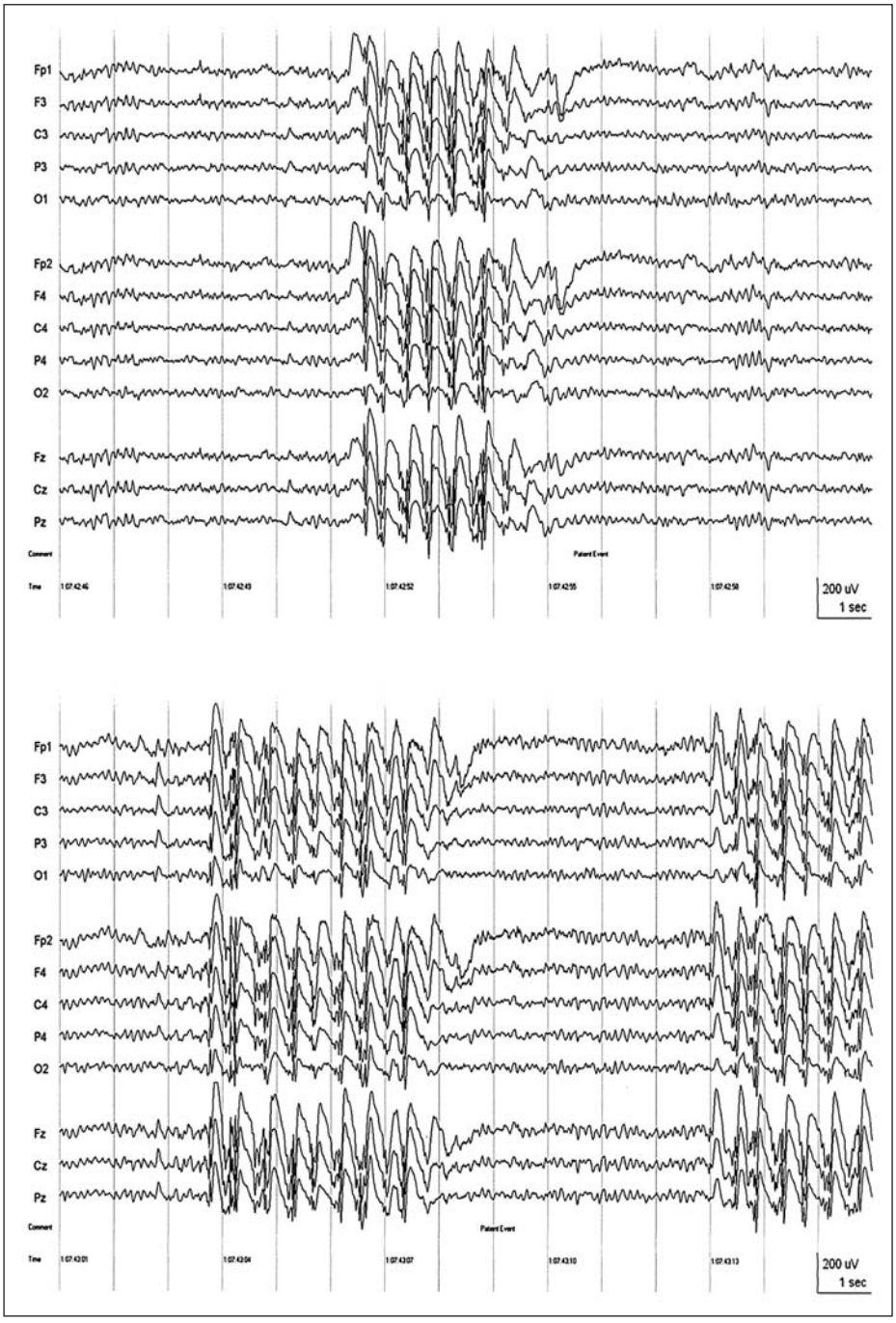

Figure 1. *Interictal EEG of patient J.L. Sequential pages of the EEG showing generalized polyspike-and-wave activity associated with myoclonic jerks (note Patient Event marker) just prior to the ictal event in Figure 2; referential longitudinal montage, t9-t10 averaged reference (all figures); 70 Hz high frequency filter (HFF), time constant (TC) = 0.3 sec.*

symmetric, early morning myoclonic jerks and myoclonic absences. The generalized tonic-clonic seizure commenced with a sustained forced head and eye version to the left with extension of the left arm, followed by a symmetric tonic phase and then bilateral clonic activity *(videosequence 1)*.

The EEG demonstrated increasing bursts of generalized spike-and-wave and polyspike-and-wave activity leading up to the ictal event, which consisted of generalized, initially 3 Hz bilaterally synchronous and symmetric slow wave activity, which increased in amplitude and frequency to 3-5 Hz, and then was obscured by muscle

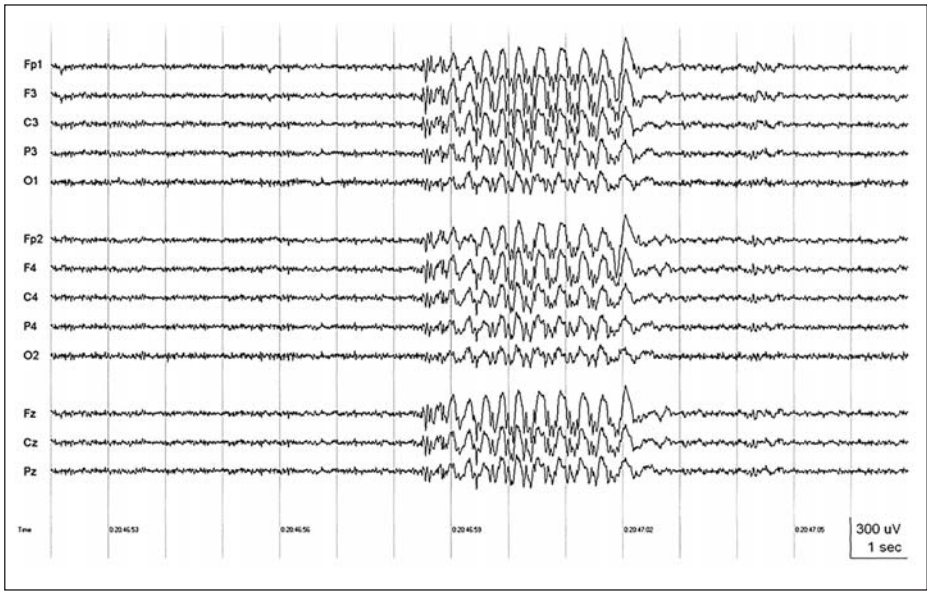

Figure 2. *Patient J.L. Ictal EEG onset of the seizure in Videosequence 1; clinical seizure onset at*; 15 Hz HFF to highlight ictal pattern (obscured by muscle artifact with 70 Hz HFF), TC = 0.3 sec.*

artifact. Subsequently, the recording showed a clonic de-recruiting response associated with clinical clonic seizure activity, followed by ictal offset *(figure 4)*.

A diagnosis of juvenile myoclonic epilepsy (JME) was made, and J.L. was changed from carbamazepine to valproic acid with complete cessation of his seizures and morning myoclonus, now with over 18 months follow-up.

Patient 2. Four separate clinical seizures were recorded. The first was a typical absence seizure lasting several seconds. The other seizures began with a definite head/eye/torso version to the right followed by a cry and subsequent generalized tonic-clonic motor activity *(videosequence 2)*.

The EEG recordings during the clinically lateralized tonic-clonic seizures showed ictal activity consisting of initially 3 Hz spike-and-wave activity that merged into lower amplitude faster activity and which ended with a clonic de-recruiting response *(figure 5)*.

A diagnosis of PGE was made, and S.W. was changed to lamotrigine and phenobarbital with over 90 % seizure reduction. S.W. has not agreed to retry valproic acid therapy.

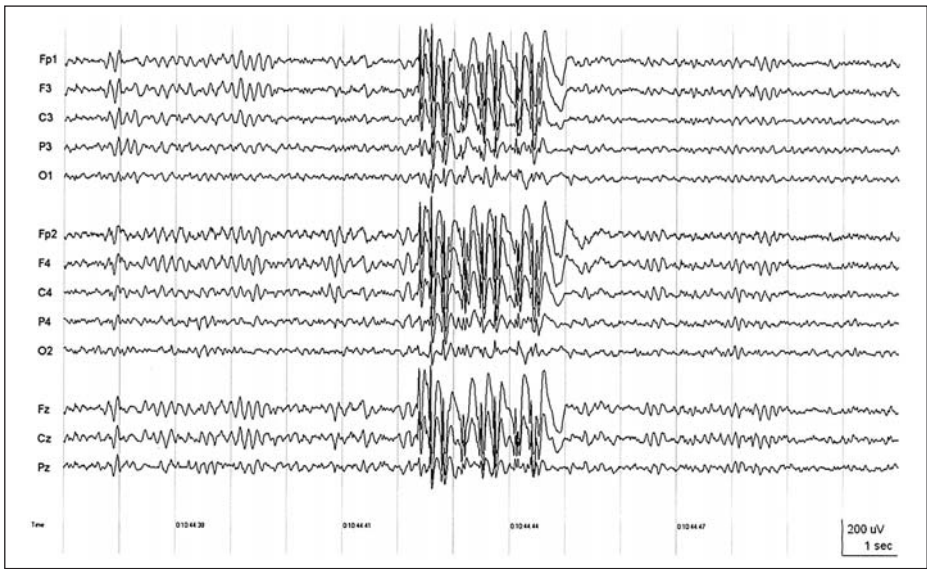

Figure 3. *Interictal EEG of patient S.W. showing a typical generalized polyspike-and-wave discharge; 70 Hz HFF, TC = 0.3 sec.*

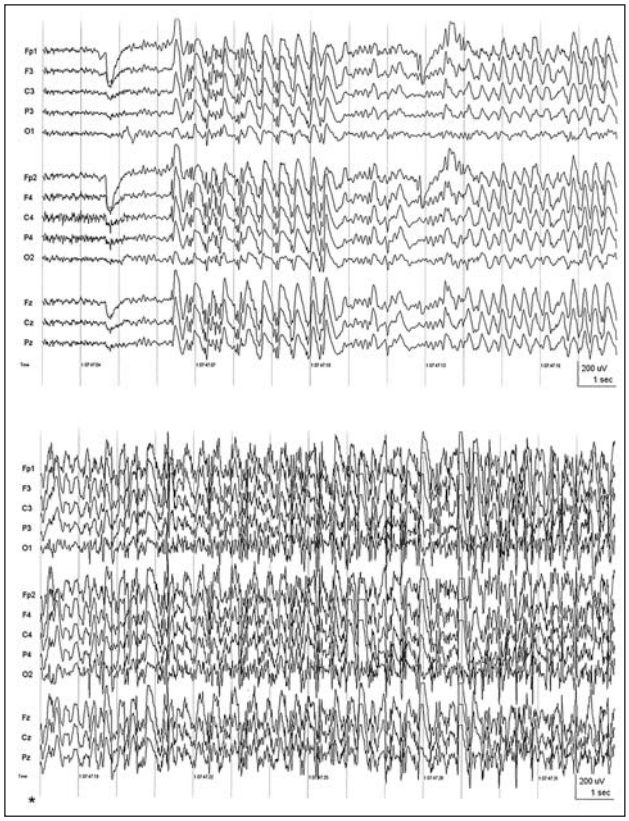

Figure 4. *Patient S.W. Ictal EEG onset of the seizure in Videosequence 2; clinical motor seizure onset at*; 15 Hz HFF, TC = 0.3 sec.*

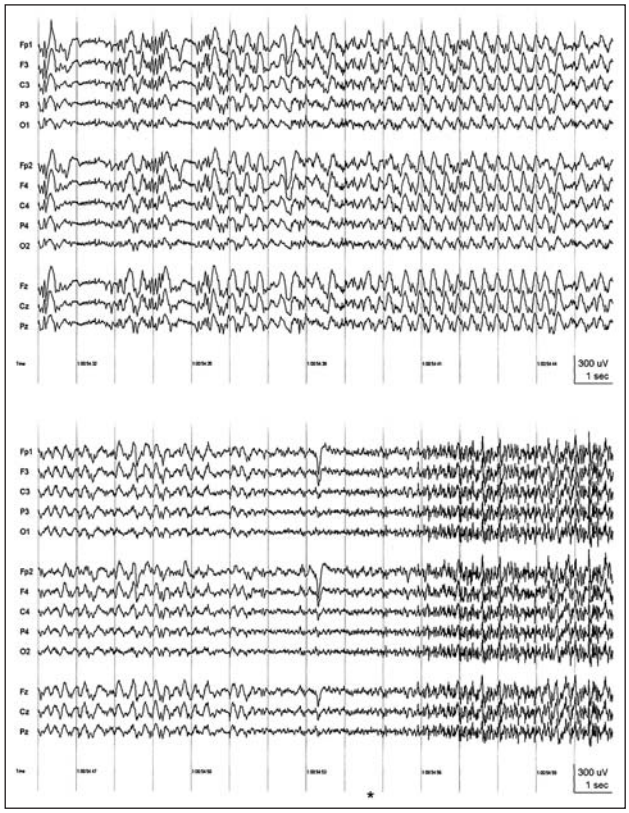

Figure 5. *Interictal EEG of patient M.M. showing a typical generalized spike-, and polyspike-and-wave discharge; 70 Hz HFF, TC = 0.3 sec.*

Patient 3. M.M. had one prolonged non-epileptic episode and two clinical epileptic seizures. The non-epileptic event lasted twenty minutes and entailed hyperventilation, followed by trembling of the face and body and finally an arrhythmic shaking of all extremities. The features fluctuated over time, and she was able to respond appropriately to questions from her nurse during the event. The clinical seizures both commenced with a forced head version to the left followed by a leftward fencing posture. The seizures evolved into generalized tonic-clonic motor activity, which at offset were briefly asymmetric involving unilateral clonic movements of the right face and arm *(videosequence 3)*.

No EEG changes were recorded in association with the non-epileptic event. The ictal EEG for the epileptic seizures showed a generalized, bilaterally synchronous and symmetric 4.5 Hz spike-and-wave activity with a bifrontal maximum. The EEG evolved into 4 Hz sharp theta wave activity before becoming obscured by muscle artifact, though at times an 8 Hz rhythmic epileptic discharge was visible *(figure 6)*.

A final diagnosis of PGE was made (as well as non-epileptic events to account for her prolonged "spells") and M.M. was taken off all of her admission medications except phenobarbital and was started on valproic acid. She has remained seizure-free (including her non-epileptic "spells") for over one and a half years.

Discussion

Generalized tonic-clonic seizures in primary generalized epilepsy (PGE) are presumed to commence clinically and electrographically in a bilaterally synchronous and symmetric fashion. The pathophysiologic substrate for these seizures includes reciprocal connections between thalamic and cortical neurons; connections that are normally responsible for oscillating rhythms including sleep spindles [1]. At the cellular level, alterations in receptor function in the thalamic nuclei have been postulated to be involved in the generation of abnormal synchronized rhythmic discharges [7] that correlate clinically with generalized seizures in animal models of PGE. To elucidate whether the initial rhythmic discharges of a generalized ictal electrographic event arise from the thalamus, several studies using depth electrode recordings within various

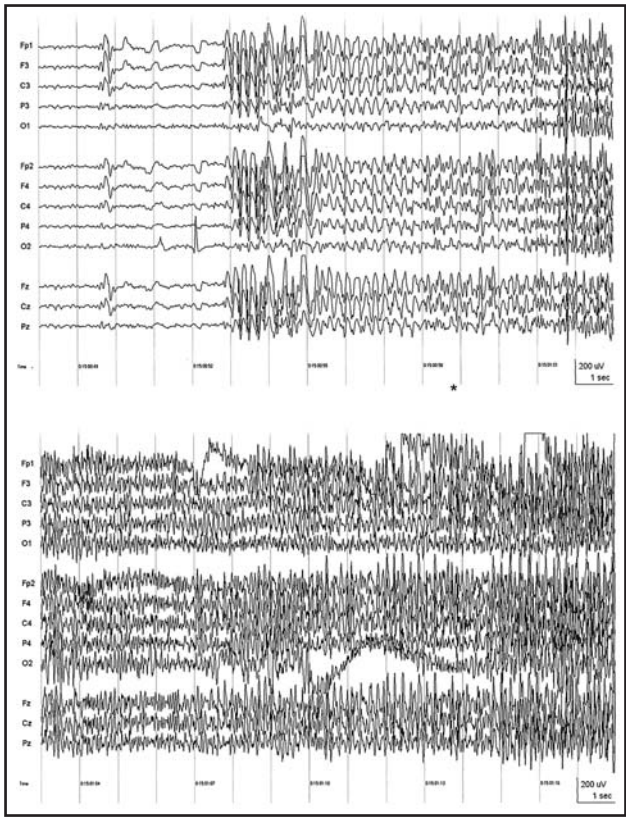

Figure 6. *Patient M.M. Ictal EEG onset of the seizure in Videosequence 3; clinical seizure onset at *; 15 Hz HFF, TC = 0.3 sec.*

thalamic nuclei compared with surface EEG recordings have resulted in conflicting results. In 1941, Penfield proposed a "centrencephalic" hypothesis: using surface EEG recordings with nasopharyngeal electrodes, Penfield and Jasper concluded that the thalamus was the focus of "grand mal" (tonic-clonic) seizures based on phase reversal of epileptiform discharges at the nasopharyngeal electrodes [8]. Other studies have refuted this hypothesis, in animal models of feline penicillin generalized epilepsy [9, 10] and in human depth electrode studies [11], showing evidence for cortical initiation of generalized seizures. At present, no definitive conclusion can be drawn as to the anatomical and physiological origin of generalized seizures in PGE though clearly an integral role exists for the reciprocal connections within the cortico-thalamocortical network in seizure propagation and maintenance [1].

Some clinical reports have provided evidence contrary to the postulated generalized onset of seizures in PGE, with either lateralized clinical features or with EEG asymmetries [3-5]. Lateralized clinical features are very common in partial epilepsies. Forced head version prior to generalization lateralizes to the contralateral hemisphere [12] and is seen in both frontal lobe seizures and temporal lobe seizures, the latter likely a manifestation of seizure spread to frontal lobe structures. Other well-defined lateralizing features include ictal fencing posture [13], asymmetrical tonic limb posture [14], contralateral ictal dystonia [15], postictal nose rubbing [16, 17], and asymmetrical terminating clonic jerks [18]. Focal features described in the context of PGE are rare, though reports of circling or versive seizures [19, 20], hemiconvulsive seizures [3] and seizures with lateralized onset [5] have provided evidence to support a focal seizure generator. Lateralized findings in JME are more commonplace and both clinical, specifically asymmetric myoclonus, and EEG asymmetries can be noted in up to 30 % of patients in some series [4].

We show here six seizures with definite clinical lateralization in three patients in whom a confident diagnosis of JME (one patient) or PGE (two patients) was made. Our patients have no focal structural, neuropsychological, or electrographic abnormalities to account for the lateralized clinical onset of tonic-clonic seizures and they meet all criteria (including clinical and EEG features, family history, and response to appropriate AED) for a diagnosis of PGE. However, all of these seizures commenced with forced head/eye/torso version or a tonic fencing posture clinically indistinguishable from frontal lobe seizures. These features support the existence of a focal cortical generator, plus or minus a lateralized propagation preference, situated in the frontal lobes of such patients with PGE who present with stereotyped lateralization at onset of clinical seizures, which may represent a region of functional hyperexcitability difficult to elucidate with current electrophysiological or imaging techniques. A recent study using focal magnetic transcranial stimulation demonstrated asymmetries in the motor thresholds in patients with PGE and versive or circling seizures, although a consistent lateralization was not found [21]. It would be interesting to know if ictal SPECT or interictal PET studies, unavailable in our patients, could demonstrate localized frontal lobe functional abnormalities in such patients. Newer techniques including transcranial magnetic stimulation, functional MRI with simultaneous EEG recording, and sophisticated models of source imaging with magnetoencephalography combined with MRI may further clarify the unresolved questions regarding the origin of primary generalized seizures.

Future efforts to better understand the underlying neuroanatomical and pathophysiological nature of the generator(s) of primary generalized seizures may benefit from a focus on patients with PGE who demonstrate clinical features of lateralized seizure onset demonstrated with video-EEG monitoring. Based on previous evidence and our findings, the hypothesis of a hyperexcitable focal cortical generator in some patients with PGE appears feasible. Whether this cortical generator is truly autonomous or, alternatively, is "triggered" by ascending, possibly normal, thalamocortical volleys remains unresolved. □

Video-EEG caption

Time sequence	Clinical features
J.L.	
00:00	Awake; lying supine on bed
00:09	Start of bilateral limb myoclonus, appearing every 5-15 sec; then increasing myoclonic jerks at 03:54
04:15	Raises right arm to adjust (lower) head of bed; ongoing myoclonic jerks
04:30	Seizure onset with left arm extension and forced head deviation to left; then generalized high amplitude limb myoclonus
04:48	Tonic extension of all limbs; then bilateral symmetric clonic movements of the extremities at 05:18
05:37	End of clinical seizure
05:50	End of video segment
S.W.	
00:00	Awake; sitting on bed holding a book and conversing with her mother
00:13	Looking to the right, stops talking and moving; mother still talking
00:19	Mother asks, "...you know that, eh ?" with no response
00:25	Sitting looking to the right, unresponsive; mother calls, "Susan ?"
00:28	Forced right head version and then sustained torso deviation to the right
00:39	Start of epileptic cry
00:47	Falls into bed sheets face down with only small movements in limbs
01:25	End of clinical seizure; starts to get up using left arm and settles into bed
****	
01:48	Start of second segment; lying supine in bed with nurse at bedside
01:52	Second seizure onset with forced head deviation to the right
02:02	Epileptic cry with sustained head and then torso deviation to the right
02:18	Head turning toward midline and lifting right arm
02:20	End of video segment
M.M.	
00:00	Awake; sitting in bed looking to the right (watching television)
00:11	Forced head and then torso deviation to the left; left arm flexed and raised in the air with notable fine shaking movements
00:23	Leftward fencing posture (left arm tonic extension and right arm flexed to right above head), then clonic jerks of right arm
00:40	Tonic extension of all extremities followed by bilateral clonic jerks
01:11	End of clinical seizure with final clonic jerk in right arm
01:25	End of video segment

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