Original article with video sequences

Epileptic Disord 2014; 16 (1): 1-4

Side-to-side axial movements

Adding a new sign to the asymmetry of the clonic phase and asymmetric seizure termination in differentiating primary and secondarily generalised tonic-clonic seizures

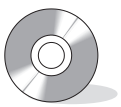
Sara Franca [1,2], Deepak K. Gupta [3], Shyam Rao [1,4], Elia Pestana [1], Joel Freitas [1,5], Jakrin Loplumlert [1], Samden D. Lhatoo [1,3]

[1] Epilepsy Center, University Hospitals Neurological Institute, Case Western Reserve University, USA
[2] Department of Neurology Centro Hospitalar de São João, Porto, Portugal
[3] Department of Neurology, Case Western Reserve University
[4] Department of Neurology, Wayne State University, USA
[5] Department of Neurology, Centro Hospitalar do Porto, Porto, Portugal

Received August 29, 2013; Accepted February 03, 2014

ABSTRACT – *Aim*. To study new semiological signs which help distinguish between primary and secondarily generalised tonic-clonic seizures (GTCS). *Methods*. We retrospectively studied 86 GTCS, 13 primary and 73 secondary, in 58 patients who underwent video-EEG (vEEG) evaluation in our epilepsy monitoring unit. Eleven patients had generalised epilepsy and 47 focal epilepsy. Two expert epileptologists, blinded to diagnosis, examined the vEEGs independently for the presence of five semiological signs. *Results*. Asymmetry of limb movements in clonic phase, side-to-side axial movements, and asymmetric seizure termination occurred more frequently ($p<0.05$) in secondary GTCS compared to primary GTCS. Combining asymmetry of limb movements in clonic phase and side-to-side axial movements provided the greatest value in differentiating secondary GTCS from primary GTCS. *Conclusion*. Careful examination of GTCS seizure semiology can help differentiate primary from secondary GTCS. The semiological sign of side-to-side axial movements, which has not previously been studied in this context, may add to existing literature of semiological signs and be of value for the evaluation of surgical patients in the epilepsy monitoring unit. In the out-patient setting, a clear history of these signs may help guide drug treatment choices. [*Published with video sequences*].

Key words: semiology, generalized tonic-clonic seizure, primary generalized seizure, secondary generalized seizure, side-to-side axial movement



Correspondence:
Samden D. Lhatoo
Department of Neurology,
University Hospitals Case Medical Center,
11100 Euclid Ave, Lakeside 3222A,
Cleveland, OH 44106, USA
<samden.lhatoo@uhhospitals.org>

doi:10.1684/epd.2014.0637

Generalised tonic-clonic seizures (GTCS) can occur as a primary phenomenon in the genetic generalised epilepsies or as a secondary generalised phenomenon in focal epilepsy, referred to as primary GTCS (PGTCS) and secondary GTCS (SGTCS), respectively. In PGTCS, clinical and electroencephalographic (EEG) features indicate immediate involvement of both cerebral hemispheres, while on the other hand, SGTCS usually have a focal clinical and/or electrographic onset followed by bilateral spread and subsequent generalised motor

involvement. Stringent semiological analysis of the various phases of GTCS often helps to differentiate SGTCS from PGTCS, and is of clinical value even before EEG characterisation. Versive head movements (Wyllie *et al*., 1986) and the "sign of four" (Bleasel *et al*., 1997; Kotagal *et al*., 2000) occur at the onset of GTCS and are of major importance for diagnosis as well as presurgical assessments of patients in the epilepsy monitoring unit. The terminal phase of GTCS also has apparent semiological value due to the sign of asymmetric seizure termination in SGTCS, whereby the terminal limb jerks are ipsilateral to the hemisphere of seizure onset (Trinka *et al*., 2002; Leutmezer *et al*., 2002; Walser *et al*., 2009). However, the period in between, after onset and before the termination of GTCS, has not attracted much attention. There is literature to suggest that this phase of the GTCS can be asymmetric or asynchronous, more often in SGTCS compared to PGTCS (Theodore *et al*., 1994; Niaz *et al*., 1999; Jobst *et al*., 2001). With this background, we hypothesized that there may be additional semiological features during the generalised phase of tonic-clonic seizures which may help distinguish SGTCS from PGTCS.

Subjects and methods

We retrospectively studied 86 GTCS (13 PGTCS and 73 SGTCS) in 58 consecutive adult patients of age ≥16 years with medically refractory epilepsy (11 with genetic generalised epilepsy and 47 with focal epilepsy), admitted to the Epilepsy Monitoring Unit (EMU) at University Hospitals Case Medical Center in Cleveland, USA, from January 2010 to October 2012. For each patient, the diagnosis was made on the basis of clinical features, vEEG monitoring, and neuroimaging data, and classified as either genetic generalised epilepsy or focal epilepsy, following the recommendations of the ILAE Commission on Classification and Terminology (Engel, 2001). Seizure videos were clipped at the onset of GTCS, which was defined as the point where there was clear, bilateral tonicity of the upper and lower limbs. This was done to avoid any bias from reviewers with regards to observation of lateralising/localising signs before the onset of GTCS. We excluded patients with incomplete data, for example partially obscured video during the seizure or generalised motor seizures where there was no clear tonic or clonic phase.

Two reviewers (SL and EP) who were completely blinded to the patients' clinical data and were not involved in the video clipping process, reviewed the seizure videos independently. They evaluated for the presence or absence of five signs, namely asymmetry of limb movements in tonic phase (AsymTP), asymmetry of limb movements in clonic phase (AsymCP), asynchrony of limb movements in clonic phase (asynCP), side-to-side axial movements (SSM), and asymmetric seizure termination (AST). Discrepancies were resolved by consensus. AsymTP and AsymCP were empirically defined as a more than 50% difference in the amplitude of right and left limb movements during the tonic or clonic phase, respectively. AsynCP was defined as a clear difference in the rhythm or phase of right and left clonic limb movements during the clonic phase. SSM were defined as brief, torsional, side-to-side, non-versive, alternating movements of axial body parts (trunk/head), occurring at least two or more times during the clonic phase. AST was defined as one or more unilateral clonic limb jerks at the end of the seizure. Data were managed on Microsoft Excel spreadsheet software. SPSS software was used for statistical analyses, including κ test, Pearson's χ^2 "t" test and Fischer exact test. A p value <0.05 was considered significant. Positive predictive value was defined as the number of true positives divided by the sum of number of true positives and false positives.

Results

In the sample of 58 patients, 11 had genetic generalised epilepsy (seizure mean: 1.18; range: 1-2) and 47 had focal epilepsy (seizure mean: 1.55; range: 1-3) and the mean age was 32.93 years (19.36 *versus* 36.11 years, respectively; p=0.06). There were 25 males and 33 females (p=0.62). There was moderate (Kappa value: 0.40 to 0.59; AsymTP, AsynCP) to substantial (Kappa value: 0.60 to 0.79; AsymCP, SSM, SST) agreement (Lhatoo and Lüders, 2008) in evaluation of semiological signs between the two epileptologists.

All of the five semiological signs occurred more frequently in SGTCS compared to PGTCS (*table 1*). However, the difference was statistically significant ($p<0.05$) only for AsymCP, SSM, and AST. SSM (*see video sequences 1 to 3*) occurred much more often in SGTCS compared to PGTCS (75.3 *vs* 15.4%).

Positive predictive values (PPV) for the five signs were also calculated (*table 1*). Different combinations of AsymCP, SSM, and AST were also tested for significance (*table 2*). The combination of AsymCP and SSM distinguished SGTCS from PGTCS with the greatest reliability (61.6 *vs* 7.1%; $p<0.01$).

For focal epilepsy, 26 patients (55.3%) had temporal lobe epilepsy, 17 (36.2%) had frontal lobe epilepsy, and parietal and occipital lobe epilepsy were present each in 4 patients (4.3%), respectively. On grouping these subtypes of focal epilepsy further, as temporal (26 patients; 55.3%) and extra-temporal (21 patients; 44.7%), the signs did not differ significantly between the two groups, with the exception of AST which occurred more frequently ($p<0.05$) in the latter.

Table 1. Semiological signs in primary (PGTCS) and secondarily (SGTCS) generalised tonic-clonic seizures.

Semiological sign	PGTCS (13) *n* (%)	SGTCS (73) *n* (%)	*p* value	PPV
1. Limb asymmetry in tonic phase (AsymTP)	6 (46.2)	50 (68.5)	0.12	89.28
2. Limb asymmetry in clonic phase (AsymCP)	4 (30.8)	52 (71.2)	0.00	92.86
3. Limb asynchrony in clonic phase (AsynCP)	10 (76.9)	67 (91.8)	0.11	87.01
4. Side-to-side movement (SSM)	2 (15.4)	55 (75.3)	0.00	96.49
5. Asymmetric seizure termination (AST)	2 (15.4)	33 (45.2)	0.04	94.28

$p<0.05$ considered significant.

Table 2. Combination of semiological signs in generalised tonic-clonic seizures.

Combinations of semiological signs	PGTCS (13) *n* (%)	SGTCS (73) *n* (%)	*p* value	PPV
1. SSM + AsymCP	1 (7.7)	45 (61.6)	0.00	97.82
2. SSM + AST	1 (7.7)	25 (34.2)	0.09	96.15
3. AsymCP + AST	0 (0)	28 (38.4)	0.01	100
4. SSM + AsymCP + AST	0 (0)	22 (30)	0.03	100

SSM: side-to-side movement; AST: asymmetric seizure termination; AsymCP: limb asymmetry in clonic phase.

Discussion

Henri Gastaut, in his monograph, accounted for asymmetry and asynchrony of SGTCS with a prescient contention that it comprises two or more simultaneous electrographic seizures (Gastaut and Broughton, 1972). This was confirmed with intracranial EEG recordings in patients with SGTCS (Lhatoo and Lüders, 2008). Asymmetric semiological seizure features such as versive head movements, sign of four, and asymmetric seizure termination, are more common in SGTCS, and have lateralising value (Kotagal *et al*., 2000; Trinka *et al*., 2002). As mentioned earlier, all of these signs are present either at the onset or just before the termination of GTCS, and there are no other signs formally described during the period in between. From a clinical standpoint, this intervening period is important as it is more frequently witnessed and reported compared to the period before the onset of GTCS.

It has been suggested that asymmetry and asynchrony in the tonic and clonic phases of GTCS are common in patients with temporal lobe epilepsy, but uncommon in the genetic generalised epilepsies (Theodore *et al*., 1994; Niaz *et al*., 1999; Jobst *et al*., 2001). Accordingly, symmetry of the tonic phase has been reported as a consistent feature of PGTCS (Niaz *et al*., 1999). In our study as well, asymmetry of limb movements in clonic phase was seen more frequently in SGTCS than in PGTCS (71.2 *vs* 30.8%; $p<0.01$).

We describe what appears to be a new semiological sign, namely "side-to-side axial movements" (SSM), which can help distinguish between PGTCS and SGTCS. As previously seen with other signs, SSM occurred much more frequently in SGTCS compared to PGTCS (75.3 *vs* 15.4%; $p<0.01$). This feature has been alluded to in an earlier study as "clonic side-to-side head movements" (Jobst *et al*., 2001), but has not been systematically analysed or reported. *Video sequences 1 and 2* illustrate SSM in SGTC seizures.

The authors hypothesised that the mechanisms behind SSM can be explained based on pathophysiology of the SGTCS, namely brain asynchrony and the concept of multiple simultaneous seizures (Gastaut and Broughton, 1972; Lhatoo and Lüders, 2008). In one study, 9 patients with SGTCS, (who underwent invasive presurgical evaluation), were screened and referenced to an uninvolved/artefact intract-free intracranial electrode); all phases of seizures were assessed for synchrony of the EEG rhythms (defined as a consistent agreement in time and/or frequency between the electrical activities of one brain region with another). It was concluded that in the majority of patients, there was a clear asynchrony with very different seizure rhythms occurring in the two hemispheres or even in one hemisphere (Lhatoo and Lüders, 2008). Thus, synchronisation of brain regions does not appear to be necessary during SGTCs and different electroencephalographic seizures appear to

occur simultaneously in the same brain regions during the same clinical seizure, producing different motor manifestations. The observation that AsymCP, AST, and SSM occur more frequently in SGTCS can be explained by this lack of synchronisation of brain regions in SGTCS.However, our study has some limitations: the sample size was small and there was a relative disproportion between the number of PGTCS and SGTCS, primarily due to the fact that patients were selected from an EMU where the vast majority of patients had focal epilepsy. Lastly, our study has all the limitations inherent to semiological analysis, namely subjectivity and potential non-agreement among reviewers, although in our study, there was good agreement between the epileptologists.Further studies with a larger number of patients and a more homogeneous sample may validate these signs in order to aid diagnosis. We speculate that the described signs can be of particular importance for patients with rapid generalisation in the clinical and electroencephalographic evolution of focal-onset seizures; in those with secondary bilateral synchrony where EEG lateralisation is unclear or in patients with normal neuroimaging findings where no other lateralising semiological signs are present, thus providing possible utility in both epilepsy clinics and monitoring units.

Acknowledgements and disclosures.
This work received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.
None of the authors have any conflict of interest to disclose.

Legends for video sequences

Video sequences 1 and 2 show a secondary generalised tonic-clonic seizure with side-to-side axial movements; brief, torsional, side-to-side, non-versive, alternating movements of axial body parts (trunk/head), occurring at least two or more times during the clonic phase.
Video sequence 3 shows a primary generalised tonic-clonic seizure with relative symmetry in the tonic and clonic phases and no side-to-side axial movements.

Key words for video research on www.epilepticdisorders.com

Syndrome: not applicable
Etiology: not applicable
Phenomenology: tonic-clonic seizure; side-to-side axial movement
Localization: not applicable

References

Bleasel A, Kotagal P, Kankirawatana P, Rybicki L. Lateralizing value and semiology of ictal limb posturing and version in temporal lobe and extratemporal epilepsy. *Epilepsia* 1997; 38: 168-74.

Engel Jr. J. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE Task Force on Classification and Terminology. *Epilepsia* 2001; 42: 796-803.

Gastaut H, Broughton R. *Epileptic seizures: clinical and electrographic features, diagnosis and treatment*. Springfield (Illinois, USA): Charles C Thomas, 1972.

Jobst BC, Williamson PD, Neuschwander TB, *et al*. Secondarily generalized seizures in mesial temporal epilepsy: clinical characteristics, lateralizing signs, and association with sleep-wake cycle. *Epilepsia* 2001; 42: 1279-87.

Kotagal P, Bleasel A, Geller E, *et al*. Lateralizing value of asymmetric tonic limb posturing observed in secondarily generalized tonic-clonic seizures. *Epilepsia* 2000; 41: 457-62.

Leutmezer F, Woginger S, Antoni E, *et al*. Asymmetric ending of secondarily generalized seizures: a lateralizing sign in TLE. *Neurology* 2002; 59: 1252-4.

Lhatoo SD, Lüders HO. Secondary generalized tonic-clonic seizures. In: Lüders HO. *Textbook of epilepsy surgery*. London: Informa UK Healthcare, 2008: 492-500.

Niaz FE, Abou-Khalil B, Fakhoury T, *et al*. The generalized tonic-clonic seizure in partial *versus* generalized epilepsy: semiologic differences. *Epilepsia* 1999; 40: 1664-6.

Theodore WH, Porter RJ, Albert P, *et al*. The secondarily generalized tonic-clonic seizure: a videotape analysis. *Neurology* 1994; 44: 1403-7.

Trinka E, Walser G, Unterberger I, *et al*. Asymmetric termination of secondarily generalized tonic-clonic seizures in temporal lobe epilepsy. *Neurology* 2002; 59: 1254-6.

Walser G, Unterberger I, Dobesberger J, *et al*. Asymmetric seizure termination in primary and secondary generalized tonic-clonic seizures. *Epilepsia* 2009; 50: 2035-9.

Wyllie E, Lüders H, Morris HH, *et al*. Ipsilateral forced head and eye turning at the end of the generalized tonic-clonic phase of versive seizures. *Neurology* 1986; 36: 1212-7.