**Ictal motor sequences: Lateralization and localization values**

*Ahmad Marashly, †Amr Ewida, ‡Rajkumar Agarwal, §Kyan Younes, and ¶Hans O. Lüders*

doi: 10.1111/epi.13322

**SUMMARY**

**Objective:** To determine the lateralization and localization values of ictal motor sequences in the setting of focal epilepsy ending with a secondarily generalized motor seizure.

**Methods:** Retrospectively, the ictal motor sequences were analyzed in patients with focal epilepsy ending with a secondarily generalized motor seizure by three readers blinded to all clinical and electrographic data. One representative seizure per patient was selected. Prevalence, positive predictive value (PPV), and Fleiss Kappa for the following motor signs were calculated: version, unilateral limb tonic posturing, unilateral limb clonic seizure, figure-of-4, M2e, hand dystonia, clonic asymmetric ending, and Todd’s paralysis. Sequences of signs with a PPV ≥ 80% were then analyzed to determine their lateralization and localization values.

**Results:** A total of 47 seizures were studied. The “reliable” motor signs with a robust lateralizing value (PPV > 80%) were version, unilateral tonic posturing, M2e, unilateral clonic seizure, asymmetric clonic ending, and Todd’s paralysis. Figure-of-4 and hand dystonia had a relatively low PPV, and therefore were not included in the following sequence analysis, which included only 38 patients with two or more motor signs of high PPV. Multiple combinations of temporal progression of motor signs were seen in these 38 patients, with version being the most common initial motor sign (29 of 38 patients) usually followed by M2e (15 of 29 patients), and/or a focal tonic seizure (7 of 29 patients). Accurate lateralization of the epileptogenic zone (EZ) with a PPV of 100% can be predicted when two or more reliable motor signs point to the same side. However, the various sequences of reliable motor signs did not differentiate between temporal and extratemporal epilepsy.

**Significance:** The presence of reliable ictal motor signs in focal epilepsy is extremely valuable in lateralizing the EZ, but not in determining the localization of the EZ. This is especially useful when epilepsy surgery is indicated.

**KEY WORDS:** Focal epilepsy, Semiology, Lateralization, Epileptogenic zone.

Dr. Ahmad Marashly is an assistant professor of Pediatric Neurology and Epilepsy at the Children’s Hospital of Wisconsin in Milwaukee.

Accepted December 23, 2015; Early View publication February 11, 2016.

*Department of Child Neurology, Children’s Hospital of Wisconsin/Medical College of Wisconsin, Milwaukee, Wisconsin, U.S.A.; †Department of Neurology, Epilepsy Center, George Washington University, Washington, District of Columbia, U.S.A.; ‡Department of Child Neurology, Children’s Hospital of Michigan/Wayne State University School of Medicine, Detroit, Michigan, U.S.A.; §Department of Neurology, University of Texas Health Sciences Center at Houston, Houston, Texas, U.S.A.; and ¶Department of Neurology, Epilepsy Center, University Hospitals of Case Medical Center/Case Western Reserve University, Cleveland, Ohio, U.S.A.

Address correspondence to Ahmad Marashly, Department of Child Neurology, Children’s Hospital of Wisconsin, 9000 W Wisconsin Ave, CCC Suite 540, Milwaukee, WI 53201, U.S.A. E-mail: amarashly@mcw.edu

Wiley Periodicals, Inc.
© 2016 International League Against Epilepsy

Analysis of seizure semiology is the first step in evaluating patients with epilepsy. Despite all the advances in clinical epilepsy, it remains the only tool to study and predict the symptomatogenic zone.

There is a rich ictal semiology literature, going back to the times of Tissot, Esquirol, Todd, Jackson, and many others in the 18th and 19th centuries.1-4 Many seizure components including auras and motor signs were studied extensively, and their values in lateralization and localization of the symptomatogenic zone and the epileptogenic zone (EZ) have been well described.5-10

However, to our knowledge, no attempt has been made to put together two or more motor signs in a sequence and
study their lateralization and localization values. We studied the sequences of the motor signs in secondarily generalized motor seizures and determined their utility in lateralization and localization of the epileptogenic zone.

**Methods**

We screened all the patients admitted to the adult and pediatric epilepsy monitoring units (EMUs) between 2009 and 2014 at university hospitals of Case Medical Center in Cleveland, Ohio. The total number of patients screened was 1,970; 236 patients had a documented secondarily generalized motor seizure.

We intended to explore the full possible sequence of seizures in the setting of focal epilepsy. Given that the common end point of any focal seizure is to evolve into secondary generalization, including seizures that reach that end point will allow for the full potential ictal sequence to be analyzed. We defined secondary generalization when a motor sign, tonic or clonic, spreads and affects both sides of the body more or less symmetrically with involvement of upper or lower extremities.

We included all the patients who fulfilled the following criteria: (1) focal epilepsy, (2) seizures captured on video manifesting two or more of the motor signs defined below, and (3) seizures evolving into a generalized motor seizure. The following patients were excluded: (1) patients who had more than one or an ill-defined EZ, (2) patients who had focal motor signs in the setting of generalized epilepsy, and (3) patients who did not experience secondary generalization during the (epilepsy monitoring unit (EMU) monitoring.

The final number of patients included was 47.

The location of the EZ was defined from data collected by extensive presurgical evaluations including surface and/or invasive electroencephalography (EEG) monitoring as well as the available imaging studies including magnetic resonance imaging (MRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT). All patients included in this study had been presented at our weekly patient management conference and an expert panel agreed on the localization and lateralization of the EZ for each one of them based on the concordance of different investigation modalities, which we considered as the gold standard in localizing the EZ.

Temporal lobe epilepsy was present in 26 patients, frontal lobe epilepsy in 13, and 8 patients had other types of epilepsy (1 parietal, 2 parietooccipital, 3 hemispheric, one frontotemporal, and one central).

An investigator (KY) screened our electronic medical records and clipped videos of a single representative seizure for each of the patients who met the inclusion criteria. That choice was based on habitual seizures as reported in history and other seizures captured on video (with or without secondary generalization). We attempted to choose a seizure that most accurately reflected the common components of a given patient’s habitual seizures. In all these seizures the patients were clearly visible with the face, trunk, and all limbs in the field of view.

A spreadsheet that included the motor signs was created for the semiology analysis. This included the type of the motor sign, the somatotopic localization of each analyzed sign, and the temporal sequence of the motor signs.

Three investigators (AM, AE, and RA), blinded to all the clinical and electrographic data, reviewed the selected seizure videos independently and entered their findings into the spreadsheet. A consensus regarding the presence or absence of each motor component was reached by only accepting those motor signs that were agreed on by two or more of the readers. Fleiss Kappa index was used to quantify interobserver agreement. Based on the ability to correctly predict the lateralization of the seizure focus, a positive predictive value (PPV) was calculated for each motor sign. Signs with PPV ≤ 80% were excluded from subsequent analysis.

Reliable signs were defined as those with a PPV > 80. Seizures that had a sequence of two or more of the reliable individual motor signs were then identified. The lateralization strength of these sequences was determined based on the consistency between the predicted lateralization (per semiology) and the actual epileptogenic zone.

In this study we restricted the analysis to simple motor seizures, which have been shown to possess significant, individual lateralization values. Complex motor seizures such as automatisms were not included. We used the
following definitions in our analysis of the motor signs evaluated in this study. The lateralizing values of these signs based on the current literature are also reviewed.

**Tonic:** A sustained contraction of one or more muscle groups. The duration is generally >3 s. The tonic contraction may affect one or more limbs but may also involve the face muscles.\(^\text{11,12}\) It usually causes the limb to be in an extended posture, but tonic seizures affecting the flexor muscles may also occur. The tonic activity usually affects proximal muscle groups and is unilateral or asymmetric and bilateral. Unilateral tonic activity has a reported lateralizing value to the contralateral hemisphere of approximately 90%\(^\text{13-15}\).

**Clonic:** A myoclonus that is repetitive and rhythmic of a limb or one side of the face at a regular interval of 0.2–5 per second.\(^\text{11,12}\) In focal epilepsy, clonic seizures affect mainly the distal parts of an extremity or the face muscles and tongue. Unilateral clonic seizures have a high lateralizing value to the contralateral hemisphere of approximately 90%\(^\text{3,13-16}\).

In our study we focused on the unilateral limb clonic and tonic seizures. Face tonic or clonic seizures were harder to detect due to the limitations with the camera angles, video resolution, or face position preventing the examiner from having a clear view of the face in many of the seizures. We therefore chose to exclude the face tonic or clonic seizure from the sequence analysis. This enabled us to decrease false negatives and select only those clonic and tonic seizures that would be more definitively classified by various observers and thus to have better values in lateralization and localization.

**Version:** A forced, sustained and unnatural turning of the head and eyes to one side, with extension of the neck muscles leading to a chin upward movement.\(^\text{6}\) Sustained, extreme eye deviation (eye version) without the classic sustained head version is still considered as version, as the symptomatic zone for both phenomena is identical or colocalized in proximity.\(^\text{17,18}\) Version occurring ≤10 s before the motor generalization has a high lateralizing value to the contralateral hemisphere of >90%.\(^\text{6,19,20}\) If there are two successive versive head movements preceding the generalization, the latter one was considered the correctly lateralizing versive component.\(^\text{20,21}\)

**M2e:** As originally described by Ajmone Marsan in 1957 in his book *The Epileptic Seizure*, M2e is a type of “tonic movement or elevation of one arm.” It begins with “flexion of the elbow to about 90 degrees and is followed by an abduction of the shoulder to approximately 90 degrees, associated with external rotation. The hand may be clenched or open, and the head is frequently deviated to look at the hand, but it may go the opposite way.”\(^\text{22}\) He also noted that in most of the cases, version would occur before, with, or after M2e. Ajmone Marsan stresses that a motor posture should be labeled M2e only if the contralateral arm is relaxed or gets involved in tonic activity later during the seizure. Following this definition, we did not classify as M2e seizures in which there was bilateral motor involvement of the arms, even if one arm clearly showed an M2e posture. In this study, if a version occurred simultaneously with the M2e posture it was classified as a separate sign. Although this sign has not been systemically studied in the contemporary literature, according to Ajmone Marsan, M2e had a very strong lateralization value, pointing to the contralateral hemisphere.

**Figure-of-4 sign** (asymmetric tonic limb posturing): Defined as tonic posturing in extension of one arm with the contralateral arm bent tonically at the elbow, either in front or behind the tonic arm.\(^\text{7}\) This sign occurs in the beginning of the tonic phase of a secondary generalized tonic–clonic seizure. It has been reported that this sign has a high lateralizing value to the contralateral hemisphere of approximately 90%.\(^\text{7}\)

**Dystonia:** The original description by Kotagal et al. in 1989 defined dystonia as a forced, unnatural posturing of an arm or leg on one side of the body, either in flexion or extension, proximal or distal, and usually with a rotatory component, and in many cases with signs of athetosis or tremor.\(^\text{9}\) It has been reported that ictal dystonia, as described earlier, almost always lateralizes to the contralateral hemisphere in temporal lobe epilepsy.\(^\text{3,23,24}\) In this study we defined ictal dystonia as a tonic posturing of the hand with rotation at the wrist leading to supination of the hand. At the same time there is extension of the middle and distal phalanges of the fingers with flexion of the proximal finger phalanges.

**Asymmetric clonic ending:** The end of the clonic phase of a secondary generalized tonic–clonic seizure is defined as being asymmetric if the last clonic jerk on one or more extremities clearly outlasts the other side. Asymmetric but synchronous jerking with higher amplitude on one side was not considered to be an asymmetric ending.\(^\text{15}\) In previous studies, a clonic activity of this kind had a specificity of 83% lateralizing the epileptogenic zone to the ipsilateral hemisphere.\(^\text{8,25}\)

**Todd’s paralysis:** Paralysis of one or more limbs and/or the face following a tonic or a clonic seizure on that side or following a secondarily generalized tonic–clonic seizure. This sign reliably lateralizes the epileptogenic zone to the contralateral hemisphere in almost 100% of the cases.\(^\text{10,26}\) In this cohort, we reported Todd’s paralysis when it was evident through a clinical exam conducted by a nurse or physician, or when there was clear inability to move one side when the other side looked to have a normal range of movement.

**Results**

Table 1 shows the prevalence of the different motor signs we analyzed, the positive predictive value (PPV), and Fleiss Kappa index.

Figure-of-4 and ictal dystonia had poor lateralization value (PPV < 80%) and were excluded from further analysis. This led to exclusion of nine seizures that had only one seizure on the contralateral hemisphere.
reliable motor sign (defined as PPV > 80%). The remaining 38 seizures were further studied to determine the strength of the “ictal sequence” in the lateralization and localization of the EZ.

Figure 1 shows the incidence of the first motor sign in the sequence.

In patients who had version as the first motor sign, we found that the most common second sign to follow was M2e posturing in 15 of 29 seizures and tonic posturing in 7 of 29. Figure 2 depicts the sequence of the seizure in the patients who had version as the first motor sign.

In one seizure version and tonic posturing occurred simultaneously as a first sign. This was followed by secondary generalization and then an asymmetric clonic ending.

Of the remaining seizures that did not start with version, the combination of version and a tonic seizure was still seen in three seizures through the sequence, even though the order was different, this is detailed in Figure 3.

In summary a total of 33 of 38 seizures showed the combination of version plus a tonic seizure in variable orders, with version likely to be the first sign.

Version was absent in 5 of 38 seizures. Four of 38 seizures started with a tonic activity and ended with an asymmetric clonic ending. Of interest, one of them had a tonic seizure starting on the right, followed by a tonic seizure on the left before it ended with an asymmetric clonic activity on the left. Three of those seizures lateralized the EZ correctly.

One seizure started with an M2e posture followed by a clonic seizure. The signs were consistent and lateralized the EZ correctly.

Of the 38 seizures that had ≥2 reliable signs forming a sequence, 32 seizures had signs consistent in lateralizing the EZ. Only 6 of 38 seizures had a mixture of signs lateralizing to either hemisphere. However, five of six of those seizures showed two or more consistent signs and only one sign that was contradictory. Only one seizure had a sequence of two signs that were contradictory. This seizure started with a tonic activity on one side and ended with an asymmetric clonic on the same side.

In all the 37 seizures that had two or more consistent signs in terms of lateralization, the combination of two or more of version, clonic, tonic, M2e, asymmetric clonic, or Todd’s, when in agreement, had a PPV of 100% lateralizing to the contralateral hemisphere.

When evaluating the localization value of seizures with version as the initial sign versus those with other initial signs, we found no correlation between its predictive ability to differentiate temporal versus extratemporal origin of the seizure (Table 2).

We also studied the motor sequence prior to the secondary generalization to determine if there was any localization value to predict the actual EZ. In the 30 patients who showed a sequence of two or more signs prior to generalization, multiple sequences were found; however, there was no correlation between a sequence and localization. This is detailed in Table 3.

**Discussion**

In the majority of seizures in our cohort (29 of 38), version was the first motor sign in the ictal sequence. A possible explanation for the prevalence of version as the most common first sign could be due to the low threshold at which the frontal eye fields produce version as seen on stimulation studies. Based on that, an ictal discharge invading the frontal eye fields and the adjacent motor strip (M1) is likely to activate the frontal eye fields before triggering motor responses from other cortical areas (M1). In seizures where version was not the first sign in the sequence, it was still seen in a significant number of patients (four of nine) occurring as the second sign and either followed or preceded by a tonic/M2e posturing.
We thus concluded that the most common combination in a sequence of motor signs is version plus a tonic and/or M2e posture, with version the most likely first sign. Clonic seizures tend to appear later during the seizure evolution. This is in keeping with previous results.27 By combining two reliable signs, it is intuitive that the strength of such a combination would be higher when compared to individual signs. This was indeed what we found. The occurrence of two or more reliable motor signs in a sequence accurately predicts the lateralization of the EZ with 100% reliability.

It is possible that temporal and extratemporal seizures travel along different pathways prior to secondary generalization, and subsequently produce different “orders” of motor sequences. However, no correlation could be found between a given sequence and the localization of the EZ. Seizures starting with version and those not starting with version could be found in both temporal and extratemporal epilepsies with no statistically significant difference.

The prevalence and PPV of individual signs was similar to the previous results published in literature for version,6,19,20 unilateral tonic seizure,5,13 unilateral clonic seizure,10,13 M2e,22 and asymmetric clonic ending.8,25 Todd’s paralysis had a moderately strong PPV when compared to the literature.10,26 Figure-of-47 and ictal dystonia9,23 showed a lower PPV in our study when compared to the literature. Previous studies reported that Todd’s paralysis had a 100% PPV.10,26 However, Todd’s paralysis is a “negative” phenomenon that frequently is missed unless it is very prominent. This is particularly frequent after a secondarily generalized tonic–clonic seizure because postictally the

---

**Table 2. Comparison of seizures with version as the initial sign versus those without**

<table>
<thead>
<tr>
<th>First sign</th>
<th>Number of seizures</th>
<th>Temporal</th>
<th>Extratemporal</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Version</td>
<td>29</td>
<td>15</td>
<td>14</td>
<td>0.693</td>
</tr>
<tr>
<td>Nonversion</td>
<td>9</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

No statistically significant difference was found between seizures from temporal and extratemporal origin.
patient is comatose and observers do not necessarily test motor strength. In this setting, Todd’s paralysis may only become evident 10–20 min after a generalized tonic–clonic seizure when the patient begins to move again. In these cases, Todd’s paralysis will be detected only if the observer reviews the video recording for 20–30 min after the secondarily generalized tonic–clonic seizure ended. This frequently is not done. In addition, less severe, shorter Todd’s paralysis may be undetected if the observers do not specifically test for it or if there is a relatively prolonged postictal coma that does not allow testing for Todd’s paralysis. The retrospective nature of our study prevented us from collecting this information, thereby restricting our ability to identify Todd’s paralysis and perhaps leading to the low prevalence of Todd’s paralysis in our study (6 of 47). In addition, the presence of Todd’s paralysis was presumptive based on evaluation of the video recordings rather than on an active demonstration of weakness by physical exam. This may have led to inclusion of a “wrong-sided” Todd’s paralysis based on subjective assessment, leading to a low PPV. This also emphasizes the importance of a meticulous physical exam in the postictal period to detect presence of focal neurologic deficits, which may aid in the appropriate classification of the EZ.

The figure-of-4 was first described by Kotagal et al. in 2000. According to the original definition, figure-of-4 occurs at the beginning of the tonic phase of a secondarily generalized tonic–clonic seizure. In that article, the authors describe how the tonic arm extension would start on the limb that is contralateral to the seizure-onset zone, but then could be followed by a figure-of-4 on the opposite side of the body, leading to confusion in which of the signs to consider. They recommend taking into account the first of the figure-of-4. Whether this strict definition was always used in the subsequent semiologic studies is not entirely clear. In this study we followed the original definition of the figure-of-4 described by Kotagal et al. However, during secondarily generalized seizures, patients adopt a variety of bilateral asymmetrical tonic postures and it is not always easy to define if a patient adopted or not a typical figure-of-4. This is also attested by the fact that we had only a relatively modest Kappa for this sign. Not infrequently, the lateralization of the figure-of-4 is also difficult to establish. All these factors may have contributed to the relatively low PPV we observed for this motor sign.

The duration at which to call a certain posturing dystonia has varied throughout the different studies, but in most studies the accepted duration was >10 s. Rusu et al. in 2005 subdivided dystonia according to the duration and complexity of posturing in terms of the movement type and parts of the limbs involved. They concluded that the earliest and/or most marked dystonic posturing was contralateral to the epileptogenic focus. This would mainly involve the most distal parts, namely the hand.

In our cohort we included under ictal dystonia only dystonic posturing of the hand. We considered the rotatory component of the hand (into extreme pronation or supination) the hallmark of ictal dystonia, as increased tonic flexion or extension is already included as a tonic seizure component. This was already emphasized in the original description of ictal dystonia. It is interesting to note that during the tonic phase of secondarily generalized tonic–clonic seizures that the hands may assume a posture similar to the dystonic posture. This similarity of posture may be a cause of confusion and a reason for higher prevalence of ictal dystonia in some studies. Moreover, despite a strict definition of dystonia, this sign had the least interrater reliability, further limiting the utility of this sign. It is important to stress, however, that in this study we analyzed ictal dystonia as presence of dystonia at any point before the generalization irrespective of its association with an automotor or dialeptic phase of the seizure. Because previous studies analyzed ictal dystonia specifically in association with these features, this difference may explain the discrepancy of PPV of ictal dystonia between the reports in the literature and the present study.

M2e is was described originally by Ajmone Marsan in 1957. According to Marsan, M2e had an excellent lateralizing value of the epileptogenic zone pointing to the contralateral hemisphere. In our cohort, M2e was the strongest sign in lateralization with a PPV of 100%. Moreover, it had the highest interrater reliability, which is very reassuring. We found that adhering to the definition outlined by Ajmone Marsan, particularly the involvement of one arm with no or late involvement of the opposite arm, and considering M2e posturing independent of version reproduced the results of Ajmone Marsan described almost 60 years ago. We conclude that M2e posturing is a highly reliable lateralizing sign and should be looked for whenever analyzing seizure semiology.

Version defined as a forced, sustained, and unnatural turning of the head to one side, usually with the neck muscle extended and the chin up, was found to lateralize the EZ to the contralateral hemisphere in all cases as reported by

| Table 3. Sequences prior to secondary generalization |
|----------------|--------------|----------|----------|
| Sequence       | Number of patients | Temporal | Extratemporal |
| Y→T            | 4             | 3        | 1        |
| Y→T→C          | 1             | 1        | 0        |
| Y→M2e          | 9             | 3        | 6        |
| Y→M2e→T        | 5             | 1        | 4        |
| Y→C            | 3             | 1        | 2        |
| Y→T→M2e        | 2             | 2        | 0        |
| Y→M2e+C→T      | 1             | 0        | 0        |
| Y→M2e→C        | 1             | 1        | 0        |
| C→V→M2e        | 1             | 1        | 0        |
| M2e→V→T        | 1             | 0        | 1        |
| C+M2e→V        | 1             | 0        | 1        |
| M2e→C          | 1             | 1        | 0        |

Variable sequences showed no localization value. V, version; T, tonic; C, clonic.
Wyllie et al. in 1986. This is opposed to the other head movements that did not meet the above definition and had unreliable lateralization value. Other studies reported a lateralization value of >90% if version occurred within 10 s of the secondary generalization or continued as the seizure generalized. Chee et al. found that if version was associated with neck extension, and if version was associated with late ipsiversio after the end of a generalized tonic–clonic seizure, it lateralized the EZ to the contralateral hemisphere in 100% of cases.

There are a few limitations to this study. Given that all the included patients were admitted to the EMU for presurgical evaluation, it is possible that there was an inherent clinical congruence enabling the patients to get this far. However, most of the semiologic studies in the literature included similar patient cohorts; therefore, our study can be interpreted in the same clinical context as other semiologic studies. Most of the patients included were adults. The youngest patient was 12 years old. This limits the applicability of this study to adults and teenagers, and the results may not be applicable to younger age groups such as neonates and toddlers.

**Conclusions**

Reliable motor signs with a high predictive value for lateralization include version, unilateral tonic posturing, unilateral clonic movements, M2e posture, asymmetric clonic ending, and Todd’s paralysis. Figure-of-4 and ictal hand dystonia, have a relatively lower PPV. In this study the combination of two or more reliable motor signs pointing to the same hemisphere, predicted lateralization with 100% certainty. When studying the sequence of motor signs, version is the most likely initial sign of the presecondary generalization motor sequence followed by M2e or a tonic seizure. The order of a sequence of motor signs is not useful in localizing the EZ.

**Disclosure**

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

**References**


*Epilepsia*, 57(3):369–375, 2016
doi: 10.1111/epi.13322