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Electroclinical features and long-term therapeutic response in patients with typical absence seizures

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ABSTRACT

Objective. To characterize in detail the electroclinical features of typical absence seizures and elucidate whether EEG or semiology features, alone or in combination, can predict long-term therapeutic outcome.

Methods. We analysed video-EEG recordings from 213 typical absence seizures from 61 patients with idiopathic generalized epilepsy. We extracted semiological features, in addition to hallmark manifestations (motor/behavioural arrest, non-responsiveness), their location, timing and frequency. We evaluated the duration and frequency of generalized spike-wave discharges and the presence of polyspikes. We used a supervised machine-learning approach (random forest) to search for classifier features for long-term therapeutic outcome (>one year).

Results. Besides the hallmark manifestations, additional semiological features were identified in 87% of patients (75% of seizures). The most common additional semiological features were automatisms and eye blinking (observed in 45% and 41.5% of seizures, respectively). Automatisms were associated with longer seizure duration, and oral automatisms occurred earlier compared to limb automatisms (4.03 vs. 6.19 seconds; p=0.005). The mean duration of the ictal spike-wave discharges was nine seconds, and the median frequency was 3 Hz. Polyspikes occurred in 46 seizures (21.6%), in 19 patients (31%). Median follow-up was five years, and 73% of the patients were seizure-free at the end of the follow-up. None of the semiological features, alone or in combination, were predictors of therapeutic outcome. The only significant classifier was the presence of polyspikes, predicting a non-seizure-free outcome with an accuracy of 73% (95% CI: 70-77%), positive predictive value of 92% (95% CI: 84-98%) and negative predictive value of 60% (95% CI: 39-81%).

Significance. Semiological features, in addition to behavioural arrest and non-responsiveness, are common in typical absence seizures, but they do not predict long-term therapeutic outcome. The presence of polyspikes has a high positive predictive value for unfavourable therapeutic outcome, and their presence should therefore be included when reporting EEGs in patients with typical absence seizures.

Key words: EEG, idiopathic generalized epilepsy, long-term therapeutic outcome, machine learning, semiology, typical absence seizure

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Typical absence seizures are generalized seizures, defined according to electroclinical features [1]. Their clinical hallmarks are brief and sudden motor or behavioural arrest and impairment of consciousness, which can vary from severe to inconspicuous. However, typical absence seizures are often accompanied by other subtle, but recognizable, semiological features, for example, eye blinking or deviation, orofacial or limb automatisms, tonic muscular contraction causing head retropulsion or arching of the trunk, atonic components leading to dropping of the head and arms, relaxation of grip and autonomic components [2, 3]. In addition, the aforementioned signs can have asymmetric, regional or focal manifestation [4, 5]. Typical absence seizures occur in patients with idiopathic / genetic generalized epilepsy syndromes [1]. In childhood absence epilepsy (CAE) and juvenile absence epilepsy (JAE), typical absence seizures are part of the syndromic definition. Frequently, but not invariably, they are encountered in juvenile myoclonic epilepsy (JME) [4, 6].

The characteristic ictal electroencephalogram (EEG) features are regular, bilateral synchronous discharges of 3-5-Hz spike (occasionally polyspike) and slow-wave complexes [1], lasting from 4 to 30 seconds, with gradual and regular (0.5-1-Hz) slowing down from the initial to the terminal phase of the discharge. The background interictal EEG is classified as normal in most cases. Non-localizing focal or multifocal abnormalities have also been demonstrated by means of magnetoencephalography (MEG) as well as EEG [4, 5, 7], without therapeutic consequences [8] and should not be interpreted as evidence of focal epilepsy with secondary generalization, which could cause errors in treatment [3]. In the majority of patients, the ictal discharges can be provoked by hyperventilation.

The clinical relevance of features, other than the hallmark electroclinical manifestation, is not yet fully elucidated. Semiological features that are often associated with focal seizures can lead to misdiagnosis. Several studies have suggested that certain semiological and EEG features can predict the therapeutic response [2, 9-11]. Our goal was to characterize in detail the electroclinical features of typical absence seizures in patients with idiopathic generalized epilepsy syndromes, and to assess whether they can predict therapeutic response. We used machine learning to search for electroclinical features that can be used as classifiers to predict the long-term therapeutic response.

Methods

We analysed recordings extracted from the video-EEG databases at Aarhus University Hospital and the Danish Epilepsy Centre, Filadelfia. The inclusion criteria were typical absence seizures occurring during the EEG recording, showing rhythmic, bilateral synchronous spike-wave discharges of at least three seconds duration, and available ictal behavioural testing. Exclusion criteria were patients younger than four years, atypical absence seizures, diagnoses other than idiopathic generalized epilepsy, and artefacts interfering with assessment of the ictal period. EEG was recorded using the standard electrode array of the International Federation of Clinical Neurophysiology [12], using the Nicolet One EEG machine (Natus Neuro, USA). Provocative methods included hyperventilation (3-5 minutes) [13] and intermittent photic stimulation [14].

Two of the authors (MV and MAK) analysed each recording, and any discordance was resolved via discussion and consensus involving a third author (SB). The following semiological features were extracted: motor or behavioural arrest, non-responsiveness, automatisms (type and somatotopic localization), eye blinking (including frequency), eye deviation (including direction), head retropulsion and elementary motor phenomena (myoclonic, clonic, tonic). In addition, we noted the timing of each semiological feature, compared to the electrographic start. The following EEG features were extracted for the bilateral synchronous ictal spike-wave discharges: duration, presence of polyspikes (defined as more than two consecutive spikes) and discharge frequency (measured after the first second of the discharge) [1]. From the electronic databases, we extracted demographic data (age and gender), diagnoses (syndromic classification), current and previous antiseizure medication (ASM) and long-term outcome (>one year after start of treatment), dichotomized as seizure-free vs. not seizure-free.

We used supervised machine learning (random forest) [15] to search for electroclinical features and combinations of features as classifiers for predicting seizure-free vs. non-seizure-free outcome. We used the scikit-learn package in Python for the machine learning section of the study (https://scikit-learn.org/stable/about.html) [16]. We divided the dataset into a training set (70% of the data) and a test set (30% of the data), and afterwards we determined positive predictive value (PPV), negative predictive value (NPV) and overall accuracy of the classifiers. Subsequently, we used the Chi-square test to compare the proportion of seizure-free patients between the sub-groups with and without the classifier. In addition, as a previous study suggested that the presence of semiological features with eye involvement but no motor automatisms was associated with worse therapeutic outcome at 16-20 weeks of follow-up [2], we specifically addressed this aspect in our dataset. To compare

the occurrence of the semiological features between the sub-groups, we used the Chi-square test. To compare the time from seizure onset to the occurrence of the different semiological features, the t-test was used.

Results

Two hundred and thirteen absence seizures from 61 patients (33 female; 54%) were included and analysed. Median age was 11 years (mean: 12.6 years). The syndromic classification of the patients is summarized in *table 1*.

The semiological features are summarized in *table 2*. The most common semiological findings were the hallmark manifestations of absence seizures: all patients had either motor/behavioural arrest or non-responsiveness. Motor/behavioural arrest (cessation of activity at seizure start) occurred in 96% of the patients. Non-responsiveness to the ictal testing was documented in 93.5% of the patients.

One hundred and sixty seizures (75%; 95% CI: 69-80) in 53 patients (86%; 95% CI: 77.2-94.7) showed additional semiological features. From the additional (not hallmark) semiological features, the most common were automatisms and eye blinking. Automatisms occurred in 67% (95% CI: 55.2-78.7) of all patients; in 45% of the seizures (95% CI: 38.3-51.6). The type of automatisms in the 41 patients with automatisms are shown in *table 3*. The mean time from the start of ictal changes on EEG to the occurrence of all automatisms was 4.81 seconds. Oral automatisms occurred earlier than limb automatisms (4.03 vs. 6.19 seconds; p=0.005). Of the limb automatisms, 32.5% were asymmetric. The majority of automatisms (75%) occurred in seizures that were longer than the median seizure duration in this cohort (p<0.0001). Eye blinking was observed in 55.7% of the patients, in 41.5% of seizures (95% CI: 43.2-68.1 and 34.3-47.6, respectively), with a mean blinking frequency at approximately 2.5 Hz. There was no significant difference between the proportion of automatisms and eye blinking, but the proportion of other semiological features (*table 2*) was significantly lower compared to automatisms and eye blinking (p<0.001). A less frequent semiological feature was eye deviation. Lateralized eye deviation was observed in 10 patients (16.3%) and 21 seizures (9.8%) (95% CI: 7.03-25.5 and 5.8-13.7, respectively). We aimed to examine whether the direction of eye deviation was consistent or alternated. Four patients had multiple seizures with lateral gaze deviation. In three of these patients, the direction was consistent from seizure to seizure.

Besides the hallmark features, we identified the following four clusters (Kessler *et al.*) of semiological features:

- automatisms only;
- eye involvement only;
- both automatisms and eye involvement;
- and neither automatisms nor eye involvement (*table 4*).

The majority (64.5%) of patients with multiple seizures during the recording experienced different semiology/clusters with different seizures (*figure 1*). The incidence of elementary motor phenomena was higher in seizure Cluster 4, compared with Cluster 1 (p=0.002) and Cluster 2 (p=0.06).

The average duration of the ictal spike-wave discharges was 9.06 seconds. *Table 5* shows the distribution of the frequency bands of the ictal discharges. The mean ictal spike-wave frequency of all seizures was 3.23 Hz (median frequency: 3 Hz). Polyspikes occurred in 46 seizures (21.6%) and in 19 patients (31%). Based on examination of eye blinking, automatisms and eye deviation, as separate clinical features, no significant differences were found regarding the presence of polyspikes (15.9%, 14.58% and 13.5%, retrospectively). Polyspikes were significantly more common in Cluster 4 when compared to Custer 1 (p=0.0331; 95% CI: 3.6-24.8) and Cluster 3 (p=0.0279; 95% CI: 5.4-24.7). When comparing Cluster 4 to Cluster 2 (which was the second most common clinical phenotype), there was no significant difference (p=0.1472; 95% CI: 9.8-31.6).

▼ **Table 1.** Syndromic classification.

Epilepsy syndrome	Number of patients *n* (%)
Childhood absence epilepsy	31 (51%)
Juvenile absence epilepsy	21 (34.5%)
Juvenile myoclonic epilepsy	5 (8%)
Idiopathic generalized epilepsy not further classified	4 (6.5%)

▼ **Table 2.** Occurrence of semiological features in absence seizures.

Semiological features	Per seizure *n*=213 % (95% CI)	Per patient *n*=61 % (95% CI)
Motor arrest	94.8 (91.8-97.7)	96.3 (91.5-100)
Non-responsiveness	87.3 (82.4-91.5)	93.5 (87.3-99.6)
Automatisms	45.0 (38.3-51.6)	67.0 (55.2-78.7)
Eye blinking	41.5 (34.3-47.6)	55.7 (43.2-68.1)
Eye deviation	18.0 (12.8-23.1)	21.3 (11.0-31.5)
Head retropulsion	6.1 (2.8-9.3)	16.7 (7.3-26.1)
Elementary motor phenomena	6.5 (3.1-9.8)	8.1 (1.2-14.9)

In eight of the 10 patients with lateral eye deviation, we observed the presence of interictal focal/pseudofocal epileptiform discharges. In five of them (62.5%), the interictal epileptiform discharges were consistently in the same location (either left or right side), while in three patients, they were alternated, originating from both the left and right side, independently. Of the four patients with multiple seizures with lateral eye deviation, two had focal discharges (in one case, the semiological and EEG findings were concordant with the interictal spikes registered contralaterally to the direction of the lateral eye deviation).

Long-term follow-up was available in 45 patients (16 patients were lost to follow-up). The median follow-up time was five years. Thirty-three patients (73%) were seizure-free. Regarding ASM, the majority of patients (58%) were on either valproate (VPA) or ethosuximide (ESM) treatment, whereas 29% received both VPA and ESM, and only 13% received other medications.

The random forest analysis did not reveal a correlation between therapeutic outcome and semiological features, either isolated or in combination (clusters). When using the EEG features as classifiers, the random forest analysis revealed a correlation between the presence of polyspikes and unfavourable outcome (not seizure-free). The selection of the training population did not significantly influence the results, thus showing greater robustness compared to

▼ **Table 3.** Types of automatisms, listed in decreasing order of prevalence.

Type of automatism	Number of automatisms (*n*=121)	
	n	%
Lip smacking or licking	43	35.5%
Subtle hand or arm movements	12	9.9%
Chewing/swallowing	11	9.1%
Other oral (opening/closing mouth, sticking tongue out)	11	9.1%
Fumbling	10	8.3%
Scratching	8	6.6%
Finger tapping	8	6.6%
M. Nasalis automatism	7	5.8%
M. Frontalis automatism	4	3.3%
Genital automatisms	3	2.4%
Grimacing	2	1.7%
Subtle leg movement	2	1.7%

▼ **Table 4.** Clusters of semiological features.

	Per seizure *n* (%)	Per patient *n* (%)
Automatisms only	42 (20%)	24 (39%)
Eye involvement only	53 (25%)	24 (39%)
Both features	53 (25%)	25 (41%)
Neither feature	64 (30%)	32 (52%)

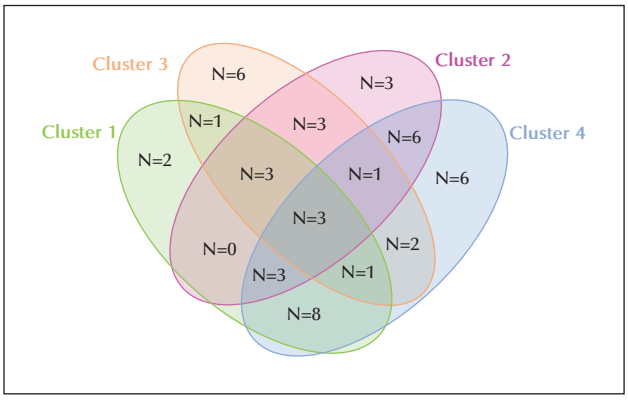
semiological features. The Chi-square test confirmed the difference in therapeutic outcome between patients with and without polyspikes, as part of the ictal discharges (p=0.018). The presence of polyspikes predicted an unfavourable outcome with an accuracy of 73% (95% CI: 70-77). The positive predictive value was 92% (95% CI: 84-98%) and the negative predictive value was 60% (95% CI: 39-81%).

Neither the random forest analysis nor the statistical analysis could confirm in our cohort the previous observation that patients with absence seizures and eye involvement only (Cluster 2) have a worse therapeutic outcome.

Regarding the patients' sex, the random forest analysis did not show any significant correlation with outcome, which was also confirmed by further statistical analysis. Seventeen of 25 female patients were seizure-free (68%), while 16 of 20 (80%) males were seizure-free (p=0.37).

Thirteen patients had at least one typical absence seizure provoked by intermittent photic stimulation (10 in the follow-up group). Of patients with seizures provoked by IPS, 80% were seizure-free, while 74% of patients whose seizures were not provoked by IPS were seizure-free (p=0.59). The random forest analysis did not indicate any correlation between photosensitivity and prognosis.

Patients with JME were more likely not to be seizure-free compared to patients with CAA (p=0.00014) and patients with JAE (p=0.003). We found no significant difference concerning the outcome between CAA and JAE groups (p=0.18). In our series, long-term follow-up data were available for three patients with JME. None of them were seizure-free and two of them had polyspikes. Due to the low number, JME was not considered in the machine learning approach. Twenty-two of 26 patients with CAA were seizure-free, and only four of these had polyspikes (18.1%). Of the non-seizure-free CAA patients (n=4), three had polyspikes (75%) (p=0.0206). Of the 15 JAE patients, 10 were seizure-free and three of them had polyspikes (30%), while 80% of the non-seizure-free patients (n=5) had polyspikes (p=0.07). For CAA and JAE patients overall, 21% of the seizure-free patients had polyspikes, while polyspikes were seen in 55.6% of non-seizure-free patients (p=0.045).



■ **Figure 1.** Seizure cluster pattern combinations in the individual participants The number of patients in each cluster and combinations of clusters [2] are shown using the colour code, as specified in the figure.

▼ **Table 5.** Distribution of the frequency of ictal spike-wave discharges in 213 seizures.

Frequency of ictal spike-wave discharge	Number of seizures *n* (%)
3.5-4.5 Hz	14 (6.5%)
3.0-3.5 Hz	191 (89.7%)
2.5-3.0 Hz	8 (3.8%)

Discussion

Motor or behavioural arrest and non-responsiveness are the hallmark semiological features observed in all patients with typical absence seizures. However, additional semiological features, consisting of accompanying motor phenomena, are often observed in typical absence seizures - in 75% of seizures (87% of patients) in our series. It is important that physicians are aware of additional features in order to avoid misclassification/misdiagnosis. The most common additional features were automatisms and eye blinking. The incidence of automatisms in our series (45% of seizures, 67% of patients) is similar to those of some previous studies [17], but somewhat lower than in other series [2].

We also observed an occurrence of asymmetric accompanying motor phenomena in typical absence seizures. Asymmetric automatisms represented 32.5% of all limb automatisms. Eye deviation with upward gaze was observed in most of the patients with this feature. However, lateralization either to the right or left was seen in 10 patients (16.3%) and 21 seizures (9.86%), with the majority of (80%) presenting accompanying interictal focal epileptiform discharges. To the best of our knowledge, lateralized eye deviation has not previously been systematically examined in other studies. These findings further support that absence seizures can also be accompanied by focal clinical signs, often leading to misdiagnosis as a focal epilepsy [4]. However, regarding the consistency of the aforementioned electroclinical signs and the relationship between them, as well as their eventual correlation with outcome, larger studies are needed for further clarification. Previously published large-scale studies did not show any correlation between focal interictal spikes and therapeutic response in patients with IGE [8].

Oral automatisms occurred earlier during the course of seizures compared to manual/limb automatisms. This is consistent with previous studies [17] and supports the theory of Stefan *et al*. [18], who proposed a consistent sequence of automatisms in time, with oral automatisms preceding manual automatisms: the cranio-caudal march of absence signs [4]. It has been hypothesized that automatisms might be reactive phenomena to external stimuli. This might explain the higher proportion of automatisms in longer seizures, due to a greater chance of reactive response. We have also found that automatisms were associated with longer seizures.

A previous report suggested that semiological features in typical absence seizures tend to cluster into four distinct seizure sub-phenotypes [2]. Therefore, we also evaluated these clusters. We found a high degree of intra-participant seizure sub-phenotype heterogeneity, with the majority of patients experiencing more than one cluster type. Similar observations have been recorded in the literature and may indicate variable patterns of activation of specific cortico-thalamic networks, or variable activation of secondary networks. We were also unable to reproduce the previous finding of a higher incidence of elementary motor phenomena in seizure types with either automatisms or eye involvement [2]. A potential explanation for the latter has not yet been put forward.

The average duration of the ictal spike-wave discharges was nine seconds, and the average ictal spike-wave frequency was 3.23 Hz. This is consistent with previous findings [1]. Polyspikes occurred in 21.6% of the seizures.

We used supervised machine-learning to identify EEG or semiological features, alone or in combination, that could predict long-term therapeutic outcome (median follow-up: five years). In contrast to a previous study [2], we did not find a predictive value for any semiological feature, alone or in any combination/clusters. This could be either due to the larger cohort (416 patients) or due to the shorter follow-up (16-20 weeks) in that study [2]. The only electroclinical feature that could predict seizure-free long-term outcome was the presence of polyspikes. This had a high positive predictive value (92%) for unfavourable outcome (not seizure-free). This outcome is in accordance with previous findings reported in the literature, showing that polyspikes/polyspike-wave discharges were more frequent in patients with treatment-refractory idiopathic generalized epilepsy [9]. A study by Michelucci *et al*., examining the characteristics of patients with IGE with seizures

persisting into adult life, showed that 75% had absence seizures with polyspikes on ictal EEG [11]. Therefore, the presence of polyspikes on EEG in patients with typical absence seizures may be a distinct, robust feature which deserves appropriate consideration. A possible explanation for the lack of correlation between semiology/clusters and therapeutic outcome could be the relatively low granularity of the features: for example, eye involvement is not sub-classified according to detailed features (*e.g.* rhythmic, saccadic, tonic).

In conclusion, additional semiological features are common in typical absence seizures, but they do not predict long-term therapeutic outcome. The presence of polyspikes has a high positive predictive value for unfavourable outcome, and this feature must be included when reporting EEGs recorded in patients with typical absence seizures. ■

Disclosures.
The authors have no conflict of interest to declare.

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TEST YOURSELF

(1) What are the hallmark semiological features of typical absence seizures, observed in all patients?
A. Behavioural arrest, non-responsiveness, impairment of consciousness
B. Automatisms
C. Eye blinking
D. Facial myoclonic jerks

(2) Which of the following statements is correct about automatisms and eye blinking:
A. They never occur in typical absence seizures
B. They always occur in typical absence seizures
C. They often occur in typical absence seizures
D. They imply poor long-term therapeutic response

(3) Which of the following EEG features are associated with unfavourable therapeutic response:
A. Duration of spike-waves, longer than 10 seconds
B. Bispikes
C. Polyspikes
D. Focal EEG features

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.