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Diagnostic decision-making after a first and recurrent seizure in adults

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ABSTRACT

Purpose: The role of EEG after a first seizure has been debated. Epileptiform EEG activity is a good predictor of seizure recurrence, but is reported in only 8–50% of first-seizure adult patients. Even if the EEG is abnormal, the opinions about treatment after a first seizure differ. The role of EEG in treatment decisions after remission or recurrence is also unclear. This study aims to identify neurologists' diagnostic strategies compared to guidelines about the use of EEG (i) after a first unprovoked generalized seizure in adults, (ii) after a recurrent seizure and (iii) in treatment decisions after recurrence or remission.

Method: All members of the Dutch Neurological Society were invited to participate in our on-line survey about the use of EEG after a first seizure, after recurrent seizures and in treatment decisions. Ten percent (N = 110) of invitees participated, including mainly clinical neurophysiologists, general neurologists and neurologists-in-training.

Results: Ninety-five percent of the respondents would request a routine EEG after a first seizure. After normal MRI and EEG findings, 4% would record a second routine EEG, 48% a sleep-deprived EEG and 45% would not repeat the EEG. If a recurrent seizure occurs within six, or after 12 or 24 months, 87%, 67% and 44% would respectively conclude that the patient has epilepsy, while 57%, 65% and 72% would request an EEG. When a patient experiences a recurrence while being treated with anti-epileptic drugs, 11% of the respondents would request an EEG. Twenty-five percent would request an EEG before stopping medication after two years of remission.

Conclusion: The variability in neurologists' reported strategies about the use of EEG in the diagnosis of seizures is remarkably large. Consequences for the individual patient may be significant, including treatment decisions and driving restrictions. The availability and use of more sensitive diagnostic methods may be necessary to enhance agreement between neurologists.

1. Introduction

When an adult presents to the emergency department (ED) after a first seizure, an important question is whether or not there is an increased risk of seizure recurrence.[1] After an unprovoked first seizure, symptomatic etiology and epileptiform EEG activity are the two most consistent predictors of seizure recurrence.[2] Therefore, MRI and routine (20–30 min) EEG including hyperventilation and photic stimulation, are both part of the standard diagnostic approach in first-seizure patients. This study specifically addresses the role of EEG in first-seizure diagnosis.

The estimated probability of seizure recurrence after a first seizure in adults with epileptiform EEG abnormalities is 49.5%, compared to only 27.4% in individuals whose EEGs are completely normal.[3] Still, the value of a routine EEG after a first seizure has been debated.[4] A normal routine EEG does not exclude the presence of a seizure disorder. Furthermore, presence of epileptiform activity was reported in only 8–50% of first-seizure adult patients.[3] Routine EEGs are therefore often repeated, or followed by a sleep-deprived EEG, as this may increase sensitivity.[5,6] Still, there are epilepsy patients in whom repeated EEGs do not show any epileptiform abnormality. The main reason may be that scalp electrodes sample only one-third of the cortex. This limits the sensitivity for IEDs arising from within sulci or with tangential dipoles. IEDs may also be generated by such a small amount of cortex, that the resulting extracellular currents are insufficient to allow reliable detection with scalp EEG.[7] Another issue is the limited duration of routine EEG-registrations, which will not show any discharges that occur infrequently. On the other hand, even if

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the EEG is abnormal, the opinions on treatment after a first seizure differ. Immediate treatment reduces the number of recurrences, but some patients may be treated unnecessarily.[8,9]

The majority of patients (92%) who present with a first unprovoked seizure and are treated with anti-epileptic drugs attain a two year remission within five years after the first event, regardless of immediate or deferred treatment.[10] When informing patients about the consequences of discontinuing treatment after such a period of seizure-freedom, accurate risk assessment is essential. In these circumstances, the routine EEG may assist, as it allows prognostication about the likelihood of remission or may be used to predict seizure recurrence in the event of epileptiform activity.[11] In children, persistent interictal epileptiform activity is associated with an increased risk of seizure recurrence if AEDs are discontinued after remission. However, in adults, the relevance of interictical epileptiform activity is much less certain.[12]

Guidelines may assist physicians in decision-making concerning the diagnosis and treatment after a first seizure or recurrent seizures. The clarity and clinical applicability of a guideline may be important attributes that contribute to the effects of practice guidelines.[13] Several guidelines or practice parameters regarding the use of EEG after a first seizure or recurrent seizures have been developed.

The American Academy of Neurology (AAN) and American Epilepsy Society (AES) developed a practice parameter for evaluation of adults presenting with an apparent unprovoked first seizure. They conclude that in these patients, the EEG is probably helpful and that the routine EEG should be used as part of the neurodiagnostic evaluation of the adult because it has substantial yield and value in determining the risk of seizure recurrence.[3]

The National Institute for Health and Clinical Excellence (NICE) guidelines about the use of EEG state that an EEG should be performed only to support a diagnosis of epilepsy in adults in whom the clinical history suggests that the seizure is likely to be epileptic in origin. In those presenting with a first unprovoked seizure, unequivocal epileptiform activity on EEG should be used to assess the risk of seizure recurrence. If diagnosis is still unclear after a standard EEG, repeated standard EEGs may be helpful but should not be used in preference to sleep or sleep-deprived EEGs. Further, when a routine EEG has not contributed to diagnosis or classification, a sleep EEG should be performed. There is no information in the guidelines about the role of EEG in the decision to stop medication after remission.[14]

The International League Against Epilepsy (ILAE) has no international guidelines on the use and role of EEG in first-seizure and epilepsy diagnosis. However, according to the Italian League Against Epilepsy, an EEG should be performed within 24 h after a seizure, particularly in children. If the EEG is normal during wakefulness, a sleep EEG is recommended.[15] The Dutch Neurological Society has, together with the Dutch League Against Epilepsy, developed guidelines for diagnosis and treatment of epilepsy (revised, 2nd version, 2006). These guidelines however do not give information about which EEGs should be used after a first seizure or recurrent seizures in adults.

In this paper, we present neurologists' reported diagnostic decisions in adults where we will specifically emphasize on the use of EEG (i) after a first unprovoked generalized seizure, (ii) after recurrent seizures at different time-intervals, and (iii) in the decision to start or change medication after recurrence or to stop medication after remission. Responses reflect neurologists' diagnostic decisions regarding patients in the Netherlands and will be compared to both national and international guidelines.

2. Methods

Approximately 1100 members (neurologists and neurologists in training) of the Dutch Neurological Society were invited to participate in our online survey about the use of EEG after a first seizure in adults, after a second seizure at different time-intervals from the first, and when making treatment decisions after recurrence or remission. The invitation included an informative letter with a link to the on-line survey at www.epilepsydata.eu. Participation in the survey was anonymous.

Participants were first asked for their educational background, type of hospital they worked at and their number of years in practice. A case was then described in which an adult presents to the ED after a first unprovoked generalized seizure. Participants were asked what their policy would be, what conclusions they would draw and which EEGs they would request for several scenarios, including normal and abnormal EEG findings and seizure recurrence. Corresponding questions and response options are listed in Table 1. Second, participants were asked whether they would perform additional EEG measurements in treated epilepsy if a recurrence occurs after 18 months of seizure freedom or when considering stopping medication after two years of remission. The survey included multiple-choice, yes–no as well as open questions. Data were analyzed using PASW Statistics version 18.0.0, SPSS Inc., by means of descriptive statistics. Non-responses were excluded.

3. Results

Ten percent ($N = 110$) of the invited neurologists (in training) responded before the deadline. The majority of the respondents (56%) had worked for more than five years as a neurologist (see Table 2). Primarily, general neurologists, clinical neurophysiologists and neurologists in training (87% in total) responded to the survey (see Table 2).

Table 1
Three survey questions for the case: 'An adult presents to the ED after a first unprovoked generalized seizure – the neurological examination was normal'.

Q1. What is your policy?	Q2. What would be your conclusion and policy after each of the findings below?	Q3. What would be your conclusion and policy after each of the findings below?
You can choose multiple answers from the options below:	The MRI was normal.	
- MRI-scan	(1) If the routine EEG is normal	(1) If the routine EEG contains 2 temporal spike-and-wave discharges
- Routine EEG	(2) If both routine and sleep-deprived EEGs are normal	
- Sleep-deprived EEG	(3) After a recurrence within 6 months after the first one	(2) If the routine EEG contains generalized spike-and-wave discharges
- Long-term EEG (~2 h)	(4) After a recurrence after 12 months after the first one	
- Start medication	(5) After a recurrence after 24 months after the first one	
- Hospitalization for one day/night		
- Routine blood tests		
- None of the options above		

Response options for Q2 and Q3: conclusion: epilepsy/first seizure, no epilepsy/possibly epilepsy but I will wait/no conclusion, I still miss information policy: no EEG/routine EEG/sleep-deprived EEG/long-term EEG (~2 h)/long-term EEG (>12 h).

Table 2
Participants' demographic data and policy after a first unprovoked generalized seizure in adults.

Response	Total: $N = 110$
Neurologist	36 (33%)
Neurologist/clinical neurophysiologist	30 (27%)
Neurologist/epileptologist	4 (4%)
Neurologist/pediatric neurologist	10 (9%)
Neurologist in training	30 (27%)
5 years or longer	61 (56%)
<5 years	19 (17%)
In training	30 (27%)
Academic medical center	39 (35%)
Peripheral teaching hospital	37 (34%)
Peripheral non-teaching hospital	24 (22%)
Epilepsy center	10 (9%)
What is your policy? (Multiple answers allowed)	
MRI-scan	105 (96%)
Routine EEG	104 (95%)
Routine blood tests	83 (76%)
Sleep-deprived EEG	12 (11%)
Hospitalization	12 (11%)
Long-term EEG (>2 h)	3 (3%)
Start medication	1 (1%)

3.1. First seizure

The large majority of the respondents would request an MRI-scan (96%) and routine EEG (95%) after a first unprovoked generalized seizure in adults. Seventy-six percent would perform routine blood tests (see Table 2).

After a normal neurological examination, MRI and routine EEG, 56% of the respondents would diagnose the patient with a single seizure, not epilepsy, and 23% would not draw any conclusions because of missing information (see Table 3). Of the respondents who reported that information was missing, 88% would request a sleep-deprived EEG. In general, 45% would not repeat the first normal EEG, whereas 48% would request a sleep-deprived EEG (see Table 3). Only 33% of the general neurologists would not repeat a normal routine EEG, whereas 53% of the clinical neurophysiologists and residents would not repeat the EEG.

If the first routine EEG contains two temporal or generalized spike-and-wave discharges, 40% and 76% of the respondents respectively would conclude that the patient has epilepsy. In the presence of temporal discharges, 35% would request a sleep-deprived EEG, whereas in the presence of generalized discharges, the large majority (93%) would not repeat the EEG (see Table 3).

3.2. Recurrent seizure

After a recurrence within six, after 12 or after 24 months, 87%, 67% and 44% of the respondents respectively would conclude that the patient has epilepsy. The percentage of neurologists responding 'possibly epilepsy, but I will wait' increases from 9%, to 30%, to 46% (see Table 4). Residents are less likely to diagnose epilepsy after a recurrence after 24 months (35%) compared to general neurologists (53%), while more residents would conclude that it is 'possibly epilepsy' (66%) compared to general neurologists (36%).

3.3. The role of EEG in treatment decisions

When a patient experiences a recurrence after 18 months of seizure-freedom while being treated with anti-epileptic drugs and in the absence of sleep-deprivation, 69% would 'wait', 11% would request an EEG, 9% would prescribe another AED, and 11% would add a second AED.

If discontinuation of medication is considered after two years of seizure-freedom, 25% would request an EEG before stopping. Seventy-five percent of the respondents would taper off anti-epileptic medication without an additional EEG.

4. Discussion

A first seizure may have a large impact on a patients' life.[16] In a small proportion of first-seizure patients, epilepsy is diagnosed soon after the event. In various patients, however, uncertainty about the diagnosis may persist quite some time.[17] Unfortunately, a reliable biomarker that would enable physicians to accurately predict the risk of seizure recurrence is still missing.[18] The EEG is generally used, but has limited sensitivity in epilepsy.[19] This causes diagnostic uncertainty after a first event, in particular if the initial routine EEG is normal. Guidelines based on scientific knowledge from large and well-performed patient studies should guide the neurologist in decision-making regarding the use of EEG after a first seizure. However, guidelines are restricted to epilepsy diagnosis, providing information about the value of EEGs in epilepsy, while they lack specific information about which decisions to make after a first seizure. Another difficulty is the fact that there is not one single definition of epilepsy. The International League Against Epilepsy defines epilepsy as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and that epilepsy requires the occurrence of at least one epileptic seizure.[20] The American Epilepsy Society, however, states that epilepsy requires recurrent

Table 3
Neurologists' reported conclusions and EEG requests following a first seizure in adults and (i) a normal routine EEG, (ii) normal routine and sleep-deprived EEGs, (iii) two temporal discharges in the routine EEG, and (iv) generalized discharges in the routine EEG.

Conclusion	Normal routine EEG	Normal routine and SD-EEG	Temporal discharges in routine EEG	Generalized discharges in routine EEG
Focal epilepsy	0 (0%)	0 (0%)	40 (38%)	0 (0%)
Generalized epilepsy	0 (0%)	0 (0%)	2 (2%)	81 (76%)
Single seizure, not epilepsy	61 (56%)	79 (72%)	21 (20%)	7 (7%)
Possibly epilepsy, but I will wait	23 (21%)	26 (24%)	37 (35%)	15 (14%)
No conclusion, I still miss information	25 (23%)	4 (4%)	6 (5%)	3 (3%)
Total	$N = 109$	$N = 109$	$N = 106$	$N = 106$
Second EEG?				
No second EEG	49 (45%)	100 (93%)	64 (61%)	96 (93%)
Second routine EEG	4 (4%)	2 (2%)	1 (1%)	4 (4%)
Sleep-deprived EEG	53 (48%)	1 (1%)	36 (35%)	1 (1%)
Long-term EEG (~2 h)	1 (1%)	1 (1%)	1 (1%)	0 (0%)
Long-term EEG (>12 h)	2 (2%)	3 (%)	2 (2%)	2 (2%)
Total	$N = 109$	$N = 107$	$N = 104$	$N = 103$

Table 4
Neurologists' reported conclusions and EEG requests after a recurrent seizure within six, and after 12 and 24 months following the first one.

Conclusion	Within six months	After 12 months	After 24 months
Epilepsy	95 (87%)	73 (67%)	47 (44%)
Single seizure, not epilepsy	0 (0%)	1 (1%)	9 (8%)
Possibly epilepsy, but I will wait	10 (9%)	32 (30%)	50 (46%)
No conclusion, I still miss information	4 (4%)	2 (2%)	2 (2%)
Total	*N* = 109	*N* = 108	*N* = 108
Policy: EEG?			
No EEG	46 (43%)	37 (35%)	30 (28%)
Routine EEG	25 (23%)	32 (30%)	44 (41%)
Sleep-deprived EEG	25 (23%)	24 (22%)	23 (21%)
Long-term EEG (∼2 h)	4 (4%)	5 (5%)	4 (4%)
Long-term EEG (>12 h)	7 (7%)	9 (8%)	6 (6%)
Total	*N* = 107	*N* = 107	*N* = 107

seizures, two or more, which are not provoked by systemic or acute neurologic insults.[21] A similar definition was proposed by epidemiologists, who define epilepsy as two or more unprovoked seizures occurring at least 24 h apart, mainly because evidence of a recurrence may be the only information available to identify an 'enduring predisposition to generate seizures'.[22] The present study was performed in order to identify neurologists' diagnostic strategies about the use of EEG after a first seizure in adults, after recurrent seizures and during treatment decisions.

Our survey among Dutch neurologists showed that a routine EEG is almost always performed after a first seizure in adults, as practically every neurologist (95%) reported to request this examination. This is consistent with earlier findings in over 400 first-seizure patients, where 95% of the patients had an EEG after their first seizure.[23] Also, this is consonant with the practice parameter of the American Academy for Neurology and American Epilepsy Society.[3] However, the NICE guidelines seem much more difficult to interpret at this point.[14] In general, there seems to be no doubt about the usefulness of the first routine EEG after a first seizure in adults.

After a normal MRI and routine EEG however, 4% would request a second routine EEG, 48% would request a sleep-deprived EEG, and 45% would not repeat the EEG. This indicates that there is no common opinion on whether or not a second EEG should be performed. The preference for sleep-deprived over routine EEGs agrees with earlier studies[5,24,25] and with NICE guidelines.[14] There is, however, not a single explanation for the finding that nearly half of the neurologists would not repeat the EEG while the other half would. In fact, the guidelines too lack information about the usefulness of a second EEG after an initial normal routine EEG in first-seizure adult patients. Our survey showed that, of the neurologists who would not repeat a normal routine EEG, 80% concluded that it was a first seizure, not epilepsy. The rest (20%) concluded to 'wait', but that the patient has possibly epilepsy. Presumably, these neurologists share the opinion that after a single seizure and normal routine EEG, sufficient information has been collected to conclude that there is insufficient evidence of epilepsy. Here, several considerations may play a role. It was estimated that about 5% of the population experiences a seizure at some point of his or her life.[26] Some of the first-seizure patients will never experience a recurrence, but the exact proportion is unknown. It was estimated that, overall, 40–50% of untreated individuals can expect a recurrence within two years after the initial seizure,[2] which would imply a remission rate of 50–60%. Also, neurologists and patients may accept the risk of having a recurrence.

If, on the other hand, the first routine EEG contains temporal or generalized discharges, 40% and 76% of the respondents respectively would conclude that the patient has epilepsy. This indicates that in the presence of generalized epileptiform discharges, neurologists are more inclined to the diagnosis of epilepsy than in the presence of temporal discharges, even after a single seizure only. It was indeed reported that in particular generalized spike and wave discharges or focal spikes are associated with a greater risk for seizure recurrence.[3] The limited percentage of neurologists who reported to diagnose the patient with epilepsy in the presence of temporal spike-and-wave discharges may be caused by the fact that we added in the description of the case in our survey that only two temporal discharges were found. Apparently, some neurologists consider the presence of two temporal epileptiform discharges not sufficient for the diagnosis of epilepsy, while for others, these abnormalities are significant. The exact relation between the number of interictal epileptiform discharges in the EEG and risk of seizure recurrence is, however, unknown.

Some patients may experience a recurrence after the first unprovoked generalized seizure. The role of the time between the first and second seizure in the actual diagnosis is unknown. The majority of our participants (87%) would diagnose epilepsy after a recurrence within six months, but only 44% would diagnose epilepsy if the recurrence occurs after 24 months. Simultaneously, the percentage of respondents reporting that it is possibly epilepsy, but to wait, increases from 9% to 46%. This indicates that there is no common opinion on what the diagnosis epilepsy requires with respect to seizure interval. It also indicates that the confusion increases with increasing time-to-recurrence. None of the guidelines includes the time between the first and recurrent seizure in the definition of epilepsy, while it seems to be a very important issue, strongly influencing the diagnostic decisions and very likely also treatment decisions in patients.

In patients diagnosed with epilepsy and treated with antiepileptic drugs, remission or recurrence may occur. Our findings suggest that, according to the responding neurologists, the role of EEG after seizure recurrence in a patient already treated with antiepileptic drugs is limited. Only 11% would request an EEG in these circumstances, while the majority (69%) would 'wait'. When considering AED discontinuance after remission, the role of EEG seems to be a little larger, as 25% of our respondents would request an EEG before stopping. Some authors suggested that the EEG may have an important role in AED discontinuation decision making.[11] However, our survey participants think that this role is quite limited. For comparison, a similar percentage (29%) indicated to follow the patients' wish directly without additional examinations, if the patient wants to stop medication. The reason may be that both physicians and patients are willing to accept the risk of seizure recurrence. Indeed, it was shown that 20% of families of children having epilepsy were even willing to discontinue AEDs with a risk of seizure recurrence of 75%.[27]

Although the results from our study are illustrative for neurologists' diagnostic decisions, conclusions should be drawn with caution, as our survey has several limitations. The cases presented were very general, which may make decision-making difficult because some information might be missing that would have been available in real practice. However, for each of the questions about the first-seizure adult patient, participants could choose for the option '*No conclusion, I still miss information*' and indeed, some respondents used this option. Further, guidelines are never based on individual cases and try to describe the best and general way of diagnosing first-seizure or epilepsy patients.

Second, the variability in our survey results may be caused by the large variety in the background of our participants, including differences in education and years in practice. We do not know exactly how well this group represents the population of

neurologists evaluating first-seizure adult patients. Furthermore, only ten percent of the invitees responded to the survey. We know the background of our participants, but we have no specific information about the background of non-respondents. The percentage of neurologists-in-training within the respondents (27%) was similar to the percentage of neurologists-in-training that are members of the Dutch Neurological Society (approximately 29%), which indicates that our sample is at least partly representative for all the members of the Dutch Neurological Society.

Opinions and attitudes may vary across specialists. For example, residents seem less likely to diagnose epilepsy after a recurrence after 24 months than general neurologists. Conclusions about the significance of these differences should be drawn with caution, as groups were relatively small and variable in size (e.g., four epileptologists compared to thirty clinical neurophysiologists).

Further, the results of the study reflect the opinions and attitudes of Dutch neurologists and are not necessarily applicable to physicians working in other countries. For example, the incidence of epilepsy differs between countries,[28] which may cause differences in (diagnostic) decisions made by neurologists in different countries. Also, differences in opinions and attitudes toward the use of EEG after a first seizure or in epilepsy may be caused by socio-cultural and educational background differences varying over countries. Besides, we do not know to what extent neurologists use (international) guidelines during diagnostic and treatment decisions.

In sum, the present study has shown that there is large variability between neurologists' reported diagnostic decisions about the use of EEG after a first seizure, after recurrent seizures, or in treatment decisions. The role of the first routine EEG after a first seizure in adults is not in question, however, there is no consensus about the role of a second EEG after an initial normal EEG and the role for EEG in treatment decisions. The large variability in diagnostic strategies reflects the limited sensitivity of the EEG. Furthermore, neurologists may follow different definitions of epilepsy.

Differences in diagnostic decisions between neurologists may have significant consequences for the individual patient after a visit to one of the neurologists, including treatment and driving restrictions. Agreement between neurologists would, therefore, be highly desirable. This may be enhanced by the use of more sensitive diagnostic methods and unambiguous guidelines.

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