Epilepsy Research (2011) **97**, 231—235

journal homepage: www.elsevier.com/locate/epilepsyres

# Premonitory features and seizure self-prediction: Artifact or real?

**Andreas Schulze-Bonhage**[a,*], **Sheryl Haut**[b]

[a] *Epilepsy Center, University Hospital, Freiburg, Germany*
[b] *Albert Einstein College of Medicine, New York, USA*

Received 10 February 2011; received in revised form 4 August 2011; accepted 8 September 2011

**KEYWORDS**
Epilepsy;
Seizure prediction;
Prodrome;
Trigger factor

**Summary** Seizure prediction is currently largely investigated by means of EEG analyses. We here report on evidence available on the ability of epilepsy patients themselves to predict seizures either by means of subjective experiences (''prodromes''), apparent awareness of precipitants, or a feeling of impending seizure (self-prediction). These data have been collected prospectively by paper or electronic diaries. Whereas evidence for a predictive value of prodromes is missing, some patients nevertheless can forsee impending seizures above chance level. Relevant cues and practical implications are discussed.


Epilepsy is characterized by the spontaneous and unprovoked occurrence of seizures. For patients and observers, these seizures appear to come out of the blue, which has considerable consequences for patients. Even if seizures occur quite rarely (e.g. a few times per year), the fact that their timing is unknown has legal consequences which hinder patients from driving motor vehicles and working in certain professions. Furthermore, spontaneous seizures may present physical risk during everyday activities such as bathing, or during sports, and may lead to social avoidance behaviour and a feeling of loss of control which may result in depression (Schulze-Bonhage and Buller, 2008). As a patient put it, *''It is the unpredictability of it that is really nerve-racking to live with''* (Murray, 1993).

Yet, from the earliest descriptions of epilepsy by Hippocrates, ''warnings'' experienced by patients prior to a visible seizure have been mentioned, and the concept of ''prodromes'' is found in textbooks on epilepsy suggesting that at least some patients experience precursors of seizures. Furthermore, patients often report that they have a sense of when their risk for seizure is high. So the question arises if certain subgroups of epilepsy patients might be able to predict their own seizures.

In principle, seizure predictions of patients could be based on two sources: subjective experiences of ''warnings'' preceding a seizure, and knowledge of factors which increase the probability of a subsequent seizure occurrence. Warnings can be divided into an epileptic aura which may precede a focal seizure by seconds to minutes, and into subjective feelings experienced longer before a seizure, so-called ''prodromes''. Auras can be very useful to patients, if they allow them to retreat from public or potential dangerous situations or even to take counter-measures

* Corresponding author.
*E-mail address:* andreas.schulze-bonhage@uniklinik-freiburg.de (A. Schulze-Bonhage).

0920-1211/$ — see front matter © 2011 Published by Elsevier B.V.
doi:10.1016/j.eplepsyres.2011.09.026

against seizures; they are considered as part of the ictal event, however, so that the experiences during an aura can be considered as subjective detection of a seizure, but not as a prediction.

Prodromes, on the other hand, are believed to be non-ictal events, i.e. events which are not accompanied by ictal discharges in the EEG. Generally, they are considered to precede a seizure by longer time periods of hours to days, and their physiological background has remained obscure so far. Prodromes may thus be preictal events based on which patients might be able to predict an impending seizure.

Aside from such subjective experiences, patients may have knowledge of trigger factors or precipitants of their seizures, upon which they may base a prediction of an impending seizure. It has been hypothesized that true unprovoked seizures, unrelated to precipitants, may actually be rare (Rajna et al., 2008). Such precipitating factors could comprise aspects temporal effects such as circadian or catamenial patterns; acute precipitants such as sleep deprivation, stress or other emotional factors, or simply non-compliance with medication intake. Awareness of any of these factors could lead to valid predictions of increased seizure susceptibility at certain periods of time.

Methodologically, the field of clinical prediction of seizures depends on reliable patient report. Examination of the relevant studies mandates acknowledgement that diary formats differ significantly. Questionnaires are commonly used to identify premonitory features and precipitants reported by patients in a cross-sectional manner. This format, while useful, is subject to recall bias, and the findings must be tested prospectively. Prospective paper diaries have been widely used, but are limited by the lack of time stamping, and the risk of backfilled or retrospectively entered data. Electronic diaries are increasingly utilized in studies of premonitory features and seizure prediction, but present other challenges of data transfer and increased cost.

In the following, studies analysing prodrome- and knowledge-based seizure predictions are addressed separately.

## Prodromes and seizure prediction

Prodromes have been the subject of descriptions in the literature (Dostoyevsky, 1868) and of scientific investigations. Most publications used questionnaires in which patients or at times also caregivers were asked if they would experience changes in their subjective perception or in their behaviour. Depending on the type of question and on the population investigated, rates of 6.9% up to 39% of patients with prodromes were reported (Giuccioli et al., 1990; Hughes et al., 1993; Rajna et al., 1997; Schulze-Bonhage et al., 2006; Scaramelli et al., 2009). A separation from auras was performed in most studies by defining a time interval before an upcoming seizure, which was mostly set as more than 30 min (Schulze-Bonhage et al., 2006), rarely also only more than 5 min before seizure onset. One study analyzed if the phenomenology of ''prodromal'' symptoms was similar to or different from auras; out of 15 patients who were able to describe their experiences with sufficient detail, 12 reported clearly different perceptions during the periods far from a seizure as compared to auras directly progressing into a seizure (Schulze-Bonhage et al., 2006). Four studies analyzed the dependency of a prodrome on the classification of epilepsy; there was a concordantly higher frequency of prodromes in structural as compared to genetic epilepsy (Hughes et al., 1993; Rajna et al., 1997; Schulze-Bonhage et al., 2006; Scaramelli et al., 2009). The exact etiology in cases of structural epilepsy did not appear to play a central role (Rajna et al., 1997).

Based on questionnaires, the phenomenology of subjective experiences during ''prodromes'' was reported. There was considerable variability between the statements of individual patients regarding their prodrome-sensation. Mostly, vegetative symptoms (e.g. palpitations, sweating, gastrointestinal symptoms), or emotional disturbances (e.g. irritability fatigue, anxiety, depression) are reported. Notably when summarizing the range of symptoms reported, there is wide variability between studies, and an impressively wide spectrum of possible complaints is reported (Table 1).

The validity of prodromes as seizure precursors has recently been questioned. Methods used for an analysis of EEG-based seizure prediction methods (Aschenbrenner-Scheibe et al., 2003; Maiwald et al., 2004; Mormann et al., 2005; Winterhalder et al., 2003; Schelter et al., 2006, 2007) generally were not applied to evaluate the validity and prediction performance of prodromes. Taylor (2007) accordingly pointed out that there are no studies which prove that prodromes are preictal events, and has put forward the hypothesis that prodromal experiences may erroneously be considered as seizure-related when epilepsy is considered to be a disease essentially consisting of seizures, and that they might be seizure-independent symptoms related to the neurobiological background manifesting in both, seizures and independent alterations in subjective experiences.

At the Freiburg epilepsy center, a prospective study using handheld computers was performed which intended to identify patients who were able to predict their own seizures. Participants were recruited from a multicentric assessment in 500 patients to identify the subgroup convinced to experience seizure precursors (Schulze-Bonhage et al., 2006). Patients with a minimum seizure frequency of 1/month were assessed prospectively to state if they experienced a prodrome every 12 h, and they were asked to perform free entries whenever a prodrome or a seizure happened. Prediction performance was assessed using a methodology developed for EEG-based seizure prediction algorithms (Winterhalder et al., 2003). Data entries into the handheld occurred patient-initiated at any time, and at standardized points of time every 12 h according to an alarm given by the handheld to the patient. Patients entered prodromes and their type as well as seizures and indicated when either had occurred. Out of nine patients in whom at least 4 weeks of continuous entries were available, none had a predictive performance which was statistically better than to be expected from a random predictor, even when the false prediction rate was chosen according to the patient's performance and when various seizure occurrence periods up to 24 h were analyzed (Maiwald et al., 2011).

It is of interest that in this study not only the time of seizures and prodromes as reported by the patient was stored but also data entry times were time stamped. An analysis of time stamps of entries for seizures and prodromes