**Epileptic Seizure Prodromes**

**Notes**

**Is the clinical phenomenon of “prodrome” a reality?**

There is evidence from a significant number of studies indicating a range of preictal symptoms (headache, nausea, mood or behavioural change are predominant) experienced by patients or observed by carers that terminate at seizure onset. In many cases patients or carers identify symptoms as seizure precursors.

Some studies have specifically addressed this question (‘Can patients with epilepsy predict their seizures?’; Haut, Sheryl R et al; 2007; ‘Seizure anticipation: Are neurophenomenological approaches able to detect preictal symptoms?’; Petitmengin, Claire et al; 2006; ‘Hungarian multicentre epidemiological study of the warning and initial symptoms (prodrome, aura) of epileptic seizures’; Rajna, P et al; 1997; ‘Prodromal symptoms in epileptic patients: Clinical characterization of the pre-ictal phase’; Scaramelli, Alejandro et al; 2009… ) whilst preictal symptoms are also frequently reported in research not primarily focused on seizure prodrome (‘Headaches associated with symptomatic epilepsy in adults’; Atic, S et al; 2014...).

**How long before a seizure or cluster of seizures are clinical prodromes experienced?**

(?) Most studies define preictal windows for prodromal symptoms, usually with a lower bound of 30 mins before seizure onset. Upper boundary is often set at 24 h before seizure onset though some studies include prodromal symptoms experienced several days, and sometimes up to a week, prior to the next seizure. Prodromal symptoms are often characterized as lasting until seizure onset.

Specific, differential data on time-to-seizure for individual symptoms is not frequently reported. A paper by Scaramelli et al (‘Prodromal symptoms in epileptic patients’; 2009) reported more narrowly defined time-to-seizure intervals for a range of prodromal symptoms (“Thirty percent of prodromes appeared less than 6h prior to seizure emergence, Five percent of PS may have started before the defined time window, i.e. 24-48 h prior to seizure onset. No association was found between prodrome type and delay to seizure occurrence.” All symptoms and time-to-seizure intervals in this study were patient-reported.

**Is the prodome clinically useful for reducing risk associated with seizures?**

Some studies (‘Hungarian multicentre epidemiological study…’; Rajna et al; 1997; ‘Initial symptoms, precipitant factors, and techniques to control epileptic seizures: The carer’s perspective’; Pinikahana, Jaya et al; 2009; ‘The lived experience of initial symptoms of and factors triggering epileptic seizures’; Pinikahana, Jaya et al; 2009…) suggest (self-reported) patient ability to arrest seizures by personal (behavioural) intervention strategies in response to prodromes. An effective level of sensitivity and specificity has been observed with respect to patient self-prediction which could potentially and is anecdotally useful in helping patients to take precautions in anticipation of an expected seizure.

Prodromes experienced by patients are often very specific to that individual. Time-to-seizure and/or duration of prodromal symptoms are also often highly variable. Often prodromes are reported many hours or days before the next seizure. Do these factors limit clinical usefulness?

Some studies have reported finding no clinical benefit of prodrome based on similar criteria to these. Petitmengin et al; 2006 (‘Seizure anticipation: Are neurophenomenological approaches able to detect preictal symptoms?’) reported that in a study of patients with partial epilepsy, prodromes were “not specific enough for clinical use” though this study was apparently based on findings from a small number of patients reporting aura or prodrome.

In some reports, prodromal mood or behavioural change is primarily evident to observers (family or cares) and patients themselves may not be aware of these markers (Scaramelli et al; 2009).

**Have the EEG algorithms to predict seizures been proven?**

Since 2007 algorithms have been tested for stastical significance against a random chance predictor. Most algorithms reported on since 2007 perform better than chance for sensitivity (% of seizures predicted) and specificity (usually measured as either False Positive Rate (number of false positives/hr) where 0.15FP/hr is considered the maximum acceptable rate for clinical applications) or % time under warning).

**Which is the best EEG algorithm to predict seizures?**

(?) There have been recent reviews comparing algorithm performance.

“Automated EEG analysis of epilepsy: A review”; Acharya, U Rajendra et al (2013).

“EEG seizure detection and prediction algorithms: a survey”; Alotaiby, Turkey N et al (2014).

“Seizure prediction for therapeutic devices: a review”; Gadhoumi, Kais et al (2016).

**Are EEG algorithms to predict seizures of practical use in the real-life situation?**

Possibly. Statistically significant results are frequently achieved for sensitivity and specificity measures vs random predictors.

The anticipated application of EEG algorithms to seizure management is in the field of implantable closed-loop intervention devices (vagal-nerve stimulators etc) or personal warning systems that might (eg) prompt patient to take preventative or precautionary action.

There has been a trial of an implanted EEG monitor, coupled with a patient warning device, in Australian clinics in 2013. The study was primarily concerned with trialing the feasibility and long-term tolerability of the device itself (manufactured by NeuroVista) with secondary consideration of system performance.

(‘Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study’; Cook, Mark J et al; 2013).

Due to the highly individualistic nature of preictal EEG patterns (both intra-patient and across seizures in the same patient) a generalised seizure-prediction algorithm has not been demonstrated. Machine predictors are trained in EEG features on an individual patient basis and learned patterns are often not demonstrated to be successful as seizure predictors across patients.

The majority of studies have tested algorithm performance on the same sets of long-duration, continuous EEG-monitoring records from the Freiburg or EPILEPSIAE (European) EEG databases. Both offer only a limited number of patient records (the Freiberg database contains records from 21 patients, the EPILEPSIAE significantly more (? actual number)). It is not clear whether significant prediction performance retrospectively achieved from small data sets can be demonstrated to be similarly performant.

Some of the proposed algorithms, whilst demonstrating statistically significant performance are computationally expensive and probably not suited to real-time applications.

A patient perspective on devices is reported in “Views of patients with epilepsy on seizure prediction devices”; Schulze-Bonhage, Andreas et al; 2010.

**Are other physiological/neurophysiological parameters, apart from EEG variables, of value in predicting seizures?**

(?) ECG measures of preictal tachycardia have been researched, but time-to-seizure is generally < 5 mins in studies. Change in HR is often observed between 220s and 80s before seizure onset.

BOLD/brain haemodynamics have been mentioned as potential seizure predictors. Often phenomena are observed before correlated EEG features. Difficult to imagine clinical application.

Preictal cell swelling/extra-cellular space constriction has been hypothesised (Toward new paradigms of seizure detection; Binder, Devin K; Haut, Sheryl R (2013)).

**How long before a seizure or cluster of seizures are “neurophysiological/EEG” prodromes experienced?**

(?) TODO: Should be possible to extract this information from algorithm papers

**How do EEG or other physiological parameters link with the clinical symptoms of prodrome?**

Study by DuBois et al (‘Seizure prediction and recall’; 2010) might be useful in answering this question (ask FB for access to full text).

Sue et al (‘Subjective and objective premonitory symptoms as epileptic prodromes’; 2009) state EEG monitoring during patient-reported prodromes reveal no ictal discharge. In this study 9 patients with prodrome had concurrent EEG monitoring and “no significant changes were observed” in EEG.

Alternatively, Zawadzka et al (2015) assessed correlation between preictal headache and EEG changes (‘Ictal and periictal headache in children with epilepsy – Correlation with type of seizures and EEG-changes’) and Schulze-Bonhage et al (2009) reported “Premonitory symptoms occur at similar periods prior to seizures as anticipatory EEG-changes have been reported using methods from time series analysis” (‘Seizure anticipation by patients with focal and generalized epilepsy: A multicentre assessment of premonitory symptoms’).

**Can neurophysiological/EEG parameters be linked to clinical symptoms of prodrome in such a way as to teach patients to predict seizures, on the basis of clinical features alone, more reliably in real life?**

See earlier point on link between EEG parameters and clinical symptoms.

Petitimengin et al (‘Microcognitive science: bridging experiential and neuronal microdynamics’; 2013) describe the possibility of training patients in experiential awareness. This might have some relevance in teaching patients to recognise and quantify preictal symptoms.