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# Prodromal symptoms in epileptic patients: Clinical characterization of the pre-ictal phase

Alejandro Scaramelli *, Patricia Braga, Andrea Avellanal, Alicia Bogacz, Claudia Camejo, Isabel Rega, Tamara Messano, Beatriz Arciere

*Instituto de Neurología, Hospital de Clínicas, Av. Italia S/N, Montevideo 11600, Uruguay*

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ABSTRACT

Although recent advances in seizure anticipation have been achieved with the development of several biomathematical electroencephalographic (EEG) methods, pre-ictal clinical phenomena have not been extensively investigated. The aim of the study was to thoroughly analyze premonitory or prodromal symptoms (PS) in a randomly selected sample of 100 adult epileptic patients. A semi-structured protocol was used for in-person interviews to both patients and observers. PS were found in 39% of patients, the most frequent ones being behavioral, cognitive and mood changes. Both patients with focal and generalized epilepsies reported prodromes, although they were more frequently found in the former group. PS were mostly perceived preceding complex partial and generalized tonic–clonic seizures. Prodromal symptoms were reported to have an insidious onset and their duration ranged from 30 min to several hours. The potential value of prodromes in seizure anticipation would allow the use of preventive and therapeutic measures, including drugs, neurostimulation procedures and behavioral intervention.


## 1. Introduction

Epilepsy is one of the most common neurological disorders, with a prevalence that exceeds 1% worldwide. These patients' quality of life tends to be impaired, not only due to social stigma and the increased risk of injury and sudden unexpected death, but also because of the unpredictability of seizures. The possibility of forecasting the occurrence of seizures, through the recognition of events taking place during the pre-ictal phase, would obviously have a positive impact on treatment efficacy and quality of life.

In recent years, advances in this field have been achieved thanks to various quantified electroencephalographic (EEG) studies.[1–6] However, the clinical phenomena occurring during this pre-ictal period, i.e. prodromal symptoms (PS) or prodromes, have not been extensively investigated. There are early references to the subject [7–9] and a few studies have reported mainly on frequency and type of symptoms using different approaches.[10–13] A prospective survey assessing patients' seizure self-prediction has been recently published.[14] A more detailed description of clinical changes during this period[15,16] has been followed by a neurophenomenological approach to symptoms preceding seizures in 9 patients.[17] A better knowledge of these prodromal or premonitory symptoms would open a "clinical window" to pre-ictal phenomenology and seizure prediction.

The aim of this study was to analyze pre-ictal events from a clinical point of view. Specific objectives were: (i) to describe the prevalence and quality of prodromal symptoms in the study population, (ii) to analyze the association between prodromes and several variables such as age, sex, seizure type and frequency, epilepsy syndrome and comorbidities.

## 2. Material and methods

### 2.1. Population

Patients with definite diagnosis of epilepsy, either partial or generalized, older than 14 years were considered for the study. Exclusion criteria were: (1) severe mental retardation (unless a reliable observer was available) and (2) coexistence of non-epileptic seizures, whenever it was difficult to clearly distinguish between both types of episodes.

* Corresponding author. Tel.: +598 2 7120168; fax: +598 2 4874080.
*E-mail address:* scaram@adinet.com.uy (A. Scaramelli).

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According to the abovementioned inclusion/exclusion criteria, 100 patients were selected through a systematic sampling from the population of outpatients assisted by the authors between November 15, 2004 and February 15, 2005.

### 2.2. Methods

Prodromes were operationally defined as signs or symptoms, perceived by the patient and/or observer as premonitory, appearing up to 24 h preceding seizure onset.

Auras, here understood as those subjective symptoms occurring at the start of a seizure and lasting less than 15 min, were specifically excluded.

In-person interviews were performed in all patients and available observers using a semi-structured protocol, beginning with an open question: "is there anything, during the preceding 24 h, that announces that you (he/she) will have a seizure?"

Subsequently, a pre-established questionnaire, including specific questions on potential PS (Fig. 1), was applied.

For each PS reported, information on detailed semiological description, duration, time to seizure and associated seizure type, was retrospectively collected. Data on seizure frequency were obtained from seizure diaries.

Patients and observers who reported cognitive, behavioral and/or mood changes as a putative PS were asked to describe those phenomena in detail, and they were referred to an additional interview performed by our group's psychiatrist (T.M.).

Information on age, sex, epilepsy syndrome, seizure type and frequency, duration of epilepsy, history of psychiatric disturbances and treatment was also collected. Association between each PS and different clinical variables was investigated through chi-square and T test, applied to string and quantitative measures respectively, with a 0.05 significance level.

## 3. Results

### 3.1. Demographic data

One hundred patients (60 females, 40 males) with a mean age of $32 \pm 13$ years, were enrolled. Distribution by epileptic syndromes, according to the international classification [18] showed 77 partial epilepsies (35 symptomatic, 42 cryptogenic) and 23 generalized epilepsies (18 idiopathic, one symptomatic and four cryptogenic). Regarding seizure type,[19] of the 77 patients with focal epilepsies, 59 had generalized tonic–clonic seizures (GTCS), 51 had simple partial seizures (SPS) and 43 reported complex partial seizures (CPS). All the 23 patients with generalized epilepsies had GTCS; 13 patients also had myoclonic jerks and 5 presented with associated absence seizures.

Mean duration of epilepsy was $17.8 \pm 14$ years.

Half the patients (50) had a seizure frequency $<$6 year; 47 had a higher frequency, whereas in three cases this information could not be accurately obtained.

At the time of interview, 52 patients were on monotherapy (Phenytoin 34, Carbamazepine 18, Valproate 9 and Clonazepam 1), 32 were receiving polytherapy and six patients were off medication.

Sixty-seven patients had no cognitive impairment; 29 had mild cognitive deficits, and relevant mental retardation was present in four cases. Thirteen patients revealed an associated history of psychiatric disturbances, particularly depression. No other relevant co-morbidity was consistently found in this population.

### 3.2. Prevalence of prodromal symptoms

Prodromal symptoms were found in 39 out of 100 patients.

Concerning the number of PS evoked in each patient, 18 revealed one PS, 14 identified two PS, and seven patients referred

| | Yes / No | Patient/Observer |
|---|---|---|
| **a. Is there anything, during the preceding 24 hours, that announces that you (he/she) will have a seizure?** | | |
| **If Yes, explain:** | | |
| **b. Specific questions on putative Prodromes** | **Yes / No** | **Patient/Observer** |
| 1. Headache | | |
| 2. Pain (other than headache) | | |
| 3. Paresthesias ("pins and needles" / numbness) | | |
| 4. Sleep disturbances (insomnia, excessive somnolence) | | |
| 5. Appetite disturbances | | |
| 6. Changes in sexual function | | |
| 7. Dysthermia (disturbed temperature related manifestations) | | |
| 8. Voiding changes | | |
| 9. Gastrointestinal symptoms (nausea, vomiting, abdominal pain, etc.) | | |
| 10. Fatigue | | |
| 11. Behavioral changes (irritability, aggressiveness, etc.) | | |
| 12. Mood changes (depressive symptoms, apathy, euphoria) or inappropriate anxiety | | |
| 13. Cognitive changes (attention, concentration, memory, slow/fast-thinking, temporal-spatial disorientation, etc.) | | |
| 14. Speech disturbances (decreased initiative, anomia, dysarthria, prosodic changes, etc.) | | |
| 15. Other (explain) | | |

**Fig. 1.** Prodromal symptoms—questionnaire.

**Table 1**
Type and frequencies of reported prodromal symptoms (PS) in the study population.

| Type of PS | *N* |
|---|---|
| Behavioral changes | 13 |
| Cognitive disturbances | 11 |
| Anxiety and mood changes | 9 |
| Fatigue | 7 |
| Sleep disturbances | 7 |
| Dysthermia | 6 |
| Speech disturbances | 4 |
| Voiding changes | 4 |
| Gastrointestinal symptoms | 3 |
| Headache | 2 |
| Changes in appetite | 2 |
| Paresthesias | 1 |
| Pain (other than headache) | 1 |
| Other | 5 |
| Total | 75 |

three or more PS. Therefore, 75 PS were reported by these 39 patients.

PS were identified, either by the patient or an observer, in response to the open question, in 29 cases.

### 3.3. Description of PS

The type of reported PS and their frequencies are shown in Table 1.

As shown in this table, the most frequently reported prodromes pertain to the neuropsychiatric domain: behavioral, cognitive and mood changes. Below is a more detailed description of these three main categories based on the semiological characteristics collected through the initial questionnaire and on the subsequent psychiatric interview.

#### 3.3.1. Behavioral changes

They were similarly described by all patients and observers, being basically characterized by irritability and decreased tolerance, lasting several hours. Some expressions used by patients were: "Several hours before I have a seizure I can't stand myself" (Patient 49); "I easily get angry and I am in bad temper; I cry easily. This lasts between approximately 4 h and a whole day, and it disappears when I have a seizure" (Patient 64). Examples of expressions used by observers were: "He is normally in good temper, but a few hours before he has a seizure, he looks upset and is irascible" (Patient 40). "... he responds angrily to everything" (Patient 66). This type of prodrome was referred as the single premonitory symptom in 5 out of 13 patients. It was found to be overlapped to fatigue in two patients and to changes in appetite in one patient. Two patients presented previous psychiatric history.

#### 3.3.2. Cognitive disturbances

The description of these symptoms was also quite homogeneous: bradipsychia, increased latency in verbal and motor responses, clumsiness, short-term memory and attention disturbances were the most frequently evoked manifestations. Some patients referred: "I have the feeling of slow thinking and I have to think everything twice; I can't remember what I have to do. It seems as if my mind were in slow motion" (Patient 83). "Sometimes, I may intend to go to the bathroom and end up in my bedroom" (Patient 12); "I want to do something and I can't. I keep walking around and don't manage to do anything" (Patient 49). Some quotations from observers were: "She shows indecision and slowness; ...that day we were too late" (Patient 34). "During those hours, nobody knows what she wants to do" (Patient 25). Only one patient presented a different profile: sensation of fast thinking, beginning a few hours prior to a seizure (Patient 31).

#### 3.3.3. Anxiety/mood changes

This group of symptoms included tension, uneasiness or, alternatively, sadness, apathy and indifference. Quoting patients and observers: "I don't care about anything and I don't want to do anything" (Patient 61). "I am more sensitive than usually; I feel like crying without any reason" (Patient 8). "I have a mixed feeling of distress and joy; at the same time I have the sensation that something is going to occur" (Patient 70). This patient's husband expressed: "She is always made-up and well-dressed; the day she isn't, we know she's going to have a fit". "Several hours before a seizure she is blue and she says she doesn't know why" (Patient 48). Elation was reported in only one case (Patient 13). None of these patients had a psychiatric history.

#### 3.3.4. Other less frequently reported prodromes

*Fatigue*: It was mainly referred as a physical complaint, being sometimes described as lack of energy. Usually, fatigue was noticed a few hours before either partial or generalized seizures. It was described in association with behavioral changes (in three out of seven cases), dysthermic sensation (3/7) and cognitive disturbances (2/7).

*Sleep disturbances*: In this group, all patients but one reported excessive day somnolence, frequently requiring the interruption of activities in order to sleep. The remaining patient referred "difficulties in getting asleep" the night preceding a generalized tonic–clonic seizure.

*Dysthermia*: Four patients reported a subjective unusual and unexplained cold sensation announcing their seizures. Another patient reported feeling hot. The remaining patient reported coldness followed by a hot sensation with excessive sweating lasting about 20 min, occurring 2–3 h before a seizure.

*Speech disturbances*: They consisted of dysarthria and less frequently anomias. For instance, patient 83 reported "slurred speech" and patient 16 said: "People do not understand what I say; they say I speak as if I were drunk"

*Voiding changes*: In all cases it was described as an increase in number and volume of micturitions, lasting several hours prior to seizures.

*Gastrointestinal symptoms*: Two patients referred diarrhea and one reported vomiting, during a period of a few hours.

*Headache*: Only two patients mentioned headache within the period defined as prodromal. One of them had hemicraneal cephalalgia and vomiting, but he was free of interictal migraine.

*Changes in appetite*: Both patients reporting this symptom had an increased appetite. Patient 64 put it into these terms: "For about 6–8 h and until the seizure begins, I am terribly hungry, much more than usually".

Two patients referred *pallor* a few hours preceding seizure onset.

Concerning *time of occurrence*, PS appeared in a variable period of time (generally several hours) before seizure onset, within the operationally defined time window. Thirty percent of prodromes appeared less than 6 h prior to seizure emergence. Five percent of PS may have started even 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.

Prodromes were mainly perceived as insidious changes rather than symptoms of abrupt onset or clear-cut temporal limits. Their *duration* ranged from 30 min to several hours; 50% of patients specified that these symptoms used to last up to the following seizure.

**Table 2**
Type of most frequently reported prodromal symptoms (PS) according to the source of information.

| Type of PS | Patient only | Patient and Observer | Observer only |
|---|---|---|---|
| Behavioral changes | 4 | 1 | 7 |
| Cognitive disturbances | 4 | 0 | 6 |
| Anxiety/mood changes | 3 | 3 | 2 |
| Fatigue | 4 | 1 | 1 |
| Sleep disturbances | 2 | 0 | 3 |
| Speech disturbances | 2 | 2 | 0 |

Regarding the *source of information*, presence of prodromes was exclusively claimed by an observer in 12 patients, while in 27 cases they were recalled by the patient him/herself or both by patient and observer. We did not find a statistically significant difference between the type of PS identified by patients themselves and those described by observers (Table 2). Nevertheless, most cases of either fatigue or speech disturbances were noticed predominantly by the patient, while behavioral changes were more frequently reported by observers.

### 3.4. Relationship between prodromes and different variables

Patients with a relatively high frequency of seizures reported PS more frequently than those with a better seizure control (x2; $p = 0.006$).

In general, there was no association between seizure type and type of PS recalled. However, in the subgroup of patients reporting cognitive disturbances as PS, these symptoms usually preceded a generalized tonic–clonic seizure (9 out of 11 cases).

Among patients with GTC seizures, 32.9% reported prodromal symptoms preceding such type of seizures. This occurred in 32.6% of those with CPS, and in 7.6% of those with myoclonic seizures. Only 3.9% referred prodromes before their SPS and none preceding their absence seizures. These differences were statistically significant (x2, 4DF; $p = 0.00037$).

Prodromes were more frequently evoked in patients with partial epilepsies (42%) as compared with those with idiopathic generalized epilepsies (IGE) (26%), without reaching statistical significance (x2; $p = 0.2$).

Although the group of IGE patients is too small for statistical analysis, it showed some common features: all subjects reported more than one PS and they were only noticed by the patient. Concerning the type of PS recalled, all these IGE patients referred at least one PS related to neuropsychiatric changes. Other prodromal symptoms that were more frequently reported in this subpopulation were sleep disturbances and a dysthermic sensation.

None of the 9 patients who experienced pre-ictal mood changes presented a past medical history of depression or anxiety disorders.

No statistical differences were found regarding age, sex and disease duration between the group that reported PS and the one that did not.

## 4. Discussion

In a context of scarce investigations focusing on the clinical changes preceding seizure onset, our study intends to contribute to the clinical characterization of this pre-ictal phase.

### 4.1. Prevalence of prodromal symptoms

The percentage of patients in whom PS were identified (39%) is by no means negligible. Rajna et al.[12] reported a figure of 47%, which is not comparable since their study included auras. On the other hand, the prevalence found in our study is higher than that referred by Giuccioli et al.[10] Hughes et al.[11] and Schulze-Bonhage et al.[13], who reported 8.6%, 29% and 6.9% respectively. Their lower prevalence could be due to methodological differences, namely the consideration of the data given only by patients and "spontaneously". Inclusion of an observer's anamnesis in the present study increases the chances of finding prodromes, while offering an "objective" source of information. If interviews to observers had not been added, 12% of cases with PS could have remained undetected.

We also found that prodromes were more frequently identified in patients with high seizure frequency. This could be related to the need of a repetitive experience in order to more easily perceive a connection between a potential PS and a seizure.

Both patients with focal and generalized epilepsies presented prodromes, although they were more frequently found in cases with partial syndromes, which would be consistent with a previous report. [13]

Interestingly, PS were perceived more frequently preceding CPS and GTCS, being rarely reported before other seizure types.

### 4.2. Type of PS

Concerning the type of PS (Table 1), there is a marked overlap between our findings and those reported by most other groups,[10–12,17] thus giving support to "what happens" during the pre-ictal phase from the clinical point of view. Transcultural homogeneity is a striking finding, particularly regarding behavioral symptoms. Most prodromes belong to the group of neuropsychiatric modifications, such as behavioral, mood and cognitive changes. The subtle nature of these symptoms, in contrast to other more overt clinical phenomena like motor manifestations, could explain why the recognition of prodromes has not been so easy, and why research in this area has not been more extensive in the past.

Among mood changes, depressive symptoms are by far more frequent than elation symptoms. This is also in accordance with other authors' findings.[10–12,16,17,20] Interestingly, such concordant observations have been made using quite different approaches, including scales applied during long-term monitoring[16] and phenomenological strategies.[17]

An increased appetite, polyuria, diarrhea, pallor and/or coldness were found to be common transitory symptoms associated to impending seizures. These PS have not been described in other surveys. Methodological issues, mainly the application of a semi-structured protocol in our study, specifically searching for this type of symptoms, may explain the results.

On the other hand, headaches have not been found to be so frequent in our study as in other surveys.[10–13]

The duration of prodromes in this population was reported to be quite prolonged. This fact not only clearly distinguishes them from auras, but it also means that the identification of PS in certain patients provides a period of several hours for potential interventions to avoid an impending seizure.

A significant number of patients (50%) reported that prodromes would not fade away until the seizure occurred, thus stressing their pre-ictal character and suggesting the presence of a developing process that ends up with a seizure.

It should be noticed that in some patients PS may begin even earlier than our arbitrarily defined 24-h time window.

### 4.3. Differentiating PS from seizures and from other peri-ictal phenomena

Prodromal symptoms must be distinguished from auras, which unequivocally belong to the seizure period. Consequently, the

latter were not taken into account in the present study. The time profile helped us to clearly differentiate auras from PS, which typically lasted several hours.

Furthermore, prodromal symptoms can usually be told apart from seizure-precipitating factors. However, in some cases, such as sleep disturbances, this differentiation may not be so easy,[10] since insomnia and sleep deprivation have a well-known role as seizure precipitants. The fact that the most frequently reported sleep change in our study was an increased somnolence (and most patients actually slept more) made it easier to distinguish these sleep changes from triggering factors. Similarly, behavioral modifications, apart from acting as premonitory symptoms, could either precipitate or inhibit seizures, according to the concept that human epileptogenic brain may be behaviorally modulated.[21–23] Therefore, it is likely that while sleep disturbances and behavioral changes may express that a seizure is "building up", they could alternatively or additionally facilitate seizure irruption.

PS can also be distinguished from prolonged seizures because they have an insidious onset and their semiology is different from that of the patient's habitual seizures. However, complex partial status or absence status could not be strictly ruled out in cases with behavioural or cognitive PS since we conducted no EEG recordings during the prodromal phase. In this sense, EEG evidence of non-convulsive status epilepticus has been found in two patients out of five undergoing video-EEG from a group of 23 patients with experiential epileptic prodromes.[24] Therefore, this possibility should be taken into account, at least in a small percentage of patients reporting this type of prodromes.

Theoretically, it could be argued that some symptoms, here characterized as prodromes, might correspond to side effects of antiepileptic drugs. However, a crucial attribute of the symptoms that were defined as PS is that they were noticed only in the time frame that preceded habitual seizures.

### 4.4. Limitations of the study

Our study has some limitations that must be taken into consideration: (1) its design is retrospective, and although that is valid for collecting the quality of pre-ictal symptoms, it is not reliable enough to allow for sound conclusions regarding seizure prediction. A prospective study would be required to assign prodromes a truly predictive value; (2) we have found some difficulties trying to define the temporal window for prodromes. In this sense, there is no accepted pre-established time span. We chose 24 h arbitrarily in order to enhance sensitivity using a relatively wide frame, and to make it easier for the patients to remember; (3) we were unable to determine duration of PS and time elapsed to seizures more precisely, probably due to the retrospective nature of the study.

### 4.5. Practical and therapeutic implications

Considering their prevalence and their potential value in seizure anticipation, prodromal symptoms should be routinely assessed in the anamnesis of epileptic patients in daily clinical practice.

From a clinical perspective, the identification of prodromal symptoms, although less accurate than EEG algorithms in temporal terms, would offer a longer time window for a broader range of therapeutic possibilities. Treatment modalities could then vary from preventive measures, such as avoiding potentially risky activities, to pharmacological or behavioral interventions. Furthermore, a deeper knowledge of the mechanisms underlying prodromes may allow the design of specific "anti-ictogenic" drugs and/or neurostimulation paradigms, capable of interrupting the pre-ictal cascade.

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