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# **Anticipatory anxiety of epileptic seizures: an overlooked dimension linked to trauma history**

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## **Abstract**

**Objective:** Fear of having a seizure called anticipatory anxiety of epileptic seizure (AAS), constitutes a daily life burden but has been rarely studied. Our aim was to assess the prevalence and the determining factors of AAS in patients with drug-resistant focal epilepsy, **a dimension that has not been thoroughly investigated before.**

**Methods:** We conducted an observational, prospective study enrolling patients with drug-resistant focal epilepsy. The psychiatric assessment aimed to evaluate psychiatric comorbidities, trauma history, and quality of life using hetero-evaluation and self-assessment tools. Dimensions of anxiety specifically related to epilepsy (peri-and-inter-ictal) were explored as exhaustively as possible.

**Results:** AAS was found in 53% of the 87 patients. We compared the two groups of patients: with or without AAS. Patients with AAS had a significantly shorter duration of epilepsy ( $p=0.04$ ). There was no difference between groups with respect to psychiatric disorders, except for cannabis dependence, more frequent in patients with AAS ( $p=0.02$ ). Compared to patients without AAS, those with AAS presented more subjective ictal anxiety ( $p=0.0003$ ) and postictal anxiety ( $p=0.02$ ), were more likely to avoid outdoor social situations due to seizure fear ( $p=0.001$ ), and had a poorer quality of life (QOLIE emotional well-being;  $p=0.03$ ). Additionally, they had experienced more traumatic events in their lifetime ( $p=0.005$ ) and reported more frequently a feeling of being unsafe during their seizures ( $p=0.00002$ ).

**Significance:** AAS is a specific dimension of anxiety, possibly linked to trauma history. AAS is strongly linked to subjective ictal anxiety but not to the objective severity of seizures or frequency.

**Keywords:** Drug-resistant focal epilepsy, anxiety, trauma, psychiatric comorbidities, anticipatory anxiety of seizures

**Short running title :** *Anticipatory anxiety of epileptic seizures*

## **Key bullets**

- Over half (53%) of our patients with refractory focal epilepsy suffered from anticipatory anxiety of seizures (AAS).
- AAS, a potentially debilitating condition leading to avoidance behaviour and poor quality of life, is largely overlooked in people with epilepsy.
- AAS was strongly linked to subjective ictal anxiety but not to objective severity of seizures or frequency.
- Patients with AAS experienced more trauma in their lifetime and reported more frequently a feeling of danger during their seizure
- A simple question could improve screening: “In your everyday life, are you afraid of having an epileptic seizure?”

## 1. Introduction

People with epilepsy (PWE) are more likely to develop psychiatric comorbidities than the general population<sup>1, 2, 3</sup>. Previous studies exploring links between epilepsy and psychiatry have essentially focused on depression and psychosis. Anxiety has been described as the forgotten psychiatric comorbidity in PWE<sup>4</sup>. For a long time, anxiety disorders were considered as the second most frequent psychiatric comorbidity after depression in PWE but anxiety disorders are now recognized as being more prevalent than depression in this population<sup>5, 6, 7, 8</sup>. Many important outcomes are significantly impacted by anxiety in epilepsy, including quality of life, seizure status and even mortality<sup>9</sup>. Indeed, anxiety has been reported as being the most significant predictor of reduced quality of life in PWE, explaining 27% of the variance compared with 12% for depression, and 3% for seizure frequency<sup>10</sup>.

Anxiety disorders addressed in previous studies of PWE were generally restricted to non-specific disorders like generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), agoraphobia, panic disorder, and social phobia<sup>11</sup>. In contrast, anxiety symptoms directly linked to epilepsy seizure or reflecting problematic adjustment to living with epilepsy (e.g., exaggerated fears of social or physical consequences of having a seizure, excessive worry about seizures) are less described<sup>12, 13</sup>. A recent review focusing on specific anxiety in epilepsy distinguished between peri-ictal anxiety symptoms and specific interictal anxiety disorder in PWE<sup>14</sup>.

Peri-ictal anxiety is classified according to their temporal occurrence to seizures: pre-ictal (preceding a seizure), ictal (presenting as part of the seizure symptoms and signs), and postictal (occurring within 72h of a seizure). Ictal fear, or ictal manifestation of anxiety, has been extensively studied. It is encountered in up to 37.5% of medial temporal seizures<sup>16</sup> and is a direct result of amygdalar epileptic discharge<sup>8, 17, 18</sup>. Besides this very specific ictal symptom, a lot of patients report their subjective experience of seizures as an extremely anxious experience. We explored this anxious experience during epileptic seizures, we have called this: subjective ictal anxiety. To the best of our knowledge, these aspects have never been specifically studied to date.

Specific interictal anxiety disorders occur independently from seizures. Interictal dysphoric disorder, defined as the association of affective and anxious dimensions, used to be considered as a mood disorder or as a mixed anxio-depressive disorder<sup>15</sup>. ~~However, other entities have been described more recently, such as seizure phobia, epileptic social phobia, and epileptic panic disorder<sup>14</sup>. Nevertheless,~~ the most widespread entity is the fear of having a seizure, as mentioned by the International League Against Epilepsy (ILAE)<sup>19</sup> and in an old case report<sup>20</sup>. We therefore decided to focus on this dimension in the present work and use the term “anticipatory anxiety of seizure” (AAS) to identify anticipatory anxiety of having an epileptic seizure<sup>14</sup>. AAS is described as a daily persistent fear, dread, or excessive worry of having a seizure. It can be conceptually compared to the anticipatory anxiety reported in panic attacks ~~where patients live with a permanent, incapacitating anticipatory anxiety, which is a source of suffering and can be associated with agoraphobia or avoidance behaviour. The same type of dynamic can be found in PWE who suffer from a feeling of insecurity as a consequence of the unpredictability of the seizures. Nevertheless,~~ to the best of our knowledge, neither the prevalence of AAS nor its potentially related factors have been studied to date. Our exploratory study aimed to measure the prevalence of AAS, to compare the profile of patients with and without AAS, and to explore the determining factors (epileptic and psychiatric) linked to AAS in patients with focal refractory epilepsy.

## **2. Methods**

### ***Population***

We conducted an observational prospective study in the tertiary epilepsy centre of Nancy, France. We enrolled consecutive patients with drug-resistant focal epilepsy (according to the ILAE criteria<sup>12</sup>) undergoing systematic psychiatric evaluation that was part of their pre-surgical work-up over 16 months. The profile of patients with epilepsy is highly heterogenous. We chose to focus on the patients with drug-resistant focal epilepsy who responded to a structured psychiatric evaluation, in order to have an homogenous group of patients.

All the patients were aged 18 and over, were able to communicate in written and spoken French. All participants signed an informed consent to use their anonymously collected data as a part of the assessments and usual examinations during their hospitalization and / or consultation. In addition, a visible poster in the unit reminds that they can object to such a use of their data at any time.

### ***Psychiatric evaluation***

Psychiatric assessment was conducted by trained psychiatrists working in our epilepsy unit. The objective was to evaluate as exhaustively as possible psychiatric comorbidities common to the entire population and psychiatric disorders specific to epilepsy, and especially the different dimensions of anxiety related to epileptic seizures. We used structured interviews, hetero-evaluation by a psychiatrist and self-assessment tools. This methodology is part of the clinical protocol used for routine screening in our epileptology department, that includes systematic psychiatric assessment.

### ***Collected data***

The collected *sociodemographic data* were age, sex, marital status, and occupation.

The *epilepsy data* comprised history of febrile seizures, age at epilepsy onset, duration of epilepsy at evaluation, type of seizures, epilepsy localization, epilepsy lateralization, duration and frequency of the seizures reported by patients and witnesses, fall, injury or loss of consciousness, number of on-going antiepileptic drugs, and presence of antiepileptic drug with known negative psychotropic effects (topiramate, levetiracetam, zonisamide, perampanel, lacosamide). Lateralization and localization of seizure foci was based on the recorded seizures during long-term video-EEG monitoring and medical imaging in all patients, and additional video-stereo-electroencephalography (SEEG) when available. Limbic seizures were defined as seizures with a clear medial temporal onset, either proven on SEEG recordings or on converging findings from phase 1 presurgical work-up: history of childhood febrile seizures, hippocampal sclerosis, exceptional secondary generalization, typical medial temporal lobe seizure semiology involving viscerosensitive symptoms, dreamy-state or

déjà-vu, warning, delayed loss of contact, delayed oro-alimentary and gestural automatisms, and duration of seizures > 1min.

We collected data on *trauma history*. Trauma history in childhood was explored through the Childhood Trauma Questionnaire (CTQ), which looks for forms of sexual abuse, physical abuse, and emotional abuse in childhood<sup>17</sup>. Through detailed questioning we also screened for a traumatic sexual, psychological/emotional and physical event that occurred in adulthood. If several forms of trauma were identified in the same patient we called it “multiple trauma”. Post-traumatic stress disorder (PTSD) was assessed using the Mini International Neuropsychiatric Interview (MINI).

We noted if there was family **psychiatric history**, a history of suicide attempts, or hospitalization in a psychiatric unit. Information about prescription of **psychotropics** (antidepressants or antipsychotics) was also collected.

*Psychiatric comorbidities* were evaluated and classified according to their temporal link with seizures.

### *Peri-ictal disorders (disorders with a temporal link to seizures)*

Pre-ictal disorder. Pre-ictal anxiety symptoms can occur a few hours or days before a seizure. We attempted to collect data on this dimension by individual examination of each patient. Nevertheless, it was difficult to specifically identify anxiety among complex polymorphic symptoms and behaviour changes from patient interviews: irritability, fatigue, vague subjective changes. Accordingly, we were unable to characterize and use this dimension.

Ictal disorder. We distinguished subjective ictal anxiety from ictal fear. Subjective ictal anxiety exclusively concerns the subjective experience during the seizure itself (included during aura), so it can be reported only by patients who remain conscious during at least a part of their seizure and who do not experience total ictal amnesia. While ictal fear is an affect that appears for a brief period of time at the beginning or during the seizure. Ictal fear reflects an epileptic discharge within medial



temporal structures (e.g., amygdala, hippocampus) without necessarily the patient noticing any symptom of fear<sup>8</sup>. We screened for subjective ictal anxiety using a general question: “During your seizures, do you have a feeling of fear or panic? Please rate its intensity between 1 and 10.” If subjective ictal anxiety was identified, we detailed its features using the following four questions: “Do you have the feeling of imminent death?, fear of doing something incongruous?, fear of being in danger, vulnerable, unsafe? and fear of what other people may think about you?” Ictal fear was assessed on video-EEG recording of seizures.

Post-ictal anxiety. A feeling of anxiety during the period following the seizure after a free interval was assessed. We evaluated the post-ictal anxiety (e.g., Did you feel anxious or worried after your seizure?) and post-ictal depression (e.g., Did you feel sadness or discomfort after your seizure?).

#### ***Inter-ictal disorders (disorders with no temporal link to a seizure)***

Non-specific psychiatric disorders associated with epilepsy. Psychiatric comorbidities were assessed through a semi-structured psychiatric interview according to the Mini International Neuropsychiatric Interview (MINI)<sup>7</sup>. We also screened for psychogenic non epileptic seizures (PNES).

Subjective and somatic manifestations of anxiety were evaluated using the STAI-A (state anxiety; positive if total score >35)<sup>21</sup>. A predisposition to anxiety in general was evaluated using the STAI-B (trait anxiety; positive if total score >35)<sup>22</sup>.

Depression and GAD were also evaluated by two specific validated scales for patients with epilepsy: respectively, the NDDIE (Neurological Disorders Depression Inventory for Epilepsy: self-evaluation questionnaire of major depression, 15 is taken as a cut-off score)<sup>23</sup> and the GAD-7 (Screening scale for GAD in patients with epilepsy; 7 is taken as a cut-off score)<sup>24</sup>.

Specific interictal psychiatric disorders associated with epilepsy. We evaluated *interictal dysphoric disorder* according to Blumer's criteria. This is defined as the occurrence of at least three episodes lasting from a few hours to a few days, grouping together at least three criteria among the following

eight: depressed mood, asthenia, atypical pain, insomnia, fear and anxiety, irritability, euphoric mood and instability of mood. We respected the criteria used by Mula et al.<sup>15</sup>, and evaluatev the occurrence of at least three of these symptoms “moderate” or “severe” to determine this disorder.

AAS is defined as the fear of having an epileptic seizure<sup>9</sup>. It was screened using the following question: “In your everyday life, are you afraid of having an epileptic seizure? If so, how would you rate this fear of having an epileptic seizure on a scale of 0 to 10?” This dimension is more fully described earlier in the Introduction section. We also explored avoidance behaviour linked to the fear of seizure like avoidance of sports, social interactions or outdoor activities (e.g., Do you avoid certain leisure activities or social gathering besides from driving or extreme sport (or anything that was forbidden from your neurologist) because of your seizures?).

### *Quality of life*

Quality of life was specifically evaluated by the QOLIE-31 (Quality of life in epilepsy inventory). This scale is composed of seven multi-item sub-scales that correspond to the following dimensions: emotional well-being, social functioning, feeling of vitality, cognitive / memory functioning, anxiety about seizures, side effects of drugs and overall quality of life<sup>20</sup>.

### *Statistical analysis*

The analyses were divided into two parts. First, we conducted an explanatory analysis to compare patients with and without AAS. For dichotomous variables, the relationship between dependent and independent variables was analysed by the  $\chi^2$  test. The Student’s t test was applied for continuous variables with a normal distribution (normality of the distribution was assessed using Kolmogorov’s test). The Mann Whitney U test was applied for continuous variables that did not follow a normal distribution (verified by Kolmogorov’s test). A p-value <0.05 was considered significant.

In the second part of the analysis, a multivariable analysis by logistic regression was fitted to model the probability of AAS. The small number of patients restricted the number of variables that could

be included in the model. The choice of variables was oriented by the literature and the results of the first analyses. The variables included in the model were chosen by means of expert judgement of their potential clinical significance. Age and sex were forced in the model. All other variables included in the model were significant at the  $p < .05$  threshold in bivariate analysis in a first step and with a clinical selection by expert in a second step. Finally, Age, sex, duration of disease subjective ictal anxiety, postictal anxiety, at least on avoidance behaviour and traumatic experience, QOLIE Emotional well-being and Generalized Anxiety disorders was added in the stepwise model. The data were processed with SPSS software v22.0 (IBM Corp, Armonk, NY).

### 3. Results

Out of the 91 patients initially screened for inclusion, four were excluded from the analysis because a diagnosis of generalized epilepsy of presumed genetic origin was finally retained after long-term video-EEG monitoring. The mean age of the patients at inclusion was  $34.3 \pm 11.9$  years. The mean age at onset of epilepsy was  $16.2 \pm 11.5$  years and the average duration of epilepsy was  $18.5 \pm 15.8$  years.

#### *What is the profile of patients suffering from AAS? Comparative analyses*

Forty-six of the 87 analysed patients (53%) reported AAS with an average intensity of  $6.12 \pm 2.4 / 10$  (2-10). We formed a group of patients with AAS (intensity  $\geq 2$ ) and a group without AAS (intensity=0). The distribution of scores of anxiety among the patients with AAS is displayed in Figure 1 (supplemental material).

*Epilepsy features.* The presence of AAS was not related to sociodemographic data such as age and sex, or to epilepsy localization and seizure severity. In contrast, patients with AAS had a relatively shorter duration of epilepsy (14.8 *versus* 20.5 years;  $p=0.04$ ) and a longer subjective duration of ictal events (10.5 min *versus* 3.4 min;  $p=0.01$ ). The results are summarized in **Table 1**.

*Psychiatric comorbidities.* Patients with AAS were more likely to have a family psychiatric history (43% versus 17%; p=0.02).

**Table 1.** Epilepsy features of patients with/without anticipatory anxiety of seizures.

	AAS group (N=46)	Non-AAS group (N=41)	OR (CI 95%)	p-value
History of febrile seizures *	5 (11%)	10 (24%)	0.37 (0.12-1.22)	0.09
Age at onset of epilepsy, mean (SD) in years **	16.6 (8.6)	15.7 (14.1)	/	0.7
Average duration of epilepsy, mean (SD) in years **	14.8 (11.3)	20.5 (14.3)	/	<b>0.04</b>
Anti-epileptic treatment with potentially negative psychotropic effects *	42 (93%)	35 (88%)		0.29
Average <b>subjective</b> duration of an epileptic seizure, mean (SD) in minutes **	10.1 (16.1)	3.9 (5.7)	/	<b>0.01</b>
Right lateralization of epilepsy *	21 (46%)	19 (46%)	0.97 (0.41-2.26)	0.8
Left lateralization of epilepsy *	21 (46%)	17 (41%)	1.18 (0.50-2.77)	0.8
Temporal localization *	34 (74%)	29 (71%)	1.17 (0.45-3.00)	0.5
Limbic localization *	25 (54%)	23 (56%)	0.93 (0.40-2.17)	0.86
Frequency of seizures, mean (SD) per month **	11.9 (17.1)	10.4 (10.4)	/	0.7
Fall during seizure *	19 (41%)	15 (37%)	1.22 (0.51-2.90)	0.65
Injury during seizure *	20 (43%)	13 (32%)	1.65 (0.90-4.00)	0.25
Loss of consciousness during seizure *	25 (54%)	20 (49%)	1.25 (0.54-2.90)	0.6
PNES associated*	6 (13%)	4 (10%)		0.4

AAS: *Anticipatory Anxiety of Seizure*; \*  $\chi^2$ ; \*\* *Student's t test*.

*Peri-ictal disorders.* Patients with AAS reported subjective ictal anxiety more frequently (61% versus 17%; p=0.0003). This was true for all four dimensions of the ictal anxiety experienced. There was also a significant relationship between AAS and postictal anxiety (p=0.02) but not with postictal depression (p=0.4). These results are summarized in **Table 2**.

**Table 2.** Peri-ictal disorders of patients with/without anticipatory anxiety of seizures.

	AAS group (N=46)	Non-AAS group (N=41)	p-value
Ictal Fear *	1 (2%)	1 (2%)	0.8
Subjective ictal anxiety of seizure *	28 (61%)	7 (17%)	<b>0.00003</b>
<i>Dimensions of subjective anxious experience</i>			
• Ictal impending feeling of death *	10 (22%)	2 (5%)	<b>0.02</b>
• Fear of what other people think during a seizure *	18 (39%)	4 (10%)	<b>0.001</b>
• Fear of doing something incongruous *	16 (35%)	2 (5%)	<b>0.0004</b>
• Fear of being vulnerable or in danger *	18 (39%)	1 (2%)	<b>0.00002</b>
Postictal anxiety *	12 (26%)	3 (7%)	<b>0.02</b>
Postictal depression*	6 (13%)	4 (10%)	0.4

AAS: Anticipatory Anxiety of Seizure; \*  $\chi^2$ ; \*\*

*Interictal disorders.* There was a significant association between AAS and the presence of trait anxiety (p=0.02) which assessed generalized anxiety and worrying in general. Avoidance behaviour was more frequent in patients with AAS (54 % versus 22%; p=0.01). AAS was associated with the presence of at least one non-specific psychiatric disorder (p=0.01). There was no statistical difference between the two groups concerning the use of psychotropics, or a personal psychiatric history like suicide attempts or hospitalizations. It is important to note that there was no difference for a GAD, panic disorder, agoraphobia or other anxiety disorders. Finally, cannabis dependence was more frequent in patients with AAS (p=0.02). The results are summarized in **Table 3**.

**Table 3.** Inter-ictal psychiatric disorder of patients with/without anticipatory anxiety of seizures.

		AAS group (N=46)	Non-AAS group (N=41)	p-value
<i>Anamnesis examination</i>				
	Antidepressants *	9 (20%)	6 (15%)	0.74
	Antipsychotics***	2 (4%)	2 (5%)	0.9
	History of suicide attempts	9 (20%)	4(10%)	0.2
	History of psychiatry hospitalization	9 (20%)	5(12%)	0.52
	Family psychiatric history	19 (43%)	7(17%)	<b>0.02</b>
<i>Mini International Neuropsychiatric Interview (MINI)</i>				
	At least one current psychiatric disorder *	30 (65%)	16 (39%)	<b>0.01</b>
	Characterized depressive episode *	8 (17%)	3 (7%)	0.15
	Generalized Anxiety Disorder *	7 (15%)	2 (5%)	0.11
	Panic disorder *	8 (17%)	3 (7%)	0.13
	Agoraphobia *	4 (9%)	2 (5%)	0.39
	Obsessive compulsive disorder *	2 (4%)	0 (0%)	0.5
	Social phobia *	1 (2%)	0 (0%)	0.5
	Post-traumatic stress disorder *	2 (4%)	1 (2%)	0.5
	Cannabis dependence *	5 (11%)	0 (0%)	<b>0.02</b>
<i>State trait anxiety scale ( STAI)</i>				
	State anxiety score, mean (SD) ***	41.4 (12.3)	33.6 (13.3)	0.07
	Trait anxiety score, mean (SD) ***	46.6 (12.5)	39.9 (11.6)	<b>0.02</b>
<i>Specific questions</i>				
	At least one avoidance behavior concerning sport and outings *	25 (54%)	9 (22%)	<b>0.001</b>
	Interictal dysphoria disorder *	12 (26%)	7 (17%)	0.3
<i>Scales validated in population with epilepsy</i>				

Depression possible with NDDIE *	11 (28%)	4 (13%)	0.14
GAD possible with GAD-7	21 (46%)	7 (17%)	<b>0.04</b>
<i>AAS: Anticipatory Anxiety of Seizure; NDDIE: Neurological Disorders Depression Inventory for Epilepsy; GAD-7: Generalized Anxiety Disorder; * <math>\chi^2</math>; ** Student's t test; *** MWU.</i>			

*Trauma history of patients with AAS.* The results showed a significant link between AAS and trauma history (p=0.005) and also multiple traumas (p=0.04). This link was particularly strong for adult physical and emotional traumas but not for abuse in childhood. There was no difference for PTSD prevalence. The results are summarized in **Table 4**.

**Table 4.** Trauma history of patients with/without AAS.

	AAS group (N=46)	Non-AAS group (N=41)	p-value
<i>Adult lifetime traumas</i>			
At least one traumatic experience *	26 (57%)	11 (27%)	<b>0.005</b>
Sexual trauma *	8 (17%)	3 (7%)	0.10
Physical trauma *	10 (22%)	3 (7%)	<b>0.05</b>
Emotional trauma *	10 (22%)	2 (5%)	<b>0.02</b>
<i>Childhood traumas (CTQ) *</i>			
Sexual abuse*	4 (10%)	4 (9%)	0.60
Physical abuse*	4 (10%)	1 (3%)	0.20
Emotional abuse*	12%	4 (9%)	0.50

*AAS: Anticipatory Anxiety of Seizure; CTQ: Childhood Trauma Questionnaire; \*  $\chi^2$ .*

*Quality of life.* The quality of life sub-dimension of the QOLIE questionnaire was not significantly different between the two groups. There was a strong link between AAS and the anxiety about seizures quality of life score (p=0.00008). Moreover, patients with AAS had a significantly more impaired quality of life in terms of emotional well-being (p=0.03) and vitality (p=0.04). The results are summarized in **Table 5**.

**Table 5.** Evaluation of the quality of life of patients with/without AAS; data from QOLIE-31.

	AAS group (N=46)	Non-AAS group (N=41)	p-value
Overall quality of life score, mean (SD)***	34.5 (21.7)	41.2 (19.7)	0.2
Emotional well-being score, mean (SD)**	57.2 (21.2)	67.1(18.2)	<b>0.03</b>
Anxiety about seizures score, mean (SD) ***	28.6 (23.9)	48.5 (22.9)	<b>0.00008</b>
Vitality sensation score, mean (SD) ***	32.9 (16.3)	43.1 (16.7)	<b>0.04</b>
Undesirable side-effects of treatment score, mean (SD) ***	29.8 (30.2)	42.6 (26.9)	<b>0.007</b>
Memory score mean (SD)***	33.9 (23.9)	41.9 (24.5)	0.1
Social functioning score, mean (SD)***	34.2 (24.1)	41.6 (24.5)	0.1

AAS: Anticipatory Anxiety of Seizure; QOLIE: Quality of life in epilepsy inventory; \*  $\chi^2$ ; \*\* Student's t test; \*\*\* MWU.

### What are the determining factors of AAS? A multivariate analysis

We applied a multivariable logistic regression model to the results in **Table 6**. This model confirmed the positive link between AAS and subjective ictal anxiety and a personal trauma history. A negative link was found between AAS and age at inclusion: older patients were less likely to present AAS. Data didn't show link between intensity of AAS and localization or severity of seizures. This model did not confirm the link between AAS and generalized anxiety.

**Table 6:** Multivariate analysis modelling the probability of AAS

	OR adjusted <sup>c</sup>	IC pour Exp(B) 95%		p
Woman	0.524	0.14	1.94	0.33
Age (years) <sup>a</sup>	<b>0.88</b>	<b>0.80</b>	<b>0.98</b>	<b>0.02</b>
Duration of disease (years) <sup>a</sup>	1.02	0.95	1.09	0.63
Subjective ictal anxiety <sup>b</sup>	<b>8.06</b>	<b>1.80</b>	<b>35.94</b>	<b>0.01</b>
Postictal anxiety <sup>b</sup>	4.10	0.65	26.01	0.14
At least one avoidance behaviour concerning sport and outings <sup>b</sup>	2.77	0.607	12.65	0.19
At least one traumatic experience <sup>b</sup>	<b>6.12</b>	<b>1.17</b>	<b>31.84</b>	<b>0.03</b>
QOLIE Emotional well-being (score) <sup>a</sup>	0.99	0.95	1.03	0.56
Generalized Anxiety Disorder possible with GAD-7 <sup>b*</sup>	3.62	0.70	18.81	0.13

a. Continuous variable included in the model

b. Categorical variable included in the model Oui/Non

b\*. Positive screen (score 8 or higher) vs. negative screen (7 or below)

c. adjusted for Age, sex, duration of disease subjective ictal anxiety, postictal anxiety, at least on avoidance behaviour and traumatic experience, QOLIE Emotional well-being and Generalized Anxiety disorders



## DISCUSSION

Anticipatory anxiety of seizures (AAS) has been described by the ILAE as a specific and separate entity<sup>19</sup> and adds to the daily life burden for people with epilepsy (PWE). To the best of our knowledge, our study is the first to prospectively assess prevalence, describe the profile of patients with AAS and investigate determining factors. Our study showed that more than 50% of our cohort of patients with drug-resistant focal epilepsy had AAS. As expected, there was a strong link between the intensity of AAS and the score of anxiety about seizures from the QOLIE-31.

Interestingly, AAS was not related to epilepsy localization or severity (ictal fall or ictal injury). In the literature, interictal anxiety has been associated with a later age of epilepsy onset, a focal temporal localization, limbic involvement, a low level of seizure control, the severity of seizures, and the presence of ictal fear<sup>5, 25, 26</sup>. However, some studies did not find a link between temporal location of epilepsy and psychiatric comorbidity<sup>1</sup>. We did not find a link between AAS with the frequency of seizure.

Our study suggests that AAS seems to be more related to painful subjective experiences of the patients during the seizure rather than to the objective severity of the seizure itself. We demonstrate a strong association (both in univariate and multivariate analyses) between AAS and subjective ictal anxiety. Subjective ictal anxiety was slightly less frequent in our overall cohort (40%) than AAS but this could be because it can only be reported by patients that remember how they felt during their seizures, i.e., without post-ictal amnesia<sup>16</sup>. The idea that AAS seems to be more related to painful subjective experience is also supported by the longer subjective duration of seizures perceived.

Patients with AAS would appear to have had epilepsy for a shorter time as supported by the multivariate model. Brandt et al. also found that people with a shorter epilepsy duration tended to be more likely to have a diagnosis of anxiety disorder<sup>27</sup>. This could mean that PWE are more prone to developing coping strategies with time and suggests a gradual decrease of anticipatory anxiety as exposure to seizures increases over the years. This phenomenon is described and used in Cognitive

Behavioural Therapies in the context of panic disorder where anticipatory anxiety is reduced by exposing the patient to anxiety-provoking situations and somatic manifestations of anxiety.

A higher prevalence of cannabis dependency was the only psychiatric comorbidity that was specifically more frequent in patients with AAS and could reflect their attempts to relieve this specific anxiety. The higher prevalence of overall psychiatric comorbidity in patients with AAS might reflect a greater level of psychological suffering. However, the similar prevalence of agoraphobia, panic disorder, generalized anxiety disorder, depression or PNES in patients with or without AAS, suggests that AAS may not be the result of a higher level of global anxiety but is more likely a specific and well-defined entity.

Univariate analysis suggested a link between AAS and QOLIE emotional well-being and feeling of vitality scores. We found that patients with AAS display more avoidance behaviour and tend to have a poorer quality of life. These results showed that the behaviours linked to the fear of seizure causes a poorer quality of life and limits the patient's daily activities. These results showed that the AAS is another disabling condition for the patients in addition to their seizures. However, these findings were not confirmed by multivariate analysis. A previous study<sup>10</sup> using multiple regression analysis showed that anxiety was the most important factor explaining lower quality of life in patients with epilepsy, followed by depression, social life dissatisfaction, and seizure frequency as confirmed in another study<sup>12</sup>. Nevertheless, the link between AAS and a lower score for the well-being dimension of QOLIE may also be related to the confounding factor of more frequent psychiatric disorders.

Unexpectedly, our study showed a significant link between AAS and a personal history of trauma. Almost 60% of our patients with AAS had previously experienced physical and emotional traumas, mainly in adulthood, a result that was confirmed by the multivariate analysis. Kwon et al. showed that subjects with epilepsy were 1.5 times more likely to have been assaulted<sup>28</sup>. Do epileptic seizures amplify the effects of psychotrauma exposure or should they be considered as a traumatic experience *per se*?. A frequent consequence of trauma is that the subject changes his vision of the

world: the world is usually perceived as being more insecure, dangerous, and the subject becomes more mistrustful. Yet, when experiencing a seizure, the subject is, by definition, more vulnerable, loses some self-control. Our results demonstrated a strong link between AAS and subjective ictal anxiety in particular “fear of being in danger, vulnerable during my seizure”, which is especially interesting. The occurrence of an aggression at the time or around a seizure could trigger AAS. In other words, a history of trauma could accentuate the feeling of vulnerability of the subject during the seizure and thus foster AAS.

The main limitations of our study are related to the absence of a specific and validated scale to evaluate the specific dimensions of anxiety. However, there is no specific validated tool for AAS. A recent study has developed a new scale to detect anxiety disorder in epilepsy –the Epilepsy Anxiety Survey Instrument (EASI)– that integrates one item about AAS: “I think a lot about the possibility of having a seizure”<sup>29</sup>. While this scale is indeed an interesting tool, it is less detailed than our methodology. Subjective ictal anxiety according to four pre-defined questions were addressed during the interictal period in our study and could therefore be assimilated to cognitions of anticipation. However, during the data collection, patients were asked if they experienced one or more of these four dimensions during their seizures. Those who were completely unconscious during their seizures evaluated these dimensions as missing. The lack of standardized and validated instruments to evaluate subjective ictal anxiety constitute an important bias. Further studies could focus on creation and validation of an instrument to evaluate these dimensions in patients with epilepsy. We considered only patient with focal epilepsies while anticipatory anxiety of seizures is also experienced by patients with generalized epilepsies but we preferred an homogeneity of population. Another limitation of our study is the relatively small cohort sample resulting in a lack of power for statistical analysis. The current study is therefore an exploratory research for anticipatory anxiety in patients with drug-resistant focal epilepsy and provides interesting results and new paths of research. However, our results need to be replicated in future studies.

## **Conclusion**

Our study demonstrates the importance of AAS as a specific entity as suggested by the ILAE commission<sup>19</sup>. AAS seems to be particularly linked to subjective ictal anxiety and trauma history but not with the objective severity of seizures or their localization.

We should pay particular attention to AAS in patients with drug-resistant temporal lobe epilepsy.

Our study highlights the important role of anticipatory anxiety on emotional well-being dimension of patient's quality of life. Therefore, we believe that a systematic screening of these patients for this specific dimension of anxiety might be beneficial. For instance, a simple question like: "In your everyday life, are you afraid of having an epileptic seizure?" could allow the physician to reassure the patient and his family and then to explore treatment options that could potentially improve the quality of life of the patient. Potentially, selective serotonin reuptake inhibitors (SSRIs), or certain anti-epileptic drugs (such as pregabalin), combined with cognitive behavioural therapies and better control of epilepsy, could provide interesting therapeutic paths. Once again, AAS underlines the interest of managing PWE by a multidisciplinary approach with psychiatrists and epileptologists<sup>30</sup>.

The current study provides some interesting findings regarding the potential mechanisms of AAS. The unexpected potential link between AAS and trauma history raises several questions and opens ways for future research. It might be interesting to validate this study in a larger sample of patients by characterizing more specifically the type of trauma and the chronology with epilepsy. These findings highlight the necessity of further complementary studies based on a multidisciplinary perspective in this area.

## **Declaration of interest**

None of the authors have any conflict of interest to disclose in relation to this manuscript. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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