Pseudoresistance in idiopathic/genetic generalized epilepsies – Definitions, risk factors, and outcome

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Abstract
Objective: The aim of the study was to determine risk factors associated with pseudoresistance in a large, representative cohort of patients with Idiopathic/Genetic Generalized Epilepsy (IGE) and the impact of pseudoresistance on socioeconomic parameters.

Methods: We performed a literature review on definitions of pseudoresistance in IGE. In an established cohort of patients with IGE from Funen, patients with current or previous pseudoresistant seizures were retrospectively identified based on a comprehensive evaluation of the patients’ medical records and direct patient contact, if required. In addition, clinical characteristics, socioeconomic, and demographic data were assessed. Personal interviews were used to determine the brief version of Barratt’s (BIS-8) impulsivity score.

Results: The literature review provided the following definition of pseudoresistance: Seizures due to (I) lacking adherence to antiseizure medication (ASM), (II) incompliance to general rule of conduct, (III) psychogenic nonepileptic seizures (PNES), (IV) inadequate choice of ASM/dosage, and (V) incorrect classification of epilepsy. Applying criteria I-III to a cohort of patients with IGE (n = 499), 73 patients (14.6%) were currently pseudoresistant and 62 (12.4%) were previously pseudoresistant, but currently seizure free. Current pseudoresistance was associated with younger age, drug/alcohol abuse, lower rate of full-time employment, and higher BIS-8 scores. We found no associations of pseudoresistance with juvenile myoclonic epilepsy, psychiatric disease, specific seizure types, or number of seizure types. Patients with previously pseudoresistant seizures have tried more ASMs and were characterized by male preponderance, higher BIS-8, and higher rates of abuse. Surrogate markers for social outcome did not differ.

Significance: In IGE, pseudoresistance may be defined as PNES or insufficient adherence to medication/conduct and is associated with younger age, drug/alcohol abuse, and higher scores for impulsivity. If transient, its impact on socioeconomic status remains limited but may be associated with a risk of overtreatment with ASM.

1. Introduction
Not all patients with epilepsy and recurrent seizures despite prescription of antiseizure medication (ASM) have difficult-to-
treat or epilepsy resistant to ASMs [1]. Pseudoresistance is an umbrella term comprising different phenomena that may mimic resistance to ASMs. There is no widely accepted definition but the term “pseudoresistance” is commonly used in the context of seizure recurrence due to permanent or occasional lack of adherence [2–4] to prescribed ASM treatment and/or psychogenic non epileptic seizures (PNES). In addition, wrong classification of epilepsy and incorrectly chosen ASMs or insufficient doses may lead to persistent seizures or seizure aggravation although the seizures are treatable provided the correct diagnosis is made [5,6].

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Seizures provoked by incompletion to what could be described as ‘code of conduct for people with epilepsy’ are additional explanations for pseudoresistance [7]. The ‘code of conduct’ may differ between patients and includes seizures due to established seizure triggers like flickering lights [8] or sleep deprivation that can be avoided provided there is adequate behavior. Important additional seizure triggers are alcohol [9] and most illicit drugs with the exemption of cannabis [10]. However, excessive drinking or drug abuse is often also associated with sleep deprivation and high risk of incompletion to the prescribed medication, which may challenge the unambiguous assignment of a single cause.

It was speculated that patients with Idiopathic/Genetic Generalized Epilepsies (IGE), in particular Juvenile Myoclonic Epilepsy (JME), may have a higher rate of pseudoresistance than focal epilepsies.[11,12] Despite plausible explanations for this belief, like the high rate of patients with photosensitivity [12–14], evidence in support of this assumption is sparse. Further, increased impulsivity and risk-seeking behavior described in patients with JME may provide a plausible explanation for the higher risk of pseudoresistance for patients with JME.[15,16] Again, substantial evidence from large clinical cohorts supporting this concept is, to the best of our knowledge, lacking.

We have previously shown that patients with IGE, and patients with current pseudoresistance in particular, have lower income and are less likely to have full-time employment as compared to age-matched controls.[14,17] However, it is unknown if this negative impact on social status remains stable over time or if it merely represents a transient phenomenon.

To identify risk factors for pseudoresistance and assess the impact of pseudoresistance on socioeconomic outcome, we here compared patients with current and previous pseudoresistance in a large, representative cohort of patients with IGE.

2. Methods

2.1. Patient cohort

Patients of this cohort were recruited in the emergency department, neurological wards, and in the outpatient clinic of the Odense University Hospital and the Danish Epilepsy Center, Dianlund. The study was evaluated by the local ethics committee and patients gave written informed consent for the use of patient-related data from the electronic medical files. Parts of the cohort were also described in.[17–19]

Inclusion criteria were identical to previous studies.[18,19] In brief, all patients aged >16 with at least one generalized seizure type (myoclonic seizures, absence seizures, generalized tonic-clonic seizures) were eligible. Patients with severe intellectual disability (defined as not being able to attend a Danish elementary school) or patients reporting typical focal seizures were excluded. Normal background activity on EEG without severe focal slowing and without focal slowing combined with focal epileptic discharges was required. Generalized spike-waves and/or generalized poly-spike wave discharges on at least one EEG were required. This criterion was waived if the patient was <25 years old at diagnosis AND had normal MRI AND typical seizure semiology.[18,19]

2.2. Assessment of socioeconomic data and clinical characteristics

Current social status of patients was assessed and documented in the electronic medical files at every contact. Based on this documentation, highest educational achievement and current employment status were evaluated. For current marital status, data were supplemented by data from the Danish Civil Registration System linked to the patients’ electronic medical files. In case of incomplete data, further information was sought to be completed by direct contact with the patients. Other clinical characteristic (e.g. seizures types, number of ASMs tried, age at diagnosis) were assessed similarly as described e.g. in [18,19]. Information on drug and alcohol abuse was derived from the patients’ electronic medical records and typically based on the treating physicians’ assessment of the information provided by the patient.[17]

2.3. Assessment of treatment response

The treatment response was assessed longitudinally for all patients and all ASMs tried. The response to individual ASMs was described in [19]. All patients were classified at last follow-up as

| Table 1 | Results of the review of the literature. |
|---------|----------------------------------------|
| Author/year | Used criteria for pseudoresistant epilepsy |
| Gelisse et al. (2001) [4] | Misdiagnosis* incl. PNES | Lacking adherence to medication | Incorrect classification | Inadequate choice of drugs or dosage | Other |
| Genton, P. (2004) [24] | X | X | X | | Psychiatric** Associated illness*** |
| Ascoli et al. (2021) [25] | | | | | |
| Constantinescu et al. (2017) [26] | | | | | |
| Nakken et al. (2012) [27] | | | | | |
| Bajacek et al. (2010) [22] | | | | | |
| Baykan et al. (2008) [21] | | | | | |
| Ghosh et al. (2021) [28] | X | | | | |
| Perucca, E. (1998) [29] | | X | X | | |
| Kurtlu et al. (2013) [30] | X | | | X | |
| Anzelotti et al. (2020) [31] | X | X | | | |
| Jovic et al. (2014) [32] | X | X | X | | |

*Misdiagnosis e.g. vasovagal syncope, cardiac arrhythmia, sleep- and movement disorders.

**Psychiatric disorders, e.g. severe intellectual disability, psychotic disorders, generalized anxiety and personality disorders.

***Associated illness e.g. hyperthyroidism or unstable diabetes mellitus.
seizure free” (defined as not having any seizure during the last 12 months or three times the longest interval between seizures), not seizure free or pseudoresistant. Patients with a seizure free follow-up of less than 12 months after diagnosis were excluded from the analysis. Pseudoresistance was defined as seizures that were likely explained by one or more of the following factors: (I) lacking adherence to ASM, (II) incompliance to general rules of conduct, or (III) clinical suspicion of PNES. Previous pseudoresistance was arbitrarily defined as persistent seizure freedom for > 12 months after having last seizure likely explained by factors I-III. Diagnosis of current or previous pseudoresistance was established based on a retrospective comprehensive evaluation of the patients’ medical records by a single non-blinded rater (JG) – if deemed necessary – direct patient contact. ASM plasma concentrations were frequently but not systematically assessed and considered by the treating neurologist as well as by the non-blinded rater. There was no minimum number of ASMs required for the classification as pseudoresistant.

### 2.4. Barratt’s impulsivity score

The brief version of Barratt’s (BIS-8) impulsivity score [20] was assessed by personal interviews, when the patient was in the outpatient clinic or by phone or by direct contact in the period from 01.01.2020 and 30.04.2020. Only patients with written informed consent to being contacted by phone were included.

### 2.5. Literature review of definitions of pseudoresistance

A review of the medical literature was performed using the databases: MEDLINE database through PubMed and Web of Science using the terms “pseudo resistant epilepsy” in various forms (search term: (pseudoresistance epilepsy) OR (pseudo-resistance epilepsy) OR (pseudo resistant epilepsy) OR (pseudo-resistant epilepsy)). Additional relevant studies were discovered within the reference lists of the obtained articles. We included English-written studies only.

### 2.6. Statistics

All data were processed using the statistical software package ‘R’ (www.r-project.org) version 4.1.1 (‘Kick Things’) and SAS version 9.4 (www.sas.com). Chi-squared and Kruskal Wallis test with a 0.05 significance level without correction for multiple testing was used. Continuous variables are given as mean and standard deviations. The statistical tests used are given in the respective tables.

### 3. Results

#### 3.1. Definition of pseudoresistance

The literature review identified 76 articles and 12 articles were included after exclusion of duplicates and full-text screening for relevance. Table 1 provides an overview of the criteria used to define pseudoresistant IGE in the articles included. Poor adherence, incompliance to general rules of conduct for patients with IGE, and incorrect classification/PNES were used in most publications and were therefore applied to our cohort. Inadequate prescription of ASM/incorrect classification was not deemed relevant for the characterization of patients with pseudoresistant IGE.

#### 3.2. Cohort and clinical characteristics associated with pseudoresistance

The characteristics of the patients in the cohort included are given in Table 2. In Table 3, a comparison of the characteristics of the patients that accepted and submitted to medical suggestions and of patients with current or previous seizures due to pseudoresistance is given. Per definition, patients with seizures classified as PNES were either categorized as currently or previously pseudoresistant. Age at inclusion, the rate of self-reported current or previous drug/alcohol abuse, and BIS-8 score were significantly higher in patients with current seizures due to pseudoresistance. Pseudoresistance was not associated with distinct ASMs (sufficient data available for lamotrigine, levetiracetam and valproic acid, barbitu-
rates, zonisamide) in exploratory studies (data not shown). In seizure-free patients with previous seizures due to pseudoresistance, impulsivity and current/previous drug abuse remained significantly different as compared to patients that never had seizures due to pseudoresistance (Table 3). Further, previous pseudoresistance was associated with a higher number of ASMs tried (see Table 4).

3.3. Social status and current and previous pseudoresistance

We assessed current employment, maximal educational attainment, having a driving license, and marital status as surrogate markers for social outcome for all patients included. Patients with current seizures due to pseudoresistance had a lower rate of employment and were less likely to have a driving license. In con-

Table 3
Risk factors for pseudoresistance in patients currently pseudoresistant, previously pseudoresistant, and never pseudoresistant Idiopathic Generalized Epilepsy (IGE).

|                              | Currently pseudo-resistant (n = 62) | Never pseudo-resistant (n = 371) | P-value | Previously pseudo-resistant (n = 64) | Never pseudo-resistant (n = 371) | P-value |
|------------------------------|------------------------------------|----------------------------------|---------|-------------------------------------|----------------------------------|---------|
| Sex                          |                                    |                                  |         |                                     |                                  |         |
| - Male                       | 30 (48.4%)                         | 144 (38.8%)                      | NS      |                                    | 35 (54.7%)                       | 144 (38.8%) | 0.021    |
| - Female                     | 32 (51.6%)                         | 227 (61.2%)                      |         |                                    | 29 (45.3%)                       | 227 (61.2%) | NS       |
| Age [mean (SD)]              | 30.8 (12.1)                        | 37.8 (17.6)                      |         |                                    | 34.6 (13.9)                      | 37.8 (17.6) | NS       |
| Age at diagnosis [mean (SD)] | 15.0 (8.6)                         | 16.1 (8.3)                       |         |                                    | 14.7 (6.2)                       | 16.1 (8.3) | NS       |
| IGE subsyndrome              |                                    |                                  |         |                                     |                                  |         |
| - EGTCS                      | 13 (21.0%)                         | 110 (29.6%)                      | NS      |                                    | 17 (26.5%)                       | 110 (29.6%) | NS       |
| - JME                        | 32 (51.6%)                         | 142 (38.3%)                      |         |                                    | 27 (42.2%)                       | 142 (38.3%) | NS       |
| - JAE                        | 17 (27.4%)                         | 119 (32.1%)                      |         |                                    | 20 (31.3%)                       | 119 (32.1%) | NS       |
| Seizure types:               |                                    |                                  |         |                                     |                                  |         |
| - One                        | 17 (27.4%)                         | 130 (35.1%)                      | NS      |                                    | 21 (32.8%)                       | 130 (35.1%) | NS       |
| - Two                        | 25 (40.3%)                         | 160 (43.1%)                      |         |                                    | 33 (51.6%)                       | 160 (43.1%) | NS       |
| - Three                      | 20 (32.3%)                         | 81 (21.8%)                       |         |                                    | 10 (15.6%)                       | 81 (21.8%) | NS       |
| Number of ASMs tried [mean (SD)] | 2.6 (1.3)          | 2.6 (1.3)                       |         |                                    | 2.6 (1.3)                       | 2.6 (1.3) | 0.01*    |
| Psychiatric comorbidity      |                                    |                                  |         |                                     |                                  |         |
| - Yes                        | 15 (24.2%)                         | 84 (22.6%)                       | NS      |                                    | 20 (31.3%)                       | 84 (22.6%) | NS       |
| - No                         | 47 (75.8%)                         | 287 (77.4%)                      |         |                                    | 44 (68.7%)                       | 287 (77.4%) | NS       |
| History of alcohol/drug abuse|                                    |                                  |         |                                     |                                  |         |
| - Yes                        | 19 (30.6%)                         | 18 (4.9%)                        | <0.0001 |                                    | 17 (26.5%)                       | 18 (4.9%) | <0.0001  |
| - No                         | 33 (69.4%)                         | 392 (95.1%)                      |         |                                    | 133 (73.5%)                      | 392 (95.1%) | NS       |
| BIS-8                        | 14.5                               | 12.9                             | 0.01*   |                                    | 14.2                             | 12.9     | 0.02*    |

*Wilcoxon rank sum test 1Chi-Squared test. EGTCS: Epilepsy with generalized tonic-clonic seizures only; JME: Juvenile myoclonic epilepsy; JAE: Juvenile absence epilepsy; ASM: antiseizure medication; BIS-8 Barratt’s impulsivity score (brief).

Table 4
Social outcome in patients with currently pseudoresistant, previously pseudoresistant, and never pseudoresistant Idiopathic Generalized Epilepsy (IGE).

|                              | Currently pseudo-resistant (n = 62) | Never pseudo-resistant (n = 371) | P-value | Previously pseudo-resistant (n = 64) | Never pseudo-resistant (n = 371) | P-value |
|------------------------------|------------------------------------|----------------------------------|---------|-------------------------------------|----------------------------------|---------|
| Level of education           |                                    |                                  |         |                                     |                                  |         |
| - Less than high school      | 36 (58.1%)                         | 164 (44.2%)                      | NS      | 30 (46.9%)                         | 164 (44.2%)                      | NS      |
| - High school                | 14 (22.6%)                         | 99 (26.7%)                       |         |                                    | 24 (37.5%)                       | 99 (26.7%) | NS       |
| - College                    | 8 (12.9%)                          | 72 (19.4%)                       |         |                                    | 5 (7.8%)                         | 72 (19.4%) | NS       |
| - Master                     | 1 (1.6%)                           | 12 (3.2%)                        |         |                                    | 3 (4.7%)                         | 12 (3.2%) | NS       |
| - Unknown                    | 3 (4.8%)                           | 24 (6.5%)                        |         |                                    | 2 (3.1%)                         | 24 (6.5%) | NS       |
| Employment                   |                                    |                                  |         |                                     |                                  |         |
| - Student                    | 19 (30.6%)                         | 82 (22.1%)                       | 0.01*   |                                    | 14 (21.9%)                       | 82 (22.1%) | NS       |
| - Full-/parttime job         | 16 (25.8%)                         | 153 (41.2%)                      |         |                                    | 25 (39.1%)                       | 153 (41.2%) | NS       |
| - Retired                    | 9 (14.5%)                          | 79 (21.3%)                       |         |                                    | 14 (21.9%)                       | 79 (21.3%) | NS       |
| - Unemployed/ Unemployed      | 17 (27.5%)                         | 56 (15.1%)                       |         |                                    | 11 (17.1%)                       | 56 (15.1%) | NS       |
| Sick leave                   | 1 (1.6%)                           | 0 (0.3%)                         |         |                                    | 0 (0.0%)                         | 1 (0.3%) | NS       |
| Marital status               |                                    |                                  |         |                                     |                                  |         |
| - Married                    | 27 (43.5%)                         | 194 (52.3%)                      | NS      | 37 (57.8%)                         | 194 (52.3%)                      | NS      |
| - Single                     | 33 (53.3%)                         | 135 (36.4%)                      |         |                                    | 22 (34.4%)                       | 135 (36.4%) | NS       |
| - Divorced                   | 2 (3.2%)                           | 23 (6.2%)                        |         |                                    | 5 (7.8%)                         | 23 (6.2%) | NS       |
| - Widowed                    | 0 (0.0%)                           | 11 (2.9%)                        |         |                                    | 0 (0.0%)                         | 11 (2.9%) | NS       |
| - Unknown                    | 0 (0.0%)                           | 8 (2.2%)                         |         |                                    | 0 (0.0%)                         | 8 (2.2%) | NS       |
| Allowed to drive?            |                                    |                                  |         |                                     |                                  |         |
| - Yes                        | 4 (6.5%)                           | 193 (52.0%)                      | <0.001  | 30 (47.6%)                         | 193 (52.0%)                      | NS      |
| - No                         | 17 (27.4%)                         | 39 (10.5%)                       |         |                                    | 5 (7.9%)                         | 39 (10.5%) | NS       |
| Allowed to obtain license?   |                                    |                                  |         |                                     |                                  |         |
| - Yes                        | 4 (6.5%)                           | 58 (15.6%)                       |         |                                    | 18 (28.6%)                       | 58 (15.6%) | NS       |
| - No                         | 36 (58.1%)                         | 73 (19.7%)                       |         |                                    | 73 (19.7%)                       | 36 (58.1%) | NS       |
| - Unknown                    | 1 (1.5%)                           | 8 (2.2%)                         |         |                                    | 0 (0.0%)                         | 8 (2.2%) | NS       |

1 Chi-Squared test.
trast, surrogate markers for social status did not differ between patients with previous pseudoresistance and the remainder of the cohort.

4. Discussion

Here we show that younger age, current or previous drug/alcohol abuse, and high impulsivity are associated with increased risk of pseudoresistance in patients with IGE. To our surprise, the diagnosis of JME, myoclonic seizures, or number of seizure types was not associated with pseudoresistance despite slightly higher impulsivity indicated by high BIS-8 scores in patients with JME as compared to patients with e.g. absence epilepsy or epilepsy with generalized tonic-clonic seizures alone (data not shown). Given the size of the cohort, our data make a clinically important association of JME and pseudoresistance unlikely. The same applies to the lack of association of psychiatric disease and pseudoresistance.

A learning process triggered by recurrent seizures and maturity likely explains the association of current pseudoresistance and age. In line with this interpretation, we found no difference in age in patients with previous pseudoresistance.

One major challenge with this and similar studies is the definition of pseudoresistance and previous pseudoresistance given the lack of objective parameters or established questionnaires assessing all dimensions. We therefore performed a literature review on publications using the term pseudoresistance. The definition used in this manuscript was identical or similar to the definitions used in the majority of publications. However, the diagnosis of pseudoresistance will always require a holistic and comprehensive assessment of the patient, the patient’s treatment course, and the patient’s self-perceived adherence and compliance to ASMs and ‘rules of conduct’. The same applies to the definition of previous pseudoresistance, which we arbitrarily defined as seizure freedom for more than one year after seizures triggered by factors defining pseudoresistance. We tried to address these challenges using a single, experienced rater who retrospectively assessed the patients’ treatment course. In this context, the mixed design of the study incl. retrospective analysis of the electronic medical files and the prospective active contact to the patient to verify and complete the dataset may have been an advantage. The longitudinal assessment used in this study allowed a more correct interpretation of the information provided by the patient as this would be the case in a short-term prospective study. Conversely, the non-systematic assessment of objective measures of pseudoresistance (e.g. ASMs plasma concentrations was not available for all patients), is a limitation of the study.

With these challenges in mind, it is difficult to exclude a bias in the assessment of self-reported current or previous drug and alcohol abuse that may have contributed to the association with pseudoresistance. The rater in this study was aware of the abuse when classifying the patients’ response to ASMs and most clinicians would agree to classifying a person with ongoing alcohol abuse, IGE, and seizures as pseudoresistant and not as resistant to ASM treatment. Despite this possible bias, we are not in doubt of the validity of the positive and null-associations found in this study, which is supported by the reproduction of key features in patients with previous pseudoresistance (e.g. high BIS-8, increased rate of abuse).

Seizures due to current pseudoresistance were seen in 16.7% of all patients, a rate that is comparable to other cohorts [range: 9.7–20.0%] [4,21–23]. Not surprisingly and in line with our previous report based on Danish registers based on the same cohort, pseudoresistance was associated with a lower rate of full-time work and a lower rate of attained driving license.[17] The data on social status of patients with previous pseudoresistant seizures were, however, reassuring indicating that the long-term impact of previous pseudoresistance on social status remained limited.

We noted a higher number of ASMs in patients that were previously pseudoresistant as compared to the rest of the cohort. The higher number of ASMs tried indicates that pseudoresistance was not always recognized and suggests that seizures due to pseudoresistance triggered futile efforts to achieve seizure freedom, e.g. by switching medication. We interpret this association as a warning, and one might consider ASM reduction or adaption if pseudoresistance becomes obvious during the course of treatment.

5. Conclusions

Pseudoresistance is associated with younger age, drug/alcohol abuse, and higher scores for impulsivity. If transient, the impact on socioeconomic status remains limited but may be associated with a risk of overtreatment with ASMs.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: CPB has received honoraria and research support from UCB, EISAI and participated in an advisory board by Arvelle. GR received honoraria from Eisai and Arvelle. The other authors have no conflicts of interest.

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