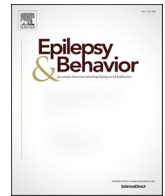


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Research Paper

Clinical characteristics of patients with refractory non-epileptic seizures

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ABSTRACT

Objectives: This incidence of non-epileptic seizures (NES) is estimated at 1–35 per 100,000 population. While many patients achieve remission, a significant fraction of patients have a poor prognosis despite optimal interventions. This study reports on the characteristics of patients with refractory NES diagnosed and treated at a comprehensive epilepsy centre.

Methods: A retrospective review of admissions to the Epilepsy Monitoring Unit identified patients diagnosed with NES over a 6-year period. Patients with refractory NES were identified through review of medical files. A diagnosis of refractory NES was assigned when patients experienced ongoing NES at least 1 year after diagnostic video-EEG monitoring. Data pertaining to predisposing, precipitating and perpetuating factors was collected on all patients and a comparative analysis was conducted between refractory and non-refractory cases.

Results: 66 patients with NES were identified, 35% were deemed refractory. There was no significant difference amongst predisposing factors between the groups. Psychosocial adversity and a clear precipitant proximate to the onset of NES were significantly more common in the refractory cohort. Unemployment at time of diagnosis was a significant perpetuating factor associated with poor outcome.

Conclusion: This study provides insight into the features associated with refractory NES and may serve to improve prognostication and management in this disabling condition.

1. Introduction

Non-epileptic seizures (NES) are defined as episodes of altered movement, sensation, or experience similar to epileptic seizures, but not associated with abnormal electrical discharges in the brain [1]. The international incidence of NES is estimated at 1–35 per 100,000 population per year [2]. The incidence of NES in Ireland, extrapolated from international studies, is estimated to be between 63 and 136 new cases per year, at an estimated total annual cost (via direct and indirect costs) to the exchequer of €20, 995 per patient per annum [3].

Outcomes in NES are often poor, with less chance of seizure freedom than a diagnosis of epilepsy. Less than half of adults diagnosed with NES can expect to become event-free within 5 years of diagnosis [4]. A study of 260 patients, found that only 38 % of patients achieved event freedom 6–12 months after diagnosis. In another study of 164 patients, at a mean of 11.9 years after onset, and 4.1 years after diagnosis, 71.2 % of patients continued to have events, and 56.4 % were dependent on social security [5].

Many studies have evaluated prognostic factors in NES, and

determined that factors such as co-existent epilepsy [6,7], psychiatric co-morbidity [8] and poor educational attainment [5,9] confer a poorer prognosis with a diagnosis of NES.

This study reports on clinical features of patients with refractory NES under active follow-up at a comprehensive epilepsy centre. The aim of this study was to examine predisposing, precipitating and perpetuating factors in a population of patients with refractory NES.

2. Methods

The study was approved by the local Ethics Committee. All patients diagnosed with non-epileptic seizures were identified through review of the Epilepsy Monitoring Unit (EMU) database of admissions over a 6-year period (2015 – 2021). Refractory NES was defined as the persistence of non-epileptic seizures at least one year post diagnosis. Patients diagnosed with NES in the EMU were managed in a standardised manner with formal mental health assessment through the Liaison Psychiatry team, psychoeducation and ongoing combined care with the Epilepsy and Liaison Psychiatry teams. We conducted a detailed review of the

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medical records of all patients diagnosed with NES over the 6-year time period. We examined information collected at all hospital visits. Demographics and data pertaining to a predefined list of predisposing, provoking and precipitating factors were collected on each patient. Patients were categorised into two groups (refractory and non-refractory) based on the above definition, and a comparative analysis was performed. Statistical analysis was performed using Graphpad Prism Version 10.2.0, fisher's exact test was used to compare two groups, a p value of < 0.05 was taken to be statistically significant.

3. Results

3.1. Baseline characteristics

We identified 71 patients with video EEG-confirmed NES over a 6 year period. Of these, a complete data set was available for 66 patients. 5 patients were either lost to follow up or were routinely followed up at another centre having been referred only for a diagnostic EMU admission. 23 (35 %) were diagnosed with refractory NES with persistence of NES 12-months after a diagnosis was established. 43 (65 %) had a good outcome, with resolution of NES within 12-months. Of those with refractory NES, 39 % had a dual diagnosis of epilepsy and NES, compared to 21 % in the non-refractory group. 86 % of the combined cohort of NES patients were female (87 % of the refractory group, and 86 % of the non-refractory group). The median age at time of diagnosis was 31 in the refractory group, and 33 in the non-refractory cohort (range 17–68 in both cohorts).

3.2. Predisposing factors

Educational attainment is described with respect to level of education completed (Fig. 1). Across the combined group of NES patients, 33 % did not complete second level education, 42 % completed second level education and 20 % completed third level education. Two patients (5 %) were in school or college at the time of diagnosis and during the follow up period. Although the rates of educational attainment appeared higher in the non-refractory group, there was no statistically significant difference between the two groups ($p = 0.88$).

The frequency of psychiatric co-morbidity was more common in the non-refractory group (58 % vs 35 %) (Fig. 2a), as were personality disorders (14 % vs 9 %) (Fig. 2b), however neither of these comparisons were statistically significant ($p = 0.12$ and $p = 0.70$ respectively), nor was there a significant difference between the groups in terms of co-existent functional neurological disorders at 26 % in the refractory cohort compared to 28 % in the non-refractory cohort ($p = > 0.99$) (Fig. 2c). The use of regular pain medications appeared higher in the

refractory cohort (26 % vs 16 %) but this was not statistically significant ($p = 0.35$) (Fig. 2d). Six patients (9 %) across the entire cohort had intellectual disability, however there was no significant difference between the groups ($p = 0.41$) (Fig. 2e).

3.3. Precipitating factors

A clear precipitating factor proximate to the onset of NES was identified in 56 % of patients with refractory NES, compared to 25 % of non-refractory cases (Fig. 3a) ($p = < 0.05$). Death of a loved one was commonly cited as a recent or remote factor in those with refractory NES, at a rate of 30 % compared to 5 % on the non-refractory group ($p = < 0.05$) (Fig. 3b). In patients with refractory NES, in whom a clear precipitant was identified, a recent bereavement was identified as a precipitating factor in 55 %. Other precipitants included medical illness, injury, assault and custodial disputes.

Psychosocial adversity was significantly more common in the refractory group, at a rate of 61 % compared to 30 % in the non-refractory group ($p = < 0.05$) (Fig. 3c). Psychosocial adversity included childhood trauma, including child sexual abuse and parental separation, severe and chronic medical illness in self or close family members, death of a loved one (death of a child in two cases), bullying and intellectual disability.

Clearly identifiable interpersonal conflict was seen at a rate of 17 % in the refractory cohort compared to 7 % in the non-refractory cohort ($p = 0.22$) (Fig. 3d). Only 3 patients with refractory NES had no identifiable precipitating or predisposing factors.

3.4. Perpetuating factors

Calculation of diagnostic latency was possible in 61 of 66 patients, with an unclear time of onset in 5 patients with a dual diagnosis of epilepsy and NES (Fig. 4a). In the combined cohort, only 31 % of patients were diagnosed within one-year. The proportion of non-refractory cases diagnosed in under one year was 35 % compared to 17 % in the refractory group. 22 % of the refractory group took over ten years to diagnosed compared to 14 % of the non-refractory group. Four cases had a diagnostic latency of over 20 years, with the longest being 37 years. There was no statistically significant difference between the groups ($p = 0.50$).

Excluding those with a dual diagnosis, 37 % of those with non-refractory NES were explicitly given a diagnosis of epilepsy before their diagnosis of NES, compared to 17 % of the refractory group ($p = 0.15$) (Fig. 4b). Despite this, 44 % of the non-refractory group and 39 % of the refractory group had been treated with anti-seizure medicines ($p = 0.79$) (Fig. 4c).

84 % of the non-refractory group had a receptive and open attitude to the diagnosis of NES compared to 65 % of the refractory group ($p = 0.12$) (Fig. 5a). In line with best practice, the majority of patients were offered referral to psychiatry. Within the non-refractory group, 63 % of patients engaged with mental health services, 25 % were not referred to psychiatry and 12 % declined to engage. Within the refractory group, all patients were offered referral. 83 % engaged with mental health services, with only 17 % declining to engage (Fig. 5b). There was no statistically significant difference between the groups ($p = 0.99$).

The rate of unemployment across the combined cohort at the time of diagnosis was 17 %. 39 % of the refractory cohort were unemployed at the time of diagnosis compared to 5 % on the non-refractory cohort ($p = < 0.05$) (Fig. 5c). Across the combined cohorts, 42 % of people discontinued work or full-time education as a result of their diagnosis. The discontinuation rate in the refractory group was 28 % compared to 46 % in the non-refractory cohort ($p = 0.36$) (Fig. 5d). 45 % of the entire cohort of NES patients were in receipt of disability allowance, 48 % of the refractory group and 44 % of the non-refractory group ($p = 0.8$). However, 17 % of all those in receipt of disability allowance were receiving it for medical reasons unrelated to NES (co-existing chronic

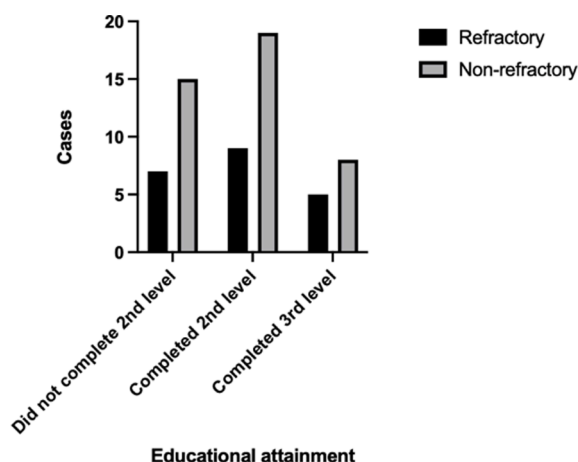


Fig. 1. Educational attainment.

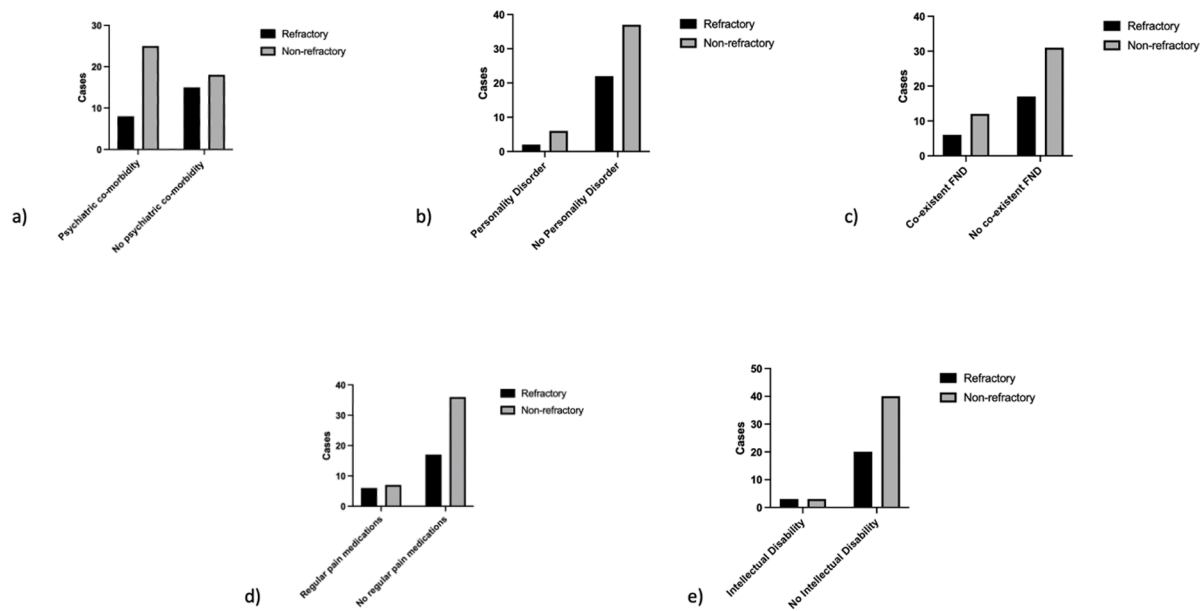


Fig. 2. A) Psychiatric co-morbidity, b) Personality disorder, c) Co-existent functional neurological disorder (FND), d) Regular pain medications, e) Intellectual disability.

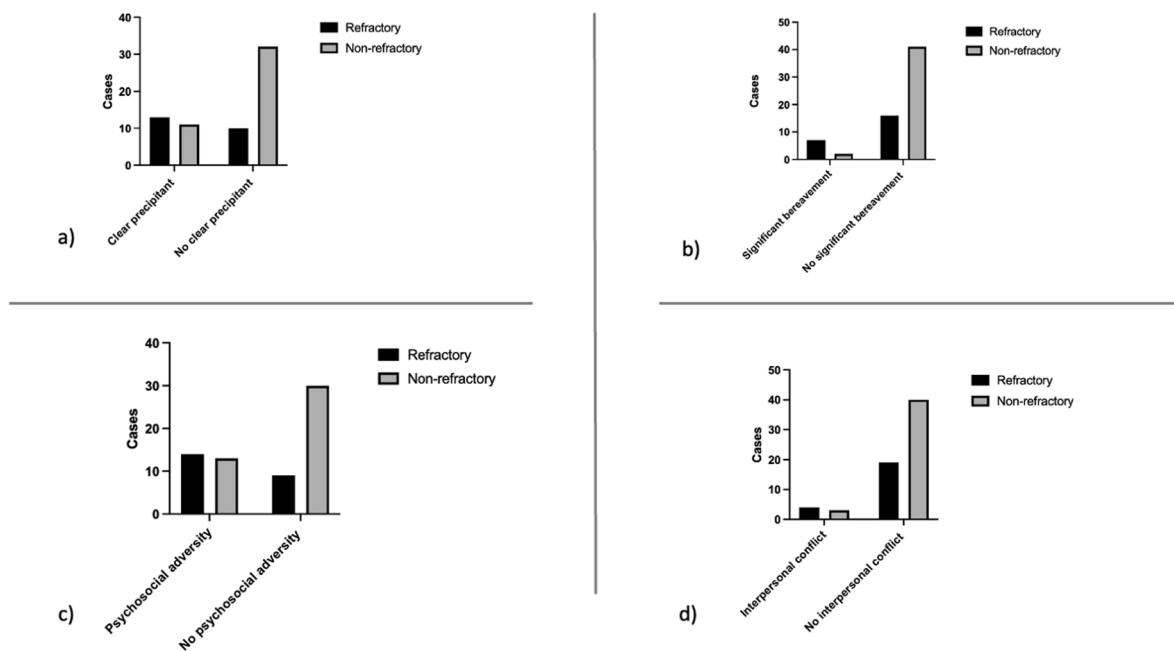


Fig. 3. A) Clear precipitant, b) Significant bereavement, c) Adverse psychosocial circumstance, d) Interpersonal conflict.

epilepsy or other chronic medical illness). One patient in the non-refractory group received disability allowance for functional hemiplegia. The number of emergency department (ED) attendances for each patient over a one-year period was reviewed. 45 % of the entire cohort had between one and five ED attendances, while 8 % attended more than five times. There was no statistically significant difference between the groups ($p = 0.07$).

The semiology of events in the majority of patients across both cohorts was hypermotoric (64 %), these were all convulsive events with one semiology of focal jerking. This was followed in frequency by akinetic or trance-like events which constituted 26 % of the overall cohort. There were no statistically significant difference between the groups (Table 1).

4. Discussion

We describe the clinical characteristics of a cohort of patients with vEEG confirmed NES, comparing those with refractory NES against those in whom events resolved within 12-months. The proportion of refractory cases (35 %) is lower than that reported in the literature, with reports of only 40 % of patients achieving seizure remission at 6 and 12-month follow up [4]. Co-existing epilepsy which has been reported to be a poor prognostic factor, occurred at a rate of 27 % across our combined study group, with no significant difference between the two groups. The gender profile of the combined groups showed female predominance at 87 %, which was equally distributed across the two cohorts. There is equivocal evidence regarding the influence of gender on the prognosis of NES with one study reporting male gender as a predictor of seizure

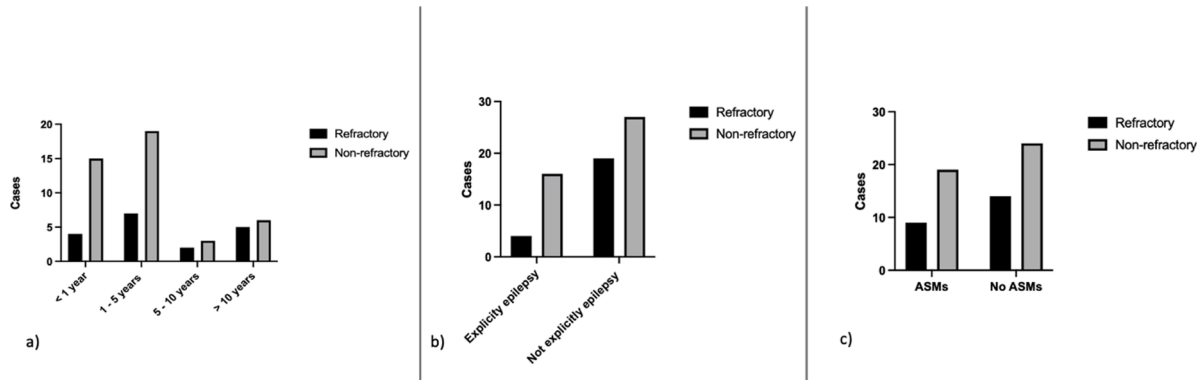


Fig. 4. A) diagnostic latency b) explicit diagnosis of epilepsy c) treated with anti-seizure medicines (amss).

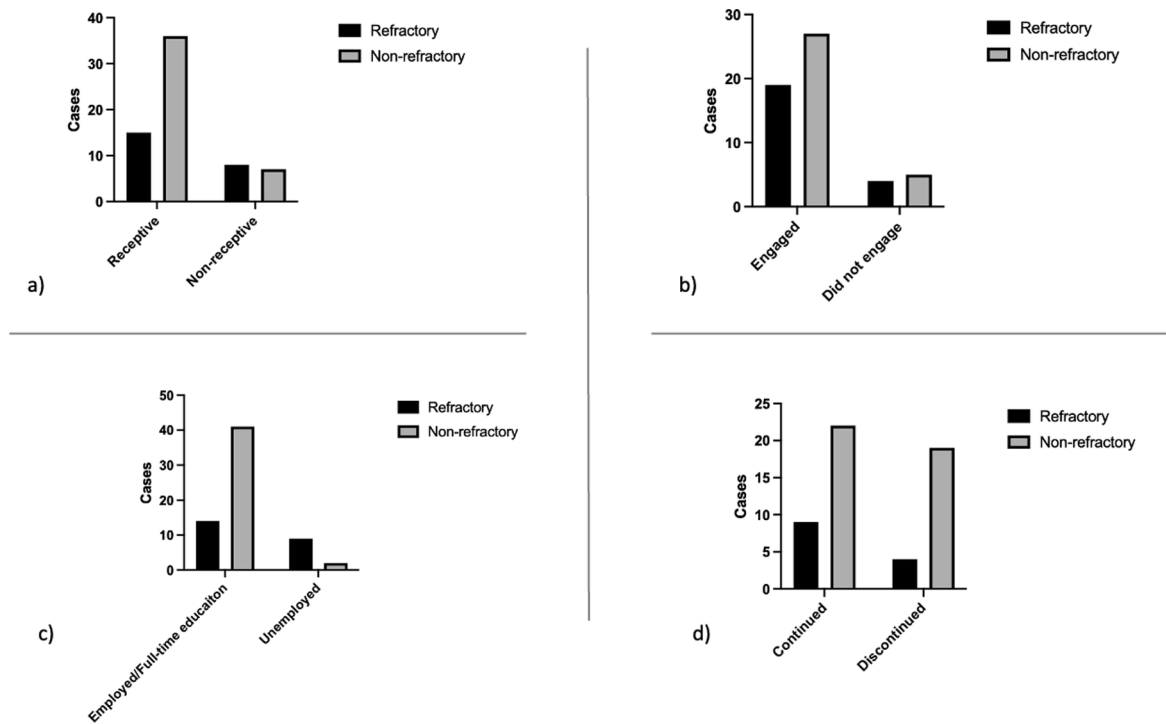


Fig. 5. A) Attitude to diagnosis, b) Engagement with mental health services, c) Unemployed at diagnosis d) Continuation of employment or education.

Table 1
Semiology of events.

	Refractory	Non-refractory	p values
Hypermotoric	52 % (n = 12)	63 % (n = 27)	p = 0.44
Akinetic	26 % (n = 6)	25 % (n = 11)	p = > 0.99
Mixed	13 % (n = 3)	0	
Atypical	7 % (n = 2)	0	
Syncope-like	0	5 % (n = 2)	

remission [10], and another smaller study demonstrating a more favourable prognosis in women [6]. Our data would support a higher incidence in women, although we found no influence on prognosis.

A number of predisposing factors for NES were examined in our comparative cohorts. Although a proportionally greater number of non-refractory patients attained a higher level of education, this difference was not statistically significant. There are conflicting reports of the influence of educational attainment on prognosis, however our study does not support a significant association with NES persistence. Our results are consistent with prior reports of low rates of educational attainment

amongst patients with NES [11], with less than half of the combined cohorts completing second level education, and only 20 % completing third level education. Psychopathology and personality disorders have been associated with less chance of event freedom [8]. However, in our cohort, the relationship between co-morbid psychiatric disease and personality disorders with persistence of NES was not significant.

A clear precipitant proximate to the onset of NES and significantly higher rates of psychosocial adversity were seen in the refractory cohort. We noted that a remote or recent bereavement was frequently cited amongst the refractory group and by comparison, was five times more common in the refractory group compared to the non-refractory group (30 % vs 5 %). The high incidence of significant bereavement in the refractory group prompts consideration for the role of grief in the persistence of NES and indeed prolonged grief disorder (PGD) has previously been reported to manifest as NES [12]. PGD can be thought of as a state of physiological disorganisation and has been linked to dysregulation of reward processing pathways, with neurobiological correlates in the subcortical, cingulate and orbito-frontal regions. Attachment figures provide not only emotional stability but are also linked to sustained reward, and loss of an attachment figure is thought to lead to

disruption of subcortical reward circuitry [13]. Secure attachment has been positively correlated with FND outcomes at 6-months and has been cited as a protective factor facilitating recovery [14]. The significant association of bereavement with refractory NES in this cohort, supports this theory.

Whilst a unifying neuropsychological model for NES has not yet been determined, there is a broad acceptance that convergence of genetic, neural and environmental factors in the context of permissible psychological conditions can give rise to such events [15]. The integrated cognitive model for NES posits the theory that internal or external cues in the context of inhibitory processing dysfunction come together to activate a seizure scaffold that results in NES [16]. With over double the rate of psychosocial adversity seen in the refractory cohort, our data suggest that a permissible psychological milieu has a greater influence on prognosis than many of the commonly cited predisposing factors.

Perpetuating factors relating to diagnostic latency, attitude to diagnosis, prior diagnostic labels and management were reviewed, in addition to socioeconomic factors such as employment. Significant delays to diagnosis in NES are frequently encountered, with one large study citing an average diagnostic latency of 7.2 years [17]. This is born out in our study, with only 31 % of patients receiving a diagnosis within one-year of onset. Only one study has demonstrated a weak association between diagnostic delay and poor prognosis [9], with two larger studies finding no association [5,6]. Our study supports the conclusion that lengthy diagnostic delays are a feature in NES, however there does not appear to have been a significant association with prognosis in our cohort. The majority of patients (77 %) were found to have a receptive attitude to the diagnosis of NES, although this did not positively impact outcome. A number of studies report that a positive attitude to diagnosis can aid recovery [4], however when directly comparing refractory with non-refractory patients in our cohort, there was no significant association seen.

The rate of unemployment across the combined cohort was only 17 %, however a diagnosis of NES led 35 % of the group to discontinue work or full-time education, further highlighting the debilitating nature of this disorder and its economic impact. There was a significant difference in the rate of employment at diagnosis between the two groups, with a higher rate of unemployment in the refractory group. This is in line with previous reports that seizure remission is more likely in those who are employed at the time of diagnosis [18].

5. Conclusions

Non-epileptic seizures represent 10–25 % of cases referred to tertiary care epilepsy centres [19]. NES are associated with high morbidity with an overall poor prognosis with respect to both seizure and non-seizure related outcomes, with 45 % of patients in this group claiming disability benefit. The rate of refractory NES in our cohort was 35 % with an estimated economic burden of €20,995 per patient per annum [3]. This study describes the characteristics of a cohort of patients with refractory NES and compares them to a cohort of patients in whom seizure freedom was achieved within 12-months. Those with refractory NES were significantly more likely to be unemployed at the time of diagnosis, to have a clear precipitant proximate to the onset of NES, and to have experienced significant psychosocial adversity in their lifetime. Commonly referenced prognostic factors such as educational attainment, attitude to diagnosis and diagnostic latency did not impact on prognosis in this cohort. The limitations of this study include its

retrospective design and its small sample size. Further large scale studies should be conducted in order to improve our understanding of this disabling condition.

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CRediT authorship contribution statement

Sarah Fullam: Writing – original draft, Methodology, Investigation, Data curation. **Daniel J. Costello:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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