What do we know about non-epileptic seizures in adults with intellectual disability: A narrative review

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Abstract

Psychogenic non-epileptic seizures (PNES) superficially resemble epileptic seizures, but are not associated with abnormal electrical activity in the brain. PNES are a heterogeneous entity and while there is increasing interest in the characterisation of PNES sub-groups, little is known about individuals with PNES who have an intellectual disability (ID). ID is a lifelong condition characterised by significant limitations in cognitive, social and practical skills. ID (commonly with comorbid epilepsy) has been identified as a risk factor for developing PNES. However, people with ID are often excluded from research in PNES. This has unfortunately resulted in a lack of evidence to help inform practice and policy for this population. This narrative review synthesises the currently available evidence in terms of the epidemiology, demographic and clinical profile of adults with PNES and ID. There is a particular focus on demographics, aetiological factors, PNES characteristics, diagnosis and treatment of the condition in this population. Throughout this article, we critique the existing evidence, discuss implications for clinical practice and highlight the need for further research and enquiry. What emerges from the evidence is that, even within the sub-group of those with ID, PNES are a heterogeneous condition. Individuals with ID and PNES are likely to present with diverse and complex needs requiring multidisciplinary care. This review is aimed at the broad range of healthcare professionals who may encounter this group. We hope that it will stimulate further discussion and research initiatives.

Keywords: Learning Disability; Non-Epileptic Attack Disorder; Dissociative Seizures; IQ; Neurodevelopmental

Introduction

Psychogenic non-epileptic seizures (PNES) are episodes of altered behavioural, sensory, motor or cognitive function which superficially resemble epileptic seizures, but are not associated with epileptiform activity. Most events are interpreted as a dissociative response to adverse internal or external cues (1). The condition represents 10-20% of referrals to outpatient seizure clinics in general adult neurology and is one of the three causes of transient loss of consciousness, accounting for over 90% of clinical presentations (2).

PNES seem to be a trans-cultural phenomenon, having been reported around the world (3). They are a rather heterogeneous clinical problem – both at an inter- and intra-personal level (4). Patients differ in terms of presumed PNES aetiology (1), semiology (5, 6), clinical characteristics such as seizure frequency and severity (7), sociodemographic and clinical factors (8), response to treatment (9), and psychological and emotional characteristics (10, 11). In view of this heterogeneity, it may aid the understanding and management of the condition to focus on specific patient sub-groups (12).

People with an intellectual disability (ID) are an important, but neglected (13), sub-group of the PNES patient population. ID is a lifelong and multi-faceted condition. In the UK, it is diagnosed based on the individual having an IQ of 69 or less, and showing significant impairments in social and adaptive functioning present since childhood (<18-years-old) (14). Approximately 1% of the general population have an ID (15), with this group being at a greater risk of experiencing neurological, psychological, emotional and behavioural difficulties (16, 17). For example, those with ID are at an increased risk of developing epilepsy: Epileptic seizures are observed in approximately 22.2% (95% confidence interval, 19.6-25.1) of people with ID, with a higher prevalence amongst those with more severe levels of ID (18). The presence of ID (especially when associated with epilepsy (19)) may also be a risk factor for the development of PNES, as people with ID

represent a greater proportion of PNES cohorts when compared to the general population (9.4% (20) vs. 1%). What is more, previous studies have suggested that there may be a number of clinical differences between this group and those without ID (20).

This article provides a narrative review of current evidence describing epidemiology, aetiology, treatment and outcomes of PNES in adults with ID, and identifies current knowledge gaps. Comparisons between PNES in people with and without ID have been made, in order to characterise the proposed ID sub-group – differences have been summarised in Table 1, including a number of implications for practice. Unfortunately, the available evidence does not allow for a differentiation between sub-groups of those with ID, although this group clearly comprises of a wide range of different pathologies and presentations. We have excluded studies focusing specifically on child and adolescent samples (17 years or younger) because these age groups present with a specific set of challenges and are typically seen by different healthcare services than adults.

Epidemiology

Difficulties in diagnosing PNES in general, and among people with ID more specifically (21), mean that obtaining accurate prevalence and incidence rates of PNES for this group is difficult. This is further impacted by a lack of available data investigating population-based cohorts. However, the rates of comorbid ID reported in cross-sectional samples of adults with PNES have varied from 0 (22) to 45.8% (23); with a median rate of 9.4% across eleven studies (12, 13, 19, 20, 22-29).

This wide range is not surprising, given that comorbidity rates of PNES and ID are likely to depend on many factors, including the reference population and how patients were investigated (both for ID and PNES). For example, Duncan & Oto (20) suggested the prevalence of 25 people with ID in their sample of 288 patients with PNES recruited in a

regional epilepsy service in the West of Scotland (UK) may not be generalisable to the larger population, as those with severe ID were likely to present to a different service. Indeed, access to specialised ID or neurology services for relevant diagnostic tests (such as video-electroencephalography monitoring (V-EEG)) may affect the ability of services to make a confident diagnosis of PNES, and lead to under- or over-reporting of PNES (and perhaps overreporting of epilepsy). This is likely to be particularly relevant for people with ID in low and middle income countries, who often have little access to healthcare professionals, let alone V-EEG (30). Similarly, PNES prevalence rates among individuals with ID seen at specialist centres may not provide accurate estimates of PNES prevalence among the whole ID population, because individuals with complex seizure disorders (potentially including PNES) are likely to be overrepresented at such centres (21, 26), making it difficult to extrapolate findings (31).

Notwithstanding the challenges in obtaining an accurate rate, the reported prevalence of ID among people with PNES suggests ID could be almost as common in PNES as epilepsy is in PNES – indeed, a recent systematic review reported a dual-diagnosis of 22% for epilepsy in patients with PNES and 12% for PNES in those with epilepsy (32). While the association of PNES and ID has been well-documented, the possible aetiological relevance of such cognitive and social deficits is not well recognised. For example, non-specialist clinicians (n=963 psychiatrists working in France) are likely to consider other factors such as personality, addiction, attention seeking or malingering as more important than ID for the development of PNES (33). This suggests the need for further educational interventions for healthcare professionals targeting perceptions of PNES in ID specifically.

Gender

Almost all cohorts without ID show that women are more likely to be diagnosed with PNES than men; with females typically representing three-quarters of patients (34). In ID patient cohorts with PNES, the evidence of a female preponderance is less clear, with rates of approximately 50-67% being reported (13, 20, 26, 35). It is important to note, however, that ID is more prevalent in males, with a male-to-female ratio between 0.7-0.9 (15), which could account for the gender difference among patients with PNES and ID being less pronounced.

Age

PNES have been described as starting at any point across the lifespan beyond the age of 4 years. However, in females there is a clear incidence peak of the disorder in the first or second decade of life, whereas in males, the age-related incidence appears more consistent between mid-adolescence and the fifth decade (34).

Due to the small sample sizes of reported cohorts, it is not clear if age of PNES onset differs between genders among those with ID. While people with ID can also experience PNES from early adulthood to older life with one study reporting a range from 19.3 – 70.6 years (13), evidence collected in Japan suggests individuals with ID (n=46) are more likely to present to services for PNES at an earlier age than individuals without ID (n=106, 23.3 vs 28.9 years, p=0.009) and report a younger age of PNES onset (17.9 vs. 24.9 years, p=0.001) (26). That said, another study investigating a sample of 288 patients found no significant difference in the age of onset or age at diagnosis of PNES (20).

Ethnicity

There is no research specifically examining the ethnicity of people with ID and PNES. While there is evidence from the UK suggesting that people without ID from white

backgrounds are more likely to present to healthcare services for PNES (or consent for their information to be used for research purposes) (34), this information is lacking in the routine reporting of demographic factors in samples with ID (and may not reflect a difference in PNES prevalence at the population level). The lack of data is particularly worrying as people with ID who are from Black, Asian and minority ethnic backgrounds may be facing additional barriers in accessing treatment for PNES (36). Furthermore, there is little data from this patient group to help inform culturally appropriate interventions. This is an area that clearly needs further research to help address inequalities often reported in such underrepresented populations.

Socioeconomic status

Among those without ID, PNES present more commonly among individuals from lower socioeconomic groups (34). Among a UK population with PNES, 88% of those with ID (n=22/25) and 57.4% of individuals without ID (n=151/263) received state benefits (p=0.003) (20). While we know that having a cognitive disability is also a persistent risk factor for lower socioeconomic status (37), there is no research exploring the cause or impact of such status among those with ID and PNES.

Clinical profile

PNES have been documented in people with 'borderline', 'mild', 'moderate' and 'severe' ID. However, this diagnosis seems to be made more commonly in people with 'mild' or 'moderate' ID; for example, one study investigating 15 patients with PNES and ID observed 33.3% had mild- and 40% moderate-ID (13, 20, 38, 39). However, this must be interpreted in light of the difficulties and heterogeneity in results when investigating psychiatric disorders in people with severe ID (40). The literature which might provide an

understanding of the relationship between IQ and PNES risk is difficult to interpret; given the variability between samples investigated and how authors have grouped, diagnosed or defined people with ID. For instance, in some studies, participants were classified as having low IQ or ID despite having an IQ of above 70 (26, 41); furthermore, participants' levels of functioning were not always assessed using standardised neuropsychological evaluations as part of research designs.

Individuals with ID and PNES may have greater impairments in social and practical adaptive skills than those with epilepsy and ID alone (n=30, p=0.013) (13); however, given the cross-sectional nature of available investigations, it is unclear whether the observed impairments are a cause or result of PNES (or related to another factor). Indeed, longitudinal studies are needed investigating patients with PNES and ID, as currently, little is known about how the condition changes over time in ID.

Several studies have observed high rates of PNES in people with ID and comorbid epilepsy, for instance, one study reported a rate of 36% (n=9/25) compared to 8.7% in people without ID (n=23/263) (13, 19, 20, 23, 38). Although the manifestation of PNES is usually preceded by that of epilepsy in those with mixed seizure disorders (41), in cohorts with ID, it is not always documented how many patients with PNES developed epilepsy, or how many of those with epilepsy developed PNES. While the presence of additional epilepsy could make it more difficult to diagnose PNES, there is no consistent evidence that comorbid epileptic seizures extend the diagnostic delay of PNES, at least in people without ID (42). If new types of seizures manifest in individuals with ID and established epilepsy, clinicians should certainly consider whether the patient may have developed PNES (43).

In samples without ID, PNES have been associated with higher rates of antecedent sexual, physical and/or emotional trauma than reported in the general population, and with higher levels of distress in response to previous negative life events (44, 45). Such trauma

appears to be reported less frequently by people with ID and PNES (20, 26), despite this population being at a heightened risk of experiencing certain forms of abuse (17, 46). This finding could also be explained by a number of factors including reporting bias - as individuals with ID have a lower tendency to recognise or report abuse than those without ID (20) - and such information may not always be available to researchers or clinicians involved in making the diagnosis of PNES.

It is well-documented that adults with PNES have higher rates of psychiatric comorbidity and psychosocial difficulties than found in the general population (47). This seems to also be true for people with ID with depression including self-harm, anxiety and panic attacks, autism spectrum disorders (ASD), aggressive behaviours, psychosis, personality disorders, adjustment disorders, 'neurotic complaints' and "medically unexplained symptoms" having been documented across different cohorts (13, 20, 26, 38). Indeed, approximately 50% of people with ID and PNES have been reported to receive daily use of psychotropic medication (13), although this may not only be a reflection of a high rate of psychiatric comorbidity, but also the result of those with ID being more likely to be receiving psychiatric care (13, 48).

In one study comparing patients with PNES (n=46) with and without ID (n=106), psychosis was reported to be more common in the presence of ID than in the population without ID (16% vs 1%, p=0.001). In contrast, "neurotic complaints" were more common among patients without ID than those with ID (27% vs 7%, p=0.004) (26). However, caution must be taken when comparing psychiatric difficulties between the two groups, given the additional challenges in diagnosing psychological conditions in people with ID (49) and considering that some conditions are already more prevalent in people with ID; for instance, psychosis has been found to be more frequent in people with ID than without ID in non-PNES cohorts (50).

In a study of patients with ID, controlling for age, sex and level of ID, those with PNES (n=15) were reported to have a higher rate of depressive symptoms ($P<0.05$) and to have experienced a greater number of negative life events over the last year (e.g. bereavement, loss and illness, $p<0.01$)) than people with epilepsy (n=15) (13). Generally speaking, people who have ID are more likely to be exposed to social factors and adverse life events that are associated with poor physical and mental health (51, 52). Adverse life events, loss, major transitions or changes could also precipitate the development of a PNES disorder in people with ID (53). However, most ID cohort studies have been too small to provide compelling statistical support for these associations.

Diagnosis of PNES

It is clear that the formulation of an accurate and timely diagnosis of PNES is crucial for the provision of the most effective and suitable treatment (54). Despite this, individuals in the general population typically experience a diagnostic delay of several years (42), with many people initially misdiagnosed with epilepsy. Diagnostic delays may be even longer for people with ID than for those without ID (10.7 vs. 6.9 years, $p=0.07$) (20). More recent studies suggest that typical diagnostic delays have become shorter (2.5 vs. 3.9 years (26)), although they can still be measured in years (26, 38, 55).

In order to allow clinicians to formulate a diagnosis of PNES in the absence of complete certainty, and to put them in a position to offer appropriate treatment when such certainty cannot be achieved, the International League Against Epilepsy have proposed four levels of certainty of a PNES diagnosis: ‘possible’, ‘probable’, ‘clinically established’ or ‘documented’ diagnosis. While the observation of a typical event by V-EEG represents the diagnostic gold standard in this categorisation, guidance suggests that the diagnosis could be sufficiently likely to initiate treatment for PNES, for instance, on the basis of an expert

assessment of the patient's history and seizure description or the direct observation of a non-epileptic seizure by an expert (56).

Investigating patients who visited an Epilepsy Unit in Japan, no significant differences were reported between people with ID (n=46) and without ID (n=106) in the ratio of 'possible' (41% vs. 38%, p=0.68), 'probable' (30% vs. 44%, p=0.11), and 'clinically established or documented' (28% vs 18%, p=0.15) diagnoses of PNES (26). This is somewhat surprising as – at least in patients with more severe ID – the patients' account of their subjective seizure experience (which typically provides a greater contribution to the diagnostic process than witness observations (57-59)) may be lacking or limited by communication difficulties.

In view of the high rates of comorbid epilepsy, V-EEG investigation is particularly important in patients with ID and seizures. Stereotypical behaviours that could be mistaken for epilepsy or PNES, and other clinical scenarios in which minor epileptic seizures trigger non-epileptic behavioural alterations that could be interpreted as PNES are particularly common in this patient group. The largest study in this area investigated 124 patients with ID undergoing V-EEG to evaluate behaviours believed by care staff to be epileptic in nature. Overall, 40.3% of patients were found to have PNES, 16.1% epilepsy and 8.9% mixed seizure disorders. V-EEG was inconclusive in 34.7% of patients. Nine out of ten patients given a PNES diagnosis experienced an event in the first session of V-EEG lasting up to six hours, compared to 70% of people with epilepsy and 46% of people with PNES and epilepsy - the remaining patients needed more than one session (up to 15 sessions) of V-EEG to obtain a diagnosis (39).

A range of conditions involving repetitive stereotyped behaviours can complicate the process of distinguishing PNES from other seizure-like events in individuals with neurodevelopmental disorders (60). This differentiation is particularly challenging when

patients with ID cannot communicate their seizure experiences because of communication impairments or when diagnosticians do not have access to witnesses who know the patient well and are able to provide an accurate clinical history (53). Motor manifestations associated with neurodevelopmental conditions, including tic disorders, Attention Deficit Hyperactivity Disorder, ASD, stereotyped behaviours and side effects of medications can all produce phenomena resembling PNES (and epilepsy (59, 60)). ASD in particular has been identified as a prevalent comorbidity in children with ID (<18 years) and PNES (61), although little research into possible associations of ASD and PNES exists in adults. Behaviours conceptualised as stereotypic, repeated blinking or swallowing, buccolingual movements, psychomotor arrest, spontaneous or vacant facial expressions or dystonic posturing seem to pose the greatest diagnostic challenge when differentiating between neurodevelopmental symptomatology, epilepsy and PNES in those with ID (43) - most likely because of the frequency, variability, and unknown function or cause of such behaviours. Moreover, caregivers of children and adults have also been confused by PNES events and stereotypic self-stimulatory or self-abusive behaviours, resulting in misdiagnosis (21, 43).

Aetiology of PNES

The clinical and demographic heterogeneity of PNES suggests that there is no single necessary and sufficient factor explaining PNES across all patients. In the general population, biopsychosocial aetiological model of PNES has been proposed, identifying a range of potential predisposing, precipitating and perpetuating factors (62). Different psychological explanations of PNES have been put forward, including dissociation, somatisation or 'conversion' of psychological distress and conflict into a physical symptom. An integrative cognitive model has been suggested which interprets PNES as a subjectively non-volitional response to arousal in which a mental representation of seizures (the 'seizure scaffold') is

activated by internal or external triggers – often facilitated by deficits of inhibitory mechanisms. Each seizure involves a transition from a state of physiological arousal to one characterised by a drop of sympathetic and increase in parasympathetic tone. Individual seizures therefore provide a form of relief in the moment, reinforcing the seizure mechanism (1).

Traditional conceptualisations of PNES in ID have tended to interpret these seizures as behavioural responses to environmental triggers and non-verbal means of communicating or reducing distress (38). PNES disorders in ID have been viewed as resulting from the reinforcement of seizure behaviours over time; for instance, related to the experience that PNES elicit a positive response from others, such as caregivers, allowing patients to avoid demands, or escape overstimulation and other unpleasant situations (38, 63).

While this conceptualisation does not explicitly imply that all PNES in ID are volitional, it involves a greater element of volition than an interpretation of PNES as dissociative responses to distress. Although it is impossible to determine objectively and with certainty whether a particular PNES event is wilfully produced, there is evidence that people with PNES may have little to no control over the events (64) – including from individuals with ID (65). Even in situations in which PNES apparently give the patient a degree of control over their immediate environment and communicate that a particular need is not being met, PNES behaviour may manifest 'automatically' as a result of heightened emotion – which may well arise in people with ID, in part, due to limited verbal and non-verbal social or communication skills. A proportion of adults with ID without PNES have been shown to use less effective coping strategies to manage stressful events, such as cognitive and behavioural avoidance (66). Suboptimal coping skills and increased avoidance tendencies have certainly been described in individuals with PNES without ID (44, 67).

In some cases, PNES in ID could be a learnt behaviour, for instance based on the patients' experience with caregivers' responses to an epileptic seizure. However, even in such cases, the learning process shaping the seizures would often be unconscious and unintentional (38). As in patients without ID, such learning processes could also explain why PNES sometimes develop in those with ID after epileptic seizures have stopped or been controlled by therapeutic interventions. This phenomenon has previously been described most commonly in patients without ID who have become free of epileptic seizures after epilepsy surgery (68), but it has also been observed in other circumstances (38). The behavioural interpretation of this scenario would be that PNES mimics or is a symptom substitute of epileptic seizures, possibly as a means of compensating for loss of attention and care received due to this reduction (32, 38). Interestingly, healthcare professionals have reported responding to PNES in ID as they would to an epileptic seizure (13). Unfortunately, for some, this response could contribute to the perpetuation of PNES, not only by 'rewarding' patients with additional attention, but also by heightening anxiety (among patients and caregivers) about individuals being left alone and unobserved, promoting dependence, reducing quality of life (QoL) and self-confidence (65).

However, as suggested above, this is not the only possible explanation why PNES may continue when more definite epileptic seizures have stopped. Moreover, given that not everyone with ID and PNES has epilepsy, and only a small proportion of those with ID and epilepsy go on to develop PNES, the interpretation of PNES as a behaviour learned through carer responses to epileptic seizures can only apply to a sub-group. What is more, caution must be taken regarding how this formulation is delivered, in order not to contribute to the stigma and discrimination that this group is at risk of experiencing due to their ID (69). Like among those without ID, most PNES in individuals with ID are likely to feel non-volitional

and, understandably, patients with ID have reported upset upon hearing messages that their seizures are a way of seeking attention (65).

While there is no evidence to the contrary, it seems best to assume that there is little difference in the aetiology or function of PNES between those with and without ID, and that for most, PNES in ID are an involuntary mechanism which functions as a means of protecting the individual from a stimulus that is experienced as overwhelming, threatening or intolerable. While PNES in ID is commonly conceptualised as learnt behaviour resulting, in part, from interactions with caregivers, this has also been proposed as a potential mechanism for the development of PNES in people without ID, in which responses from others can serve as a perpetuating and reinforcing factor (70). However, what may be different for people with ID is that the nature and intensity of such interactions may be different (and more easily observable) given the additional needs and involvement of carers typically associated with a developmental disorder. Moreover, individuals with ID may have greater difficulty in communicating their needs, therefore increasing the likelihood of eliciting a response that could be reinforcing.

PNES Triggers

The observation that PNES in ID can act as a means of allowing individuals to exert a degree of control over their environment or function as a distress-reducing mechanism, has been supported by the finding that events are often triggered by immediate or situational circumstances (20, 71). For example, heightened emotions, stress, negative mood, anger, anxiety, boredom, fatigue, effects of medication, overdemanding or overstimulation situations and unexpected life events have all been reported as triggers of PNES events (or at least observed in patients with ID prior to event onset) (13, 20, 43, 65, 72). Nursing staff have claimed to recognise precipitants of PNES in almost 90% of cases in patients with ID (13) -

although such observations are difficult to objectify and may themselves be subject to attentional or recollection bias.

People with ID may experience PNES in different settings, including at home, day centre and medical care settings (20). In some cases, PNES may exclusively happen when the patient is in a certain situation; for example, only at home, in the morning or in the afternoon (13). The interpretation of this is difficult, as it is not always clear if the environment is causing a degree of distress triggering an event, or the events happen in a relatively safe setting while experiences in another environment are causing emotional distress. Unfortunately, the literature on PNES triggers is not of high quality and often fails to describe how information concerning onset of the PNES event has been gathered, for instance, whether the event was witnessed or whether it occurred in the presence of another. This may be particularly relevant, given the proposed communicative function of PNES in some individuals with ID.

Like in patients without ID, PNES in people with ID have been observed during the day and night (13). In patients without ID, self- or witness-reports of nocturnal seizures have been reported (73), although video-EEG recordings of apparently sleep-associated seizures (with very few exceptions (74)) tend to document that PNES arise from the waking state, rather than actual sleep. In view of the higher prevalence of epilepsy in those with ID, reports of seizures from apparent sleep may have a different clinical significance; for example, indicating epilepsy or comorbid epileptic seizures, but this hypothesis has yet to be examined.

PNES Characteristics

PNES have been observed as an enduring and persistent condition in people with ID, spanning several years to decades (38). Given the limited data, it is unclear if PNES can also present as a more acute and self-limited disorder in ID. The frequency of PNES events varies,

with evidence suggesting people with ID can experience events daily, weekly or monthly (13). As in the general PNES population, individuals with ID can also experience multiple PNES events within a single day (72). Two self-report studies suggests that the duration of episodes can range from several minutes to an hour (65, 72).

Studies of the phenomenology of PNES in ID are complicated by the more limited insight that people with ID may have into their subjective seizure experience, and their reduced communication skills. This may increase the focus on the visible seizure manifestations which underpin the behavioural interpretations of PNES in patients with ID. Gordon et al., (23) found that adults with ID, epilepsy and PNES struggled to correctly distinguish between different types of their seizures, although similar difficulties are also common in patients with mixed seizure disorders without ID (23, 75).

Characteristics of PNES in people with and without ID have been described as heterogeneous and no single feature of PNES is pathognomonic (76). PNES semiology in ID has been thought to be similar to epileptic seizures in (80%) most cases (13). PNES in ID may resemble tonic-like (i.e. stiffening of muscles), tonic-clonic-like (i.e. jerking and twitching or generalised convulsions) and absence-like (i.e. blanking out) seizures (13). Episodes resembling myoclonic jerks, arc en circle and akinetic seizures have also been observed (38). There may however be some differences in PNES semiology between people with and without ID; for example, in one study, 'blanks' (possible describing absences) were only observed in people without ID (20). However, as another study reported absence-like seizures in people with ID (13), differences seem to depend on the samples investigated.

In unselected patient cohorts, over 30% of adults without ID report PNES-related injuries (77). Similarly, in ID, one small study (n=15) reported that minor injuries occurred in just over 25% of people, but no specific details of the injuries were provided (13). As in those without ID, PNES in ID can certainly result in falls (43) and may lead to the need for

protective clothing, such as joint pads and a soft helmet (63). No data is available on the frequency of other symptoms often observed in epileptic seizures in those with PNES and ID, such as tongue biting or urinary incontinence. In patients with PNES without ID, unspecified self-reports of these symptoms do not differentiate between the two diagnoses (only 'lateral' tongue biting was found to be suggestive of epilepsy) (78, 79).

Compared to those without ID, people with ID are more likely to have a documented history of seizure-status (44% (n=11/25) compared to 16% (n=42/263), $p<0.001$ – this is a prolonged or repeated PNES event misdiagnosed and treated as status epilepticus in hospital, often described as 'pseudostatus' (20, 71). However, no conclusions can be drawn as to whether this is a reflection of how PNES presents in ID, or how carers respond to episodes in adults with ID given the challenges in diagnosing the condition.

It has been reported that people with ID (like those without ID (80)) may have some level of awareness of their surroundings during a PNES episode, be responsive to others (63) and recall events afterwards. For example, individuals may remember receiving treatment by caregivers, with nursing staff also able to soothe or engage them in conversation (13, 53). Of course, this observation does not imply that the seizures must therefore be deliberate or faked.

Largely what we know regarding the experience of PNES events in ID tends to come from visual observations of behavioural manifestations. There has been no research (qualitative or quantitative) investigating subjective cognitive, emotional and physiological experiences of PNES events, whereas in those without ID, such investigations have produced important diagnostic, therapeutic and prognostic implications (6).

Treatment

Communicating the diagnosis

A clear communication of the diagnosis of PNES is an important step in treatment and can even be associated with a reduction or cessation of seizures in those with ID (38) and without (81). However, the explanation of this diagnosis is often perceived as a challenging process by healthcare professionals, not least because patients (and their caregivers) may resist the diagnosis (82). While a number of studies provide guidance on how to tackle this important clinical task in those without ID (83-85), less is known about how best to communicate the diagnosis to patients with ID, their family and caregivers – despite clinicians being likely to face additional challenges in this group.

Supporting patients with and without ID in understanding the nature of their symptoms, and recognising and challenging unhelpful narratives concerning the function of PNES have been helpful for the treatment of the disorder in people with PNES (65, 86). Nevertheless, patients with ID may be less likely to remember receiving their diagnosis of PNES than those without ID (36.4% of 11 people with ID could remember vs 84.6% in 13 people without ID, p=0.02) (23). Additional steps may be required to adapt communication and develop resources to support people with ID in understanding and retaining their diagnosis.

Further interventions

Currently, there are no widely agreed guidelines for the treatment of PNES, although psychological interventions are recommended as the treatment of choice (54). Psychotherapeutic approaches originally developed for the general population can be effective for individuals with ID; however, they must be adapted to the clients' abilities and needs, and may require additional sessions (87). In the case of PNES, care plans may also

need to be adapted to take account of different aetiological profiles, and treatments must be deliverable by clinicians who are accessible to, and familiar with, individuals with ID.

Existing treatments for PNES focus on reducing seizure frequency, as well as managing psychosocial difficulties and improving QoL (7, 88). This approach seems particularly important to people with ID, given the prevalence of comorbid psychopathology and social problems in this group. From our clinical experiences, treatment for people with confirmed (and suspected) ID presenting with PNES, may begin with a comprehensive needs assessment, screening for mental health conditions and medical disorders including epilepsy; medication review; assessment of social care and housing requirements; and a neuropsychological review or assessment.

A decision about the use of anti-seizure medications (ASMs) is a particularly important part of the medication review. Healthcare professionals tend to prescribe ASMs for patients with suspected PNES as a precaution when they are uncertain about this diagnosis (89). While there is no research specifically examining professionals' practice toward people with ID and PNES, it stands to reason that diagnostic uncertainty would be greater (and the assumption of comorbid epilepsy more likely) in patients with ID. In fact, there is evidence to suggest that, after controlling for comorbid epilepsy, those with PNES and ID (n=17/36) are more likely to be prescribed ASM than people without ID (n=25/89, $p<0.04$) (20, 26). However, the gradual withdrawal of ASMs, which have been erroneously prescribed to patients with PNES without comorbid epilepsy, is a key aspect of treatment as there is no evidence that such drugs treat PNES. In contrast, it has been shown that the continuation of ASMs after a diagnosis of PNES (and no epilepsy) is associated with a poorer outcome (90, 91). What is more, ASM treatment is often associated with toxicity, as treatment is titrated upwards on the assumption that the patient's continuing seizures must be epileptic. ASM toxicity is therefore a particular risk in individuals with ID as such patients may not complain

of minor side effects of ASMs or their complaints may not be understood. In some cases, ASM toxicity may facilitate PNES (92). The use of emergency intervention protocols for prolonged seizures (for instance with drugs such as midazolam) is particularly problematic in patients with ID with PNES and epilepsy. Unless caregivers have learnt reliably to distinguish between prolonged epileptic and nonepileptic seizures, there is a high risk of inappropriate use of such medicines for PNES.

In addition, the prescription of ASMs for causes other than epilepsy can result in confusion about the diagnosis among patients, caregivers and health professionals and lead to the misdiagnosis of non-epileptic phenomena as epilepsy (93). This is a particular problem with the common practice to use ASMs as mood stabilisers or to manage aggression in the context of ID (94). If ASMs seem absolutely unavoidable for this purpose, clinicians, patients and families must be clear that the treatment is intended to help stabilise mood and not as a treatment of seizures. It would also be essential to closely monitor the effectiveness of this intervention, as there is evidence showing use of ASMs in people with developmental disorders with a cognitive impairment is often associated with adverse emotional and behavioural symptoms (95).

Before discussing specific interventions in people with ID, it is important to recognise that the therapeutic modality offered is likely to be influenced by a range of factors, including the formulation of the client's presenting problem(s), training of the healthcare professional and the service providing treatment. For example, PNES have been described as an 'orphan disorder' (96), falling in between the care of different specialists, with lack of clarity about who is responsible for the treatment of this patient group (89). People with ID and PNES are likely to face similar, if not greater, difficulties with access to appropriate treatment, with professionals working within general services feeling ID specific providers are better suited to meet the needs of people with ID, who in turn, may lack the specialist knowledge of

treating PNES. Patients with ID may find it more challenging than those without ID to seek help proactively and overcome such barriers to service provision.

While behaviour modification and deconditioning techniques are suggested and commonly used as a treatment for PNES events in those with ID (38), there is little evidence discussing the content of treatments or their effectiveness - at least in adults (97-99). In two case studies, involving a male and a female with ID in their 40s, both with PNES, epilepsy and other neurological and neurodevelopmental conditions, bespoke behavioural interventions were delivered by care staff. One treatment focused directly on PNES behaviours using a hierarchy of behavioural reinforcement techniques, for example, verbal redirection (i.e., saying "no" with the aim of preventing a PNES event), formulating the function and perceived cause of the behaviour and rewarding cessation of PNES events. A reduction of PNES was observed over an 18-month period (63). The other study used a series of indirect interventions aimed at reducing situational distress and social isolation, rewarding positive behaviours and helping the client develop more adaptive ways of expressing and communicating her emotions (53).

This evidence demonstrates the value of helping caregivers gain a better understanding of PNES in ID, how to distinguish between nonepileptic events and other behavioural manifestations, including epileptic seizures, and respond in a more adaptive manner. Such interventions also helped caregivers feel more confident in managing PNES events alone without the need for hospital admissions and visits to emergency services (53), thus reducing the emotional and financial burden of the condition. Indeed, avoidable presentations to emergency departments for PNES are high in people with and without ID (20).

Both of the case studies outlined above are based on altering the responses of the patient's social environment to PNES. This is also likely to be a key component of the

'environmental adjustment' measures which were reported as one of the most popular form of PNES treatment in a survey of clinicians from Japan (3), and which Japanese clinicians were particularly likely to recommend for patients with PNES and ID (26). Examples of these measures include altering the patient's environment to help reduce their stress – presumably, following an initial assessment and formulation of precipitating factors that can be attributed to the patient's environment, changing caregivers' attitude towards PNES events and helping them to recognise and manage unhelpful elements of the client's environment, such as antecedents and maintenance factors. Caregivers and family members will be essential in the implementation of such interventions, especially in clients with more severe difficulties. As such, in addition to research investigating outcomes of treatments for PNES in people with ID, studies should also aim to document and evaluate the process of implementation and change, as this insight could be used to help inform the training and support of caregivers.

Evidence is growing for the use of adapted Cognitive Behavioural Therapy (CBT) for PNES (88, 100). Indeed, practice-based evidence exists supporting CBT for the treatment of PNES in people with mild-moderate ID. Such interventions have aimed to help clients with ID develop more adaptive coping strategies and break out of maintenance cycles, thus making them less susceptible to experiencing PNES events (65, 72). In separate case studies from the UK involving two females with ID in their 20's, CBT interventions were delivered, which consisted of psychoeducation; helping clients gain greater insight into their thinking styles, emotions, behaviour and PNES; and developing coping strategies for their difficulties, including PNES. Interventions ranged from 12-13 sessions focusing on symptoms of PNES and mood disorders. Attrition was low, indicating this treatment was acceptable. A reduction or cessation of seizures was reported at the end of therapy; however, scores on psychological outcomes, such as anxiety and depression, were relatively unchanged and anxiety remained above the clinical cut off (65, 72).

While practice-based research has played a crucial role in the development of treatments for people with ID, the lack of more robust research methodologies has resulted in findings being associated with a high or unclear risk of bias. For instance, the aforementioned case studies did not include any long-term follow-up assessments and therefore it is not documented whether any benefits were maintained beyond the end of treatment.

Treatment outcomes

Unfortunately, there are no prospective treatment outcome studies focusing on patients with PNES and ID. The only larger-scale evidence regarding the outcomes of interventions for PNES in those with ID comes from retrospective cohort studies, which have yielded mixed findings.

People with ID have been reported to be more likely to consent to treatment following the initial assessment (p=0.03), and 3.7 times more likely to attend appointments, compared to those without ID (24, 26). While this could mean that treatments for PNES are more acceptable or appropriate for people with ID than for those without ID, this has not been specifically examined. This finding could also be explained, in part, by the high levels of acquiescence often observed in people with ID (101). Moreover, it is not clear whether greater attendance is associated with prognosis. Indeed, the available data is mixed in relation to whether or not having a diagnosis of ID is associated with poorer treatments outcomes, including a greater risk of PNES events continuing after the communication of the diagnosis and at the end of treatment (24, 26, 29). Interventions have consisted of non-specified psychological treatment, cognitive therapy, brief weekly visits, environmental adjustments and pharmacological therapy (24, 26). These results must also be interpreted in light of a number of limitations: samples sizes are relatively small and therefore, studies are not sufficiently powered to detect statistical change and clinical change is not examined;

treatments are not always clearly defined; effectiveness of specific therapeutic approaches have not been evaluated or reported; and the heterogeneity in methodologies across studies means that it is difficult to meaningfully compare effectiveness between samples. In addition, no researchers have, as of yet, stratified samples based on variables with potential effects on the acceptability, adherence or impact of treatment. Such data could help to inform a treatment-matching approach (102), for example, taking account of factors such as ID severity, nature of PNES, comorbid conditions or quality of support systems.

Table 1 Summary of main differences in PNES between people without and with ID

	People without ID	People with ID	Implications for ID in PNES
Epidemiology	Within the general population, PNES account for 10-20% of presentations to seizure clinics *Figures will include people with ID	No available data regarding incidence or prevalence rates specifically. Median rate of 9.4% (range 0 - 45.8%) of comorbid ID in cohort samples of PNES.	Extrapolating rates from PNES cohort samples and notwithstanding heterogeneity, approximately 9.4% of patients with PNES have ID
Gender	Female preponderance of up to 75%	Evidence is less clear regarding the existence and degree of female preponderance	Likely to have a female preponderance, although ID is more common in males.
Age	Onset across the life span (>4 years old). Gender differences are reported: onset in females most common in second to third decade; in males between adolescence and 60 years.	Onset across the lifespan. Mixed evidence regarding whether people with ID are more likely to develop PNES at an earlier age. No evidence investigating possible gender differences.	Can develop at any age and no data on gender differences.
Ethnicity	People from white backgrounds are more likely to present to services for PNES care.	No data available.	People with ID and PNES from non-white backgrounds may experience additional barriers to accessing treatment for PNES.
Socio-economic status	People from lower socio-economic groups are more likely to develop PNES.	People with ID and PNES are more likely to receive state benefits compared to people with PNES without ID.	Having a diagnosis of ID and PNES is likely to be associated with greater social deprivation.
Clinical profile	Lower IQ may increase likelihood of developing PNES. High rates of previous trauma and negative life events. Greater prevalence of	PNES occur in people with differing levels of ID, although less commonly identified in people with severe ID. Higher rates of PNES in people with ID and comorbid	PNES can occur in people with varying levels of ID. Comorbid epilepsy, psychological disorders and negative life

	psychological conditions than the general population.	epilepsy – although unclear whether people with PNES develop epilepsy or people with epilepsy develop PNES. Less likely to report trauma than people with PNES without ID. Higher rates of psychological conditions than the general ID and non-ID population, with approximately 50% receiving psychotropic medication.	events are prevalent in the group, which may precipitate or perpetuate PNES disorders.
Diagnosis of PNES	Delay in PNES diagnosis is common. Diagnosis based on International League Against Epilepsy recommendations for PNES with V-EEG representing diagnostic gold standard.	More likely to experience a delay in PNES diagnosis. Diagnosis based on International League Against Epilepsy recommendations for PNES also used in this population.	Difficulties linked to ID may affect diagnostic process, such as obtaining patients' account of their seizure experience and presentation of repetitive, stereotyped behaviours.
Aetiology of PNES	Conceptualised using a range of theories, including an integrative cognitive model.	PNES viewed as a behavioural response to environmental triggers and non-verbal means of communication, which could have also been reinforced by the reaction of caregivers.	PNES in ID can be viewed as an involuntary response with the function of reducing distress and protecting the individual from difficult stimuli.
PNES triggers	Triggered by internal and external events, but absence of triggers also common. Can occur in a range of settings.	More likely to be triggered by immediate and situational events. Can occur in a range of settings or be linked to a particular situation.	Apparent differences in the nature of triggers; however, the evidence is largely based on the interpretation of observers.
PNES characteristics	Can be an acute or chronic disorder. Heterogeneity in frequency and duration of PNES episodes, and semiology. Patients report difficulties in differentiating between the	Appears likely to be enduring and persistent. Heterogeneity in frequency and duration of events and semiology. Greater difficulties in patients differentiating between subjective experiences associated with PNES and	PNES may be a more chronic disorder in this population. Heterogeneity in the characteristics of PNES events with no single feature

	subjective experiences associated with PNES and epileptic seizures. PNES related injuries occur in approx. 30%. Impaired consciousness observed during PNES episodes and patients may respond or later recall events.	epileptic seizures. PNES related injuries occur in approx. 25%. More likely to have a history of 'pseudostatus'. Impaired consciousness observed during PNES event and patients may respond.	pathognomonic. Similar risk of PNES-related injurie, although no data on severity of injuries. 'Pseudostatus' more common. Varying levels of impaired consciousness during PNES events.
Treatment			
Communicating the diagnosis	Clear communication of the diagnosis is essential and can impact seizure frequency.	Clear communication of the diagnosis is essential and can impact seizure frequency. People with ID less likely to remember receiving the diagnosis.	The diagnosis is an important stage in care. Adaptations to language and resources may be required to facilitate this step.
Further interventions	No widely agreed treatment guidelines for PNES, although psychological therapy recommended. Treatments focus on reducing seizure frequency and improving psychosocial difficulties. Medical assessment including review of ASM (if relevant). A range of psychological treatments has been investigated including CBT, psychodynamic therapy and eclectic interventions.	No widely agreed treatment guidelines for PNES. More likely to be prescribed ASM, although this could be prescribed for other difficulties. Greater use of behaviour modification and deconditioning techniques, although evidence is limited and treatments poorly described. Caregivers and family members are often involved in the implementation of interventions. Some evidence to suggest the effectiveness of CBT and cognitive or non-specified psychological therapies.	No widely agreed treatment recommendations. Treatment may begin with a comprehensive needs assessment considering comorbid conditions, medication review, social care needs and neuropsychological evaluation. Behaviour-focused interventions are more likely to be used, however treatments should be guided by an initial assessment and formulation of the clients' difficulties and needs.
Treatment outcomes	Some prospective cohort studies. Uptake and adherence to treatment can vary. Findings are heterogeneous and suggest treatments are effective in reducing PNES events or cessation of	Evidence generated from retrospective cohort studies. Patients more likely to consent to and attend treatment. Mixed evidence of ID being a risk factor for poor prognosis.	Evidence is mixed regarding treatment outcomes. Current data limited by high risk of bias.

		events in approximately 50% of patients. Treatments also effective in reducing comorbid psychological difficulties.

ID = Intellectual Disability; PNES = Psychogenic Non-Epileptic Seizures; ASM = Anti-Seizure Medication; CBT = Cognitive Behavioural Therapy

Conclusions

To our knowledge, this is the first comprehensive overview of the literature describing PNES in adults with ID. The findings support the notion that PNES are a heterogeneous condition and highlights the benefits of differentiating between patient sub-groups in research and clinical practice. Both ID and PNES are conditions associated with considerable emotional, behavioural and social impact on patients and their caregivers, which also pose significant challenges to service providers and are costly for society at large. Sadly, the mental health needs of people with ID are often overlooked, partly due to diagnostic overshadowing and a lack of reliable assessment tools (16), thus contributing to significant inequalities in care (103). People with ID represent a neglected, yet important subgroup of the whole PNES patient population (13).

The many gaps identified in our review demonstrate that more work needs to be done to achieve a better understanding of this particularly complex patient group. People with ID are frequently excluded from PNES research resulting in a lack of data (26). Combined with the difficulty of extrapolating results from the general population to those with ID, there is only a small evidence-base to inform care for people with ID who experience PNES. Most of the available evidence which is not generalised from patients with PNES without ID, comes from retrospective datasets often collected in routine practice contexts and is therefore likely to be associated with a high or unknown level of bias. Moreover, despite the described differences between ID and non-ID PNES populations, authors rarely present data separately for these two sub-groups, further limiting the availably and reliability of results.

It is a limitation of this review that studies were not identified using a systematic search strategy. Instead, a narrative approach was adopted discussing what we believe to be key factors in understanding PNES in ID and informing future practice. We came to the conclusion that the narrative approach best suited our aim of targeting this review at the

broad range of healthcare professionals who are likely to provide care for patients with ID and PNES, for instance in multidisciplinary settings.

The international scope of this review should improve the generalisability of the findings, although we acknowledge that research from non-English speaking and lower income countries is (as is often the case) under-represented. Going forward, research at all levels of the hierarchy of scientific evidence will be required to gain a better understanding of the characteristics and needs of people with PNES and ID, and to develop effective and accessible treatments for this population. We hope that this review will stimulate discussion and further enquiry in this area.

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