

Title: Autism spectrum disorder in children and young people with non-epileptic seizures

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ABSTRACT

Purpose

Non-epileptic seizures are paroxysmal events which to an observer resemble epileptic seizures. Proposed risk factors incorporate biopsychosocial aspects including factors in the affected individual. Unexpectedly high rates of autism spectrum disorder (ASD) occurred in the clinical population reported here. Although elevated levels of psychiatric co-morbidity are known to be present in patients with NES, ASD has only been previously described in a single case report.

Methods

This case series captures rates of ASD in 59 children and young people who were referred to a specialist paediatric mental health service at Great Ormond Street Hospital, London, UK for assessment and treatment of non-epileptic seizures between 2012 and 2016.

Results

10/59 (16.9%) of the children and young people with non-epileptic seizures also had ASD, with 5/10 (50%) of these undiagnosed with ASD before referral. Children and young people with ASD were significantly more likely to have tics or attention-deficit hyperactivity disorder than those without ASD.

Conclusion

ASD may be a common co-morbidity in non-epileptic seizures. Careful clinical assessment with consideration of ASD traits is therefore important in the non-epileptic seizures population. It is beneficial to diagnose ASD early as its presence is likely to require a modified approach to assessment and treatment of non-epileptic seizures. Study of the development of non-epileptic seizures in ASD may suggest hypotheses for the pathogenesis of non-epileptic seizures in the wider population.

Keywords

- non-epileptic seizures
- functional neurological symptoms
- autism
- children

Highlights

- Assessment of non-epileptic seizures should include detailed screening for autism
- Assessment of epilepsy in autism should involve considering non-epileptic seizures
- Possible reasons for an association between NES and ASD are discussed

Purpose

Non-epileptic seizures (NES) are paroxysmal events which to an observer resemble epileptic seizures, but do not have the electrophysiological correlates of epilepsy. NES are regarded as psychogenic in origin, but the diagnosis can be made without requiring identification of a psychological stressor [1]. Semiology can vary greatly between patients and a range of alternative names are used for the disorder [2].

Research in the paediatric age range with NES is poorly developed [2]. Children and young people with NES often have significant psychiatric comorbidity and a sibling-control study has shown higher rates of depression, anxiety and post-traumatic stress disorder (PTSD), though not attention deficit hyperactivity disorder (ADHD) [3]. Acquiring a diagnosis of NES is frequently experienced as a lengthy journey, involving multiple investigations and causing frustration for children and families [4]. There is limited research on effective interventions for NES, with no treatment trials in children and young people.

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterised by deficits in social communication and interaction, restricted or repetitive interests and consequent impairment of functioning and is a common comorbidity in children and young people with epilepsy [5]. ASD has been reported as being associated with NES only in a single case report [6].

The Psychological Medicine Team at Great Ormond Street Hospital, a tertiary paediatric hospital in London, receives referrals from paediatricians and psychiatrists across the UK to assess and treat NES. The team has anecdotally observed high rates of ASD and autistic traits in these cases.

This study, through case note analysis, aims to capture rates of ASD in a consecutive sample of children and young people with NES referred to the service, to give an overview of their characteristics, compare these to the patients with NES but no ASD, and describe features of the clinical work. Assessment, treatment and liaison with other services when working with NES and ASD will be described, supplemented by two case examples.

Methods

A database of all children and young people referred to the service and diagnosed with NES between 2012 and 2016 was analysed. The medical records of this cohort were obtained by the research team retrospectively, and 59 consecutive referrals for NES during this time period were identified. Inclusion criteria were: age under 18 at time of assessment, diagnosis of NES had been confirmed during the routine clinical assessment described in the medical record. All patients who attended the mental health assessment were included.

Outcomes of the initial clinical assessment were summarised from the medical records. This detailed diagnostic assessment was undertaken by a multi-disciplinary team, involving a consultant psychiatrist, a clinical psychologist and with consultation from neurology if the child had not received a neurology opinion before referral. A priority at this assessment was detection of psychiatric and neurodevelopmental co-morbidity, including ASD, and pre-existing diagnoses were reviewed and re-considered at this point. Multiple appointments were sometimes required for a satisfactory formulation, further assessments with other teams were arranged, and information was incorporated from other sources (medical and psychiatric specialties, family members) before generating ICD-10 diagnoses.

Full access to medical records, investigations and reports, allowed the researchers to collect features of the cases, including demographics, age of first non-epileptic seizure, psychiatric co-morbidity and intellectual disability. The diagnostic procedures had varied between local centres, including use of structured tools and particular diagnostic classification systems. Features of approaches to psychological treatment were collected using a qualitative log.

According to the case notes, diagnosis of NES had been made by a range of clinicians, including neurologists and psychiatrists working in general and specialist settings. There are consensus guidelines that the gold standard of diagnosis should be with video EEG (vEEG) capturing an event of question [1]. However, inter-rater reliability of diagnosing NES using vEEG is only moderate [7]. In our sample, vEEG did not always take place or was not successful. However, the neurologists in the local centre and elsewhere often made the diagnosis if other features suggested NES, such as witnessed or videoed semiology, and this was often done in consultation with psychiatric teams. Sometimes additional work-up by neurologists had taken place at our centre to confirm the diagnosis of NES and with video-telemetry when necessary. A full chronology of all assessment and diagnoses was collated prior to initial assessment, and integrated with the findings of the specialist clinic evaluation.

Descriptive statistics were used to describe key features of the samples. Statistical testing was used to compare the ASD and non-ASD groups, with independent t-tests and Fisher's exact test for continuous and categorical variables, respectively.

Approaches to psychological treatment are described through two case examples. These introduce presentations of ASD and NES seen commonly by the team and are intended to highlight characteristic features, and to allow description of suggested approaches to assessment, treatment and liaison from the clinical team.

Results

Of the 59 children and young people with NES, 10 (16.9%) had a diagnosis of ASD meeting ICD-10 criteria. 5/10 (50%) of these had not been diagnosed with ASD at the time of referral for NES and 5/10 were diagnosed subsequently, either by the assessing clinical team or following a recommendation for further assessment elsewhere. In 7/10 cases, there was evidence that a structured tool had been used to make the diagnosis: the Autism Diagnostic Observation Schedule (1st or 2nd edition) [8] (n=6), the developmental, dimensional and diagnostic interview [9] (n=4), the Autism Diagnostic Interview [10] (n=1) and the Asperger Syndrome Diagnostic Interview [11] (n=1). In the 3 cases where no structured tools were used, 1 of these was a diagnosis made by the multi-disciplinary team at our centre, according to ICD-10 criteria. The final 2 cases had received diagnoses of ASD from local referring teams.

Figure 1 describes the sex of patients and ages of first non-epileptic seizure. Data on ethnicity were not collected because routine recording of ethnicity in the case notes was often not completed. High rates of additional psychiatric diagnoses were seen. Figure 1 also compares patients with and without ASD. Presence of ASD was not associated with gender, epilepsy status or age of first non-epileptic seizure. There was no difference between the ASD and non-ASD groups regarding rates of all psychiatric co-morbidity (ASD 70% vs. non-ASD 47%, $p=0.184$). Patients with ASD had significantly higher rates of specific additional diagnoses, namely ADHD and tic disorders. There was a trend towards higher rates of intellectual disability in children and young people with NES and ASD (2/10: both of moderate severity) than in those without ASD (2/49: 1 mild and 1 had moderate severity).

Other significantly impairing physical symptoms unexplained during work-up by paediatricians were common in children with ASD: headache (5/10), weakness (3/10), visual disturbances (2/10), aphasia (2/10), memory loss (1/10), vomiting (1/10). Significant bullying was identified as a trigger in four children with ASD.

Figure 2 describes case examples of typical presentations and model treatment approaches. Intervention always involved child, family and school, and the psychological therapy employed a cognitive-behavioural framework tailored to the needs of a young person with ASD.

Discussion

ASD was an important co-morbidity in the 59 consecutive referrals seen with NES at this tertiary referral centre, with ASD having not been identified in 50% of cases prior to referral. This is the first detailed description of ASD in NES beyond a single case report. The children with both ASD and NES had a high level of neurodevelopmental comorbidity highlighting the complex needs in this group of children and young people.

There is widespread discussion that rates of ASD diagnosis in general are increasing [12], with suggested explanations including changes in true prevalence, classification systems or increased recognition by families and professionals [13]. However, a governmentally-commissioned, UK population-based survey concluded that underlying rates of ASD were stable in recent years in 5-15 year olds, finding a prevalence of 1.3% in 2017 and 1.0% in 2004 (with no comparable figure for 1999) [14]. It may be that ASD is becoming a more commonly diagnosed co-morbidity across a range of conditions, although the current study found a very high rate at 16.9% in a clinic sample. Referrals of NES to tertiary centres may not represent the underlying population closely, so these results must be viewed with consideration of this bias, with more complex cases likely being seen at our centre. Of note, although a specialist ASD service does exist at Great Ormond Street Hospital, none of the children with ASD were referred by this service.

The biological, psychological and social factors that may predispose, trigger, and maintain NES remain poorly understood and a variety of mechanisms have been proposed [15]. Difficulties in recognising internal emotional states (known as alexithymia) have been associated with somatic complaints in children and young people [16]. Nemiah and Sifneos explained somatisation as a process whereby individuals communicate distress below the level of awareness [17]. Individuals with autism may have problems with social participation and a tendency to rigid thinking, and difficulty understanding and communicating emotions may cause children and young people to decompensate at times of increasing social and academic pressures, with somatisation and NES resulting. Non-specific neurological abnormalities have previously been discussed in children with NES, including an important connection between NES and a predisposition to hyperventilation [18]. Alterations in brain structure found in children with ASD might then predispose them generally to greater cerebral arousal and hence NES [19].

Study of the development of NES in ASD may suggest hypotheses for the pathogenesis of NES in the wider population. The theory of "active inference" [15] states that over-attention to and misinterpretation of somatosensory input lead to formation of functional neurological symptoms, and aberrant interoceptive processing has indeed been demonstrated in ASD [20]. With suggestions that the "broader autistic phenotype" is common in family members of children with ASD [21], studying families and home life could reveal how social processing of emotions and physical symptoms, in an environment with clearly-defined rule structures, interacts with development of NES.

Clinicians working with children with NES should be vigilant for presence of ASD. Conversely, when assessing seizures in a child with known ASD, the possibility of NES should be considered. This will lead to improved early recognition of NES and shorter times to more appropriate treatment. The presence of ASD should ensure that affected youth follow distinct and developmentally appropriate pathways through the health system including input from community paediatrics, mental healthcare and education services. The clinical formulation of these combined NES and ASD cases frequently suggested that NES were likely precipitated by the psychological stress of living with unacknowledged or inadequately managed ASD. Interventions related to impairments associated with ASD (for example educational adjustments or social support) led to a reduction in frequency of NES without using a treatment targeted directly at the functional symptoms [6]. It is not known whether ASD is common in other functional disorders or in adults. If additional psychological therapy is delivered – either for the NES or for commonly occurring associated problems, such as anxiety – this should be tailored to the needs of the person with ASD and the family around them.

The higher rates of tics and ADHD in the current small sample of youth with ASD are expected, given other findings in neurodevelopmental disorders [22]. It may be that children and young people with a pre-existing tendency to involuntary movements and restlessness, are also predisposed to developing functional neurological symptoms such as NES.

Our study was limited by a retrospective and descriptive design, using data gathered for routine clinical care by an expert multidisciplinary team. It is possible that referrals to a tertiary centre constitute atypical cases; nonetheless, study of these children and young people with more complex presentations may be informative for understanding the broader population with functional neurological symptoms. Other authors have shown associations between ASD and particular types of epilepsy, with a rate of ASD of 5% in one community sample of children and young people with epilepsy [23]. The sample size was too small to explore the known relationships between epilepsy syndromes and ASD in the current study.

Conclusions

The occurrence of ASD has not previously been described in detail in children and young people with NES. Our study suggests it is a common comorbidity in a clinic sample. Careful clinical assessment with consideration for ASD traits is therefore important for this population. Early diagnosis of ASD might warrant a modified approach to assessment and treatment of NES. The diagnostic recognition itself can often be therapeutic. Children with undiagnosed ASD may experience significant misunderstanding and stress, which improve once the ASD is diagnosed and appropriate educational, social and other environmental modifications are implemented.

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Figures attached in separate files

Fig 1: Summary characteristics of children and young people

Fig 2: Case examples

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Figure 1

Features of patients with and without ASD				
	Total (n=59)	ASD (n=10)	No ASD (n=49) ^a	p-value
sex female	37 (62.7%)	6 (60.0%)	31 (63.3%)	0.557
epilepsy	22 (37.3%)	3 (30.0%)	19 (38.8%)	0.406
age of first non-epileptic seizure (years; range, standard deviation)	12.5 (5.4-17.5, 2.6)	11.8 (7.2-15.0, 2.7)	12.7 (5.4-17.5, 2.5)	0.291
co-morbid psychiatric illness (any)	30 (50.1%)	7 (70.0%)	23 (46.9%)	0.184
ADHD	5 (8.5%)	3 (30.0%)	2 (4.1%)	0.030*
tic disorder (any)	3 (5.1%)	3 (30.0%)	0	0.004*
intellectual disability	4 (6.8%)	2 (20.0%)	2 (4.1%)	0.068

^aexcept age, where n=45 *statistically significant

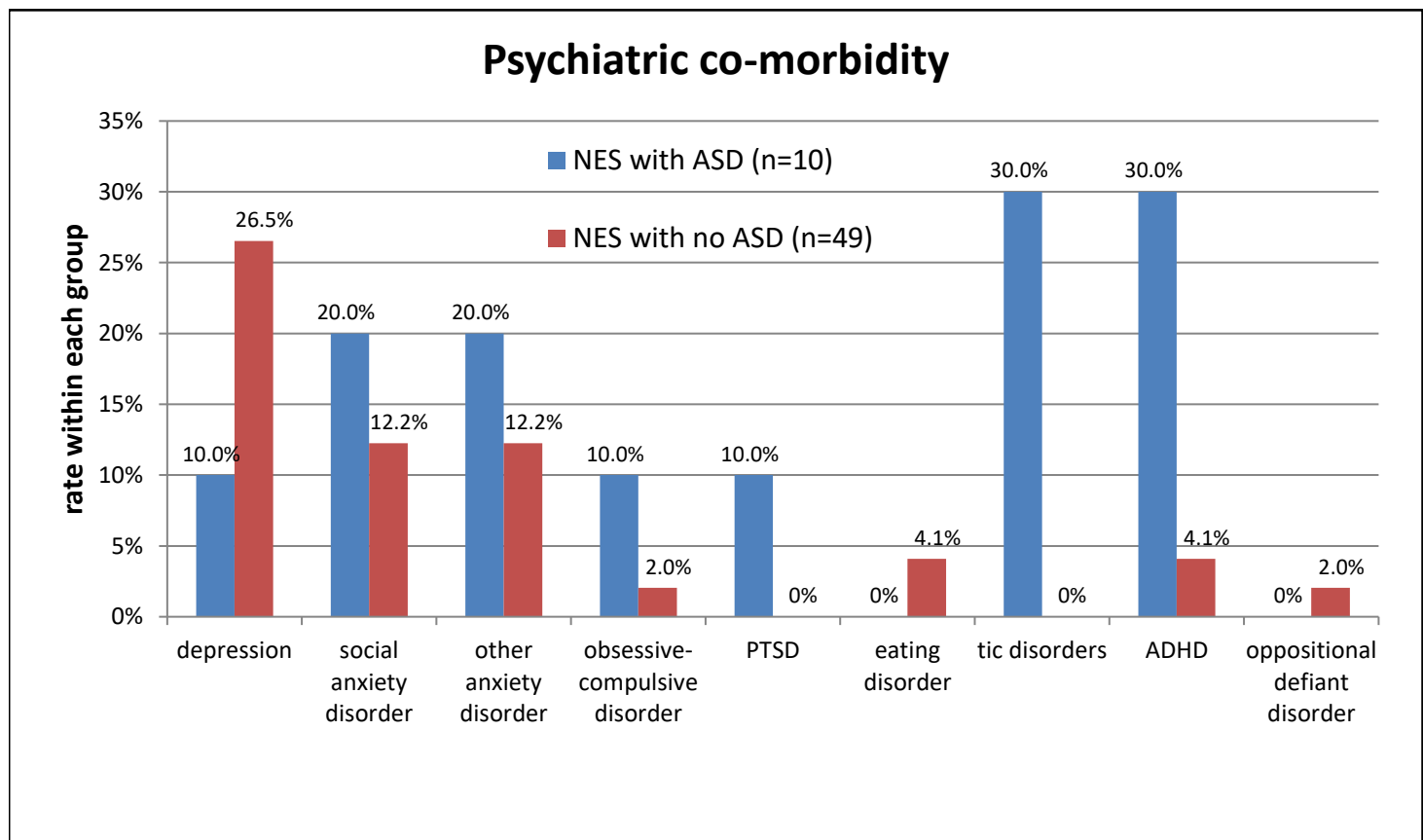


Figure 2

Patient X: boy with established ASD

X was diagnosed with ASD aged 9, when his schoolteachers became concerned that he had an unusual social manner and struggled with change in class. After moving to a special school, he developed episodes of collapse and unresponsiveness. Diagnosed initially with epilepsy, several anti-epileptic medications failed to control events. Video telemetry subsequently captured a typical paroxysm without EEG changes and the diagnosis of NES was confirmed.

He benefited from an intensive programme of 10 sessions of tailored cognitive behaviour therapy (CBT) with family involvement. Initially, family members were supported to identify situations where NES were likely to occur, and then modify their own behaviours to reduce anxiety in the family environment at these times and prevent inadvertent reinforcement through enhanced attention. Psychoeducation about interpretations of physical experiences explored X's relationship with his body, before developing techniques to modulate his response to physical symptoms. Liaison with the school revealed an environment where a number of children had epilepsy, such that teachers had standard routines to respond to seizures. The school and family were helped to create a new action plan to divert focus from X during seizures and re-integrate him back into lessons quickly.

Patient Y: girl with undiagnosed ASD

Y developed generalised tonic-clonic epileptic seizures at age 3 years, which were well-controlled with medication by age 6. Aged 12, approaching both school examinations and puberty, she became increasingly withdrawn. She had a lengthy seizure which led to intensive care admission and intubation. On the first day back at school she lost power in the right leg and required a crutch. After diagnosis with non-epileptic seizures, a full mental health team assessment diagnosed high-functioning ASD and depression. High family expectations of educational achievement and some bullying at school were also identified.

Treatment included 12 sessions of family-focussed CBT-based therapy incorporating psychoeducation about autism. Initial behavioural work involved behavioural activation. She was helped to identify feared settings, and to decrease avoidance via graded exposure. Focus then moved to training in social skills and re-integration. Key sessions explored recognising and communicating emotions verbally and learning to tolerate change. Liaison with schools was crucial, to plan for managing seizures in a consistent manner, avoid unnecessary emergency responses and develop supportive networks for her to communicate her needs.