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Epilepsy, an orphan disorder within the neurodevelopmental family

Rohit Shankar ,[1,2] Bhathika Perera,[3] Rhys H Thomas[4,5]

In 1997, the neurologist Rajendra Kale stated in the *British Medical Journal* 'The history of epilepsy can be summarised as 4000 years of ignorance, superstition, and stigma followed by 100 years of knowledge, superstition, and stigma'. Epilepsy remains an orphan disorder, in so much that it remains ostracised from the family of neurodevelopmental disorders (NDDs).

The NDDs primarily refer to intellectual disability (ID), attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), communication disorders, specific learning disorders and motor disorders such as tics/Tourette. The Diagnostic and Statistical Manuel of Mental Disorders fifth edition (DSM V) description emphasises that NDDs typically have a childhood onset, with manifestations in early period as developmental deficits. Epilepsy and epileptic encephalopathy are not listed under NDDs, but epilepsy in particular genetic epilepsy is a remarkably common comorbidity of NDDs. Significantly higher epilepsy prevalence is observed in ID (22.5%), ASD (20%) and ADHD (15%) than the population prevalence (0.8%).[1–3] Prevalence data are not sufficient to explain the variation in care outcomes between people with NDD, with and without epilepsy. We conclude that this driven by ignorance, lack of evidence and indifference. We argue that genetic epilepsy deserves to be considered as a key member of the NDDs and that doing so will lead to improvements in holistic care. Seizures and epilepsy which have a known aetiology due to drugs, environmental toxins, infections, head trauma, stroke or dementia are not considered under the umbrella of NDDS in this paper.

SHARED ORIGINS

There is compelling epidemiological and biological evidence to propose that the primary pathology causing maldevelopment of/or damage to the brain[1] produces both NDD *and* epilepsy.[1] Nowhere, is this more prominent than in the understanding of the shared genetic causes of NDD with and without epilepsy.[4] Single-gene epilepsies diagnosed before the age of 3 years,[5] are common and present at a rate of one per 2120 live births. From these data 10–43 adults per 100 000 will need to see a neurologist or a professional trained in epilepsy management, many of whom will also have an NDD.[6]

Various common syndromes presenting with NDD or epilepsy issues are recognised to overlap. Epileptic encephalopathies (such as Dravet syndrome, Lennox- Gastaut syndrome, West syndrome) characterised by a shared origin of intractable abnormal electric discharges (epileptic in nature), occurring from an early age and leading to progressive psychomotor dysfunction which has significant impact on development. This leads to residual deficits in cognition, behaviour and personality which has a symptomatic appearance of NDDs.[7] The level of NDD is dynamic, meaning that aggressive and early seizure control may reduce the severity of NDD.[1 2]

Whereas, many NDD dominant conditions, which may not be true epileptic encephalopathy such Rett syndrome, fragile X, trisomy 21, tuberous sclerosis, still demonstrate a very high seizure burden.[1 2]

ASSOCIATIONS WITH MAJOR NDDS

Epilepsy and ID

Clinical research of NDD and epilepsy largely focuses on ID, ignoring the fact that ID and epilepsy rarely present in isolation, without other NDDs. In the UK it is estimated that 22.5% of people with ID have comorbid epilepsy and those with ID form approximately 30% of all people with epilepsy.[1 2 8] To understand the relationship between epilepsy and ID it is critical to correctly partition the population in to those with mild ID, where the biological causes are more similar to the average IQ population, and those with severe and profound ID who present with completely different needs (table 1). Even making this distinction may be hard; it is rare for adults to receive adequate psychometric testing to estimate their cognitive abilities. Furthermore ID in literature is a nebulous concept complicated in this cohort by the relationship with antiseizure medication.[7]

Epilepsy and ASD and ADHD

It is estimated that 20%–30% of autistic people develop epilepsy. There are clear genetic syndromes where ASD may present before seizures and may be the more 'dominant' phenotype, such as Landau-Kleffner and Retts syndromes.[1 2] Where epilepsy and ASD coexist, it predicts a greater involvement of other NDDs, and severe ID in particular.[1 2] The management of this group particularly given the higher levels of association with complex mental health and physical coexisting conditions often require specialist multi-disciplinary approaches.[8–10]

Despite ADHD almost certainly being under-diagnosed in adults and children with epilepsy, it is certain over-represented: epilepsy has a prevalence rate of 15%–20% in ADHD, and ADHD has been found in 20%–50% in children with epilepsy. This speaks to a likely bi-directional link between ADHD and epilepsy, which may or may not be independent of coexisting ID.

Psychiatric overlap

Another area of association is that both NDDs and epilepsy independently are significantly associated with a range of major psychiatric disorders. A principal example is that of psychosis. The life time prevalence of psychosis is approximately 3%.[11] People with epilepsy have an increased risk with prevalence rates of 6%.[12] The prevalence of psychosis in a population with ID is at least three times higher than that in the general population.[13] Psychotic disorders are highly prevalent in ADHD with the lifetime prevalence around 10%[14] and a similar prevalence (9.6%) is reported in ASD.[15]

CURRENT EPILEPSY–NDD CONUNDRUM

Both NDD and epilepsy populations independently are disadvantaged groups from a physical health, mental health and social perspectives.[3] People with NDD commonly have a more challenging epilepsy to control and diagnose, have multiple seizure types and are often resistant to drug treatment.[9 10] Epilepsy is the clinical expression of a physiological state that permits unprovoked seizures and as such it is a disease with a multitude of causes; considering it as a singular disorder is deeply unhelpful. The 2017 ILAE classification of epilepsy prompts us to classify epilepsy not only in terms of aetiology but in the context of comorbidities, such as NDD[16]; with the ambition of achieving optimal seizure control and improving quality of life.[9 10] People with NDD too are a heterogeneous group, and the expression of their varied NDD are manifold. This can make diagnosis and management challenging.[1 2 8–10] People with NDD have

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Table 1 Key areas of differences in epilepsy characteristics between people with ID and general population

	Intellectual disability (ID)	General population
Prevalence of epilepsy in the UK	20%–22.5%, 10%–12% in those with mild ID and 30%–50% in those with moderate to profound ID	0.6%–1%
Treatment resistance to antiseizure drugs	Up to 60%	20%–30%
Comorbidity	10–12 conditions	Two chronic health conditions, rising to six in people older than 65 years
Sudden unexpected death in epilepsy (SUDEP) rates	3–9 times higher that general population with epilepsy	20–24 times higher than general population without epilepsy
Representation of epilepsy in premature mortality	5%	0.2%
Approximate reduction in life expectancy in the UK	15–30 years depending on the degree of ID	2–10 years depending on the nature of epilepsy
Prevalence of psychiatric conditions	49.1% in non-epilepsy	20%–30%
Presence of psychiatric conditions in those who died	N/A	41%
Crude average number of antiseizure medication prescribed	2–4	0–2
Polypharmacy	Very high	Likely

diverse needs with a higher likelihood of communication, psychiatric, behavioural and drug sensitivity problems that make it more difficult to be treated than those without an NDD.[1 2 8–10] For an example, 60% of people with epilepsy and ID are considered to show a poor response to antiseizure medication.[10] Thus, when developing a care plan attention should be paid to the increased risk of adverse cognitive and behavioural effects of AED treatment, because people with NDD carry the brunt of the burden of polypharmacy.[10] Unfortunately, there is a poor understanding and limited evidence base supporting suitable prescribing and deprescribing in this vulnerable population. There is no government led campaign like the the Stop The Over Medication of People with learninig disability or autism or both (STOMP) run in England for reducing the burden for psychotropic medication for antiseizure medicines, and it may not always be safe to de-prescribe.

Critically, people with NDD are over-represented in the population with greater than 15 years of pharmaco-resistant epilepsy who carry sudden unexpected death in epilepsy rates of up to 42%.[1] A further issue speculated but poorly researched is the role of antiseizure medication predisposing to NDDs.[17] Valproate has been indicted as a major cognitive teratogen predisposing to a range of NDDs including ID and ASDs.[18 19]

It may not be possible or desirable to separate the effects of an individual's epilepsy from their underlying NDD holistically, so considering the individual as a whole is crucial.[1 2 8–10] Recognition is needed that the anticipated outcomes will be dissimilar to different populations of NDD.[1 10] For example, for people with mild impairment focusing on full remission of seizures, treatment adherence and understanding any mental state and behaviour changes is foremost.[1 10] Meaningful person centred communication to enable a sustainable therapeutic relationship is essential. Focus on facilitating *independence* for the individual while ensuring safety (loneliness, injury, pregnancy) is imperative.[1 2 8–10] Whereas, people with moderate-profound impairment have more complex health needs, likely treatment resistance, genetic conditions, structural brain damage and a requirement of higher support levels.[1 10] As 30%–50% of this population have seizures, their treatment needs focusing on factors such as coexisting health conditions, medication impact, side effect recognition, treatment resistance, and overall short and long term best interest on 'best manner to be living with seizures'.[1 10] Identifying even more common epilepsy comorbidities such as depression and sleep-disorders are significantly more challenging in this cohort.

The UK is considered to be a vanguard in NDD related healthcare due the presence of a nationalised health service, universal social care provisions, presence of an evolved structure to support diagnosis and management of needs of people with NDD and a bespoke competency/training framework to meet the unique needs and challenges of people with NDD. However, there are significant gaps visible in care delivery particular to those with epilepsy and NDD.[8 10 20] These gaps are not trivial; the UK-based learning disabilities mortality review inquiry consistently highlights poor epilepsy care as one of the most important factors associated with premature mortality.[21] Contrary to the opportunities provided by a nationalised health service, epilepsy care for people with NDD is a postcode lottery as it is managed by a range of services led by general practitioners, NDD specialists, general neurologists and epileptologists, respectively across the UK.[8 10] Communication is not automatic among these specialists and for opaque organisational reasons commonly genetic results and psychiatric care records are kept separately from physical health reports. That psychiatrists and neurologists can prescribe for people with epilepsy and NDD without automatic sight of each other's care records is an opportunity for disaster. This fragmentation produces fewer opportunities to provide parity of holistic care, increases diagnostic overshadowing and thus increases the threat of overall failure.[8 10] The whole process perpetuates the existing premature mortality risk and adversely impacts on social well-being and access to community.[8 10] There are also difficulties with access to specialist medications/therapies which accentuates care fragmentation in England. New therapies are not currently automatically rolled out following National Institute of Clinical Excellence (NICE) approval, but instead are governed at a local Clinical Commissioning Groups (CCG) level.[8 10]

WHY SHOULD EPILEPSY BE PART OF THE NDD FAMILY?

There is ample evidence that a condition based approach to epilepsy in the presence of NDD can by pursuing short term goals lead to long term harm.[1 2 8–10] When epilepsy is comorbid in a person with NDD, the impact is significantly greater than just the sum of two parts.[1 2 8–10] This is a vicious spiral with many interlocking components. The influence of comorbidity and condition specific treatments raise the hazard of side effects particularly long term.[1 2 8–10] For example, with antiseizure drugs, there is an increased risk of challenging behaviour, constipation, metabolic conditions and negative influence of bone health. This then can lead to the 'treatment' of the side effects by another group of specialists.[1 2 8–10] The inability to suitably cognitively process or communicate

decisions further increases the danger of diagnostic overshadowing and prescribing leading to worse health outcomes and poor quality of life.[1 2 8–10] Considering epilepsy to be an important dimension or symptom of the NDD can shift focus to optimisation of holistic person centred care as opposed to treatment of specific conditions which has negative consequences overall to the individual.[9 10] Recognition of epilepsy to be a facet of NDDs will also help specialists in NDD and epilepsy to work together to facilitate overlapping competencies to provide a 'joined up' approach focused on the patient outcome goals as opposed to disease treatment.[8 10] It would help identify the gaps in competency/training needs currently created by the specialism led silos which are condition based and not person based.[8 10]

There are also legal and moral dimensions to consider. The UK Equality Act and similar provisions globally assure this population's human rights whether it be the right to life or access to care with suitable adjustments. Morally, it is important to recognise this group includes some of the most vulnerable in our societies with highly limited access to expression of their need and wishes. It is our prerogative to take care of the most vulnerable. This population deserves more resource, more joint working, more multidisciplinary working, longer appointments, greater access to specialist nursing. Care should be designed for people with NDD from the ground up, rather than adapting existing models of care.

'Life for people with major disabilities supported by good services will often look quite ordinary, but this ordinariness will be the product of a great deal of careful planning and management' (Mansell).[22] People with NDD and epilepsy deserve more than they currently receive and indeed more than 'good services'. This is exactly the need of the hour for people with NDD and epilepsy and recognition of epilepsy as part of the larger family of NDD would be a major step towards this.

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REFERENCES

1 Shankar R, Walker M. Chapter 22: Epilepsy in people with Intellectual Disability.. In: *Oxford textbook of the psychiatry of intellectual disability*. 1st edn. London: Oxford university press, 2020.
2 Shankar R, Watkins L, Brown S. Chapter 10: Intellectual disability and epilepsy. In: Pasher V, Janicki M, eds. *Physical health of adults with intellectual and developmental disabilities*. 2nd edn. Switzerland: Springer Nature, 2019: 187–202.
3 Steer S, Pickrell WO, Kerr MP, *et al*. Epilepsy prevalence and socioeconomic deprivation in England. *Epilepsia* 2014;55:1634–41.
4 Hamdan FF, Myers CT, Cossette P, *et al*. High rate of recurrent de novo mutations in developmental and epileptic encephalopathies. *Am J Hum Genet* 2017;101:664–85.
5 Symonds JD, Zuberi SM, Stewart K, *et al*. Incidence and phenotypes of childhood-onset genetic epilepsies: a prospective population-based national cohort. *Brain* 2019;142:2303–18.
6 Lewis-Smith D, Ellis CA, Helbig I, *et al*. Early-onset genetic epilepsies reaching adult clinics. *Brain* 2020;143:e19.
7 Panayiotopoulos CP. Chapter 7: Epileptic Encephalopathies in Infancy and Early Childhood in Which the Epileptiform Abnormalities May Contribute to Progressive Dysfunction. In: *Epilepsies: seizures, syndromes and management*. Oxfordshire, UK: Bladon Medical Publishing, 2005. https://www.ncbi.nlm.nih.gov/books/NBK2611/
8 Royal College of Psychiatrists. College report 203 management of epilepsy in adults with intellectual disability, 2017. Available: http://www.rcpsych.ac.uk/usefulresources/publications/collegereports/cr/cr203.aspx
9 Shankar R, Doran Z, Kerr M. The Use of Antiepileptic Medication in Adults with Intellectual Disabilities: A Serious Conundrum. In: *Epilepsy and intellectual disabilities*. 2nd edn. Switzerland: Springer Nature, 2016: 115–45.
10 Royal College of Psychiatrists. College report 206 prescribing anti-epileptic drugs for people with epilepsy and intellectual disability, 2017. Available: http://www.rcpsych.ac.uk/usefulresources/publications/collegereports/cr/cr206.aspx
11 Perälä J, Suvisaari J, Saarni SI, *et al*. Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Arch Gen Psychiatry* 2007;64:19–28.
12 Clancy MJ, Clarke MC, Connor DJ, *et al*. The prevalence of psychosis in epilepsy; a systematic review and meta-analysis. *BMC Psychiatry* 2014;14:75.
13 Aman H, Naeem F, Farooq S, *et al*. Prevalence of nonaffective psychosis in intellectually disabled clients: systematic review and meta-analysis. Available: https://eprints.keele.ac.uk/2031/7/S%20Farooq%20-%20Prevalence%20of%20nonaffective%20psychosis%20in%20intellectually%20disabled%20clients.pdf [Accessed 12 Aug 2020].
14 Visser SN, Danielson ML, Bitsko RH, *et al*. Trends in the parent-report of health care provider-diagnosed and medicated attention-deficit/hyperactivity disorder: United States, 2003-2011. *J Am Acad Child Adolesc Psychiatry* 2014;53:34–46.
15 De Giorgi R, De Crescenzo F, D'Alò GL, *et al*. Prevalence of Non-Affective psychoses in individuals with autism spectrum disorders: a systematic review. *J Clin Med* 2019;8:1304.
16 Scheffer IE, Berkovic S, Capovilla G, *et al*. ILAE classification of the epilepsies: position paper of the ILAE Commission for classification and terminology. *Epilepsia* 2017;58:512–21.
17 Doran Z, Shankar R, Keezer MR, *et al*. Managing anti-epileptic drug treatment in adult patients with intellectual disability: a serious conundrum. *Eur J Neurol* 2016;23:1152–7.
18 Weston J, Bromley R, Jackson CF, *et al*. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. *Cochrane Database Syst Rev* 2016;11:CD010224.
19 Christensen J, Grønborg TK, Sørensen MJ, *et al*. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *JAMA* 2013;309:1696–703.
20 Kerr MP, Watkins LV, Angus-Leppan H, *et al*. The provision of care to adults with an intellectual disability in the UK. A special report from the intellectual disability UK chapter ILAE. *Seizure* 2018;56:41–6.
21 University of Bristol. Learning Disabilities Mortality Review (LeDeR) [Internet]. Available: http://www.bristol.ac.uk/sps/leder/
22 Mansell J. *Services for people with learning disabilities and challenging behaviour or mental health needs*. Department of Health, 2007.