

## **Epilepsy - Gilby**

The essential criterion for a diagnosis of epilepsy is the presence of at least one epileptic seizure. Still, an ever increasing number of scientists and clinicians are beginning to recognize that epilepsy is a much more complex and dynamic disorder than was originally believed. In fact, some investigators now speak of epilepsy as a 'spectrum' disorder, given the heterogeneity in clinical presentation and the high degree of comorbidity with other cognitive, behavioural and psychiatric disorders.<sup>1</sup> In patients that will receive a diagnosis of epilepsy, the initial focus of attention is appropriately placed on the presenting seizure. However, as clinicians probe a little deeper into patient history they often discover that prior medical visits have involved a variety of complaints relating to behaviour, cognition and/or mood. Indeed, epilepsy patients are frequently co-diagnosed with anxiety disorders, depression or broader indications of cognitive and emotional dysfunction. Importantly, these symptoms are often present prior to the first seizure, thus indicating that it is unlikely that the comorbidity arises out of biological processes related to the neurological consequences of recurrent seizures or long term administration of anti-epileptic drugs.

In children, there is also a particularly strong link between epilepsy and autism spectrum disorder (ASD). ASD is a neurodevelopmental disorder that is primarily characterized by social communication and interaction impairments and restricted, repetitive behaviour. Cautious estimates of co-diagnoses currently sit at approximately 20-25 percent of patients<sup>2</sup> but rise to nearly 40% within the ASD population<sup>3-5</sup>. Seizures in these patients are most often generalised, with the majority experiencing complex partial to secondary generalised seizures<sup>6</sup>. Adding more strength to the link between epilepsy and ASD is the fact that abnormal epileptiform activity has been documented in about 60% of ASD patients that have yet to have their first seizure<sup>7-9</sup>. This suggests that those patients are also at high risk for epilepsy. Findings such as these make it very difficult to reach an official consensus on the rate of coexistence for epilepsy and ASD, and we are even further challenged by the fact that both spectral disorders are continually evolving diagnostically. For instance, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), the classification of ASD includes patients with Rett syndrome (RTT), a neurodevelopmental disorder predominant in females<sup>10,11</sup>, but more recent diagnostic profiles listed in the DSM-V exclude RTT from the autism spectrum of disorders<sup>11</sup>. This type of discrepancy clearly influences the reported comorbidity rates given approximately 70% of RTT patients exhibit seizures and nearly all exhibit evidence of abnormal electroencephalography (EEG)<sup>12,13</sup>.

Seizure, or risk thereof, is not the only symptom common to both epilepsy and ASD. Overt symptoms like developmental delay, intellectual disability, cognitive dysfunction and behavioural impairments are routinely observed in patients from both diagnostic populations<sup>14,15</sup>. Moreover, there have also been reports of similar secondary symptoms in both epilepsy and ASD, which receive far less clinical attention than the hallmark features of either disorder. For instance, both patient groups often report symptoms that may be indicative of a similar metabolic disturbance, including excessive thirst and dry skin. Within the past few years, there has been increasing interest in these more subtle symptomatic commonalities in the hope that they will provide clues to causal mechanisms supporting the comorbidity and thereby provide new venues for treatment development. New treatment strategies based out of novel symptom exploration is vital given that, despite numerous additions to the pharmacological arsenal used to treat these disorders over the past 25 years, there are still no disease-modifying therapies for either condition<sup>16</sup>. Examination of shared metabolic disturbances in these disorders is currently a 'hot topic' and is made even more interesting by the fact that fasting has been recognized for over millennia to effectively treat

seizure disorders. Whether it was believed that seizures were a sign of demonic possession or an accumulation of toxins, treatment of epilepsy often involved strict dietary regimens. Early clinical observations also showed robust fasting-induced seizure control in various seizure disorders. However, anorexia is a prescription of limited usefulness to those afflicted with epilepsy; therefore, dietary treatments such as the ketogenic diet (KD), modified Atkins diet, and low glycaemic index diet have been developed and refined to treat a significant portion of refractory epilepsy disorders. Given the overlapping symptoms between epilepsy and ASD and a strong suspicion of common underlying mechanisms, it is not surprising that there has been a near parallel effort in ASD research to examine the therapeutic benefit of the same dietary therapies designed to mimic the effects of fasting in epilepsy. This strategy has already proven efficacious in the treatment of some ASD symptoms<sup>17</sup>.

1. Jensen, F.E. Epilepsy as a spectrum disorder: Implications from novel clinical and basic neuroscience. *Epilepsia* **52 Suppl 1**, 1-6 (2011).
2. Woolfenden, S., Sarkozy, V., Ridley, G., Coory, M. & Williams, K. A systematic review of two outcomes in autism spectrum disorder - epilepsy and mortality. *Dev Med Child Neurol* **54**, 306-312 (2012).
3. Danielsson, S., Gillberg, I.C., Billstedt, E., Gillberg, C. & Olsson, I. Epilepsy in young adults with autism: a prospective population-based follow-up study of 120 individuals diagnosed in childhood. *Epilepsia* **46**, 918-923 (2005).
4. Mouridsen, S.E., Rich, B. & Isager, T. A longitudinal study of epilepsy and other central nervous system diseases in individuals with and without a history of infantile autism. *Brain Dev* **33**, 361-366 (2011).
5. Gillberg, C., Billstedt, E., Sundh, V. & Gillberg, I.C. Mortality in autism: a prospective longitudinal community-based study. *J Autism Dev Disord* **40**, 352-357 (2010).
6. Steffenburg, S., Steffenburg, U. & Gillberg, C. Autism spectrum disorders in children with active epilepsy and learning disability: comorbidity, pre- and perinatal background, and seizure characteristics. *Dev Med Child Neurol* **45**, 724-730 (2003).
7. Chez, M.G., *et al.* Frequency of epileptiform EEG abnormalities in a sequential screening of autistic patients with no known clinical epilepsy from 1996 to 2005. *Epilepsy Behav* **8**, 267-271 (2006).
8. Kim, H.L., Donnelly, J.H., Tournay, A.E., Book, T.M. & Filipek, P. Absence of seizures despite high prevalence of epileptiform EEG abnormalities in children with autism monitored in a tertiary care center. *Epilepsia* **47**, 394-398 (2006).
9. Hara, H. Autism and epilepsy: a retrospective follow-up study. *Brain Dev* **29**, 486-490 (2007).
10. Tidmarsh, L. & Volkmar, F.R. Diagnosis and epidemiology of autism spectrum disorders. *Can J Psychiatry* **48**, 517-525 (2003).
11. Percy, A.K. Rett syndrome: exploring the autism link. *Arch Neurol* **68**, 985-989 (2011).
12. Glaze, D.G., Schultz, R.J. & Frost, J.D. Rett syndrome: characterization of seizures versus non-seizures. *Electroencephalogr Clin Neurophysiol* **106**, 79-83 (1998).
13. Kim, H.J., *et al.* Genetic and epileptic features in Rett syndrome. *Yonsei Med J* **53**, 495-500 (2012).
14. Khetrapal, N. Overlap of autism and seizures: understanding cognitive comorbidity. *Mens Sana Monogr* **8**, 122-128 (2010).

15. Close, H.A., Lee, L.C., Kaufmann, C.N. & Zimmerman, A.W. Co-occurring conditions and change in diagnosis in autism spectrum disorders. *Pediatrics* **129**, e305-316 (2012).
16. Galanopoulou, A.S., *et al.* Identification of new epilepsy treatments: issues in preclinical methodology. *Epilepsia* **53**, 571-582 (2012).
17. Frye, R.E., Sreenivasula, S. & Adams, J.B. Traditional and non-traditional treatments for autism spectrum disorder with seizures: an on-line survey. *BMC Pediatr* **11**, 37 (2011).