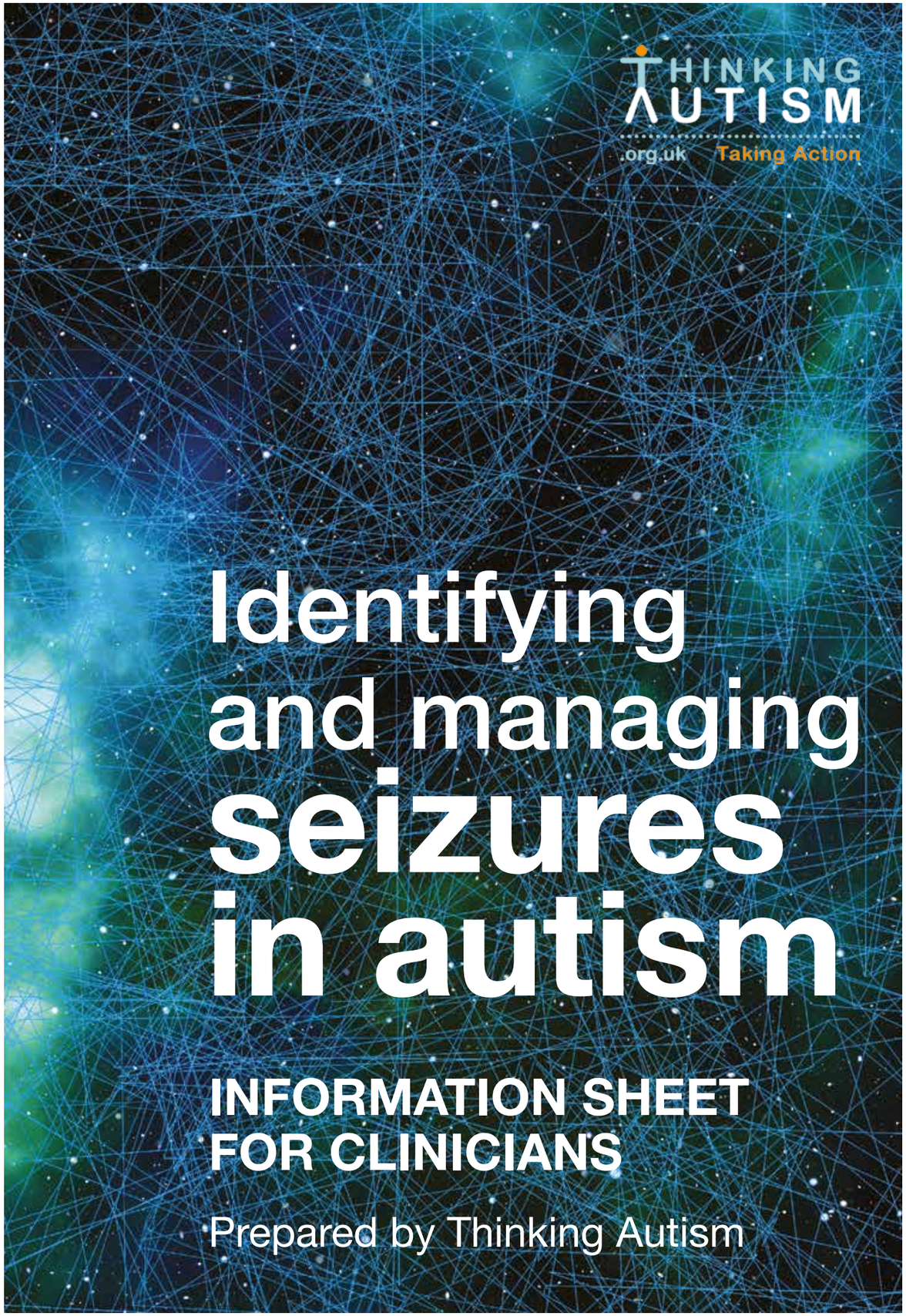
THINKING AUTISM
.org.uk Taking Action
Identifying and managing seizures in autism
INFORMATION SHEET FOR CLINICIANS
Prepared by Thinking Autism

"Epilepsy and autoimmune disease frequently co-occur; patients with either condition should undergo surveillance for the other. The potential role of autoimmunity must be given due consideration in epilepsy so that we are not overlooking a treatable cause."
(Ong 2014)

"The incidence of epilepsy may be higher for individuals with ASD who scored higher on the Social Responsiveness Scale; these individuals may benefit from thorough neurologic assessments and evaluation for epilepsy as part of their routine follow-up."
(Ko 2016)

Premature mortality in autism is estimated to be up to ten times higher than in the general population. Currently, an autism diagnosis is based on the presence of abnormalities in social communication and repetitive behaviours; however many common medical conditions are significantly more prevalent in both children and adults with autism compared to the general population. These include diseases and dysfunctions of nervous, circulatory, respiratory, digestive and immune systems. The severity of these conditions most often correlates with the severity of autism.

While mortality is higher across a variety of medical conditions, the single most common cause of early death in autism is epilepsy.

The prevalence of seizure disorders is significantly higher in people with autism. Furthermore, subclinical epileptiform activity—especially abnormal EEG discharges during sleep, has been found in a large majority of individuals with autism, even in the absence of clinical seizure disorder. When epileptiform activity is present, therapeutic strategies aimed at its control can sometimes lead to improvements in language and autism-related behaviours, in addition to reducing seizure activity.

Epilepsy and autism likely share common etiology. Individuals with autism and epilepsy are more likely to have severe social impairments and life-long dependency than those diagnosed solely with autism. Autism often occurs in epilepsy-associated syndromes such as Landau-Kleffner syndrome, Dravet Syndrome, and tuberous sclerosis. At the same time individuals with epilepsy are at increased risk of autism, especially if epilepsy appears in childhood. According to findings from large nationwide cohort studies from Sweden, people with epilepsy are 10 times more likely to develop autism compared to people without epilepsy. The risk of autism is especially high in the offspring of mothers with epilepsy. Rates of autism are also higher in the siblings of epilepsy sufferers. The data from this large cohort also showed a significant association between **febrile seizures** and all neurodevelopmental disorders, including autism.

IDENTIFYING EPILEPSY AND SEIZURE DISORDERS IN AUTISM

Estimated prevalence rates of epilepsy in individuals with autism range between 5 to 46%. Patients with both autism and epilepsy generally suffer more severe impairments, including cognitive and motor difficulties, compared to their counterparts with autism without epilepsy. Even in the absence of a learning disability patients with both autism and seizures, including abnormal isolated epileptiform discharges (IEDs), frequently display more severe autism symptoms and aberrant behaviours including irritability, inattention, hyperactivity, impulsivity, and aggression towards self and others. The occurrence of seizures and abnormal brain discharges may lead to changes in brain function that impact core autism symptoms and associated maladaptive behaviours *(Deona 1995, Ko 2016, Sivalingam 2018, Viscidi 2014)*. While the strong association between the severe forms of autism symptoms and epilepsy has been known for many years, recent detailed investigations have observed a higher rate of EEG abnormalities and epilepsy risk in individuals with high-functioning forms of autism *(Ertürk Çetin 2017)*.

Seizure onset in autism spectrum conditions can happen at any time – while it most commonly occurs either in early childhood or during adolescence, **high index of clinical suspicion has to be maintained at all times across a patient's lifetime**. Children and adults with autism who display symptoms indicative of seizure activity should be referred for full investigation.

Importance of obtaining prolonged slow wave sleep EEG in autism, ideally MEG:
Prolonged studies and those including the sleep state are more sensitive in picking up abnormalities, and investigative strategies of choice include a 24-hour slow wave sleep EEG. A magnetoencephalography (MEG) investigation should also be included, whenever available. A normal routine EEG investigation lasting less than 2 hours will often give false-negative results and miss important abnormalities such as electrical status epilepticus in sleep. Detailed investigations utilizing both prolonged overnight EEG and MEG have revealed that subclinical epileptiform abnormalities, in particular nocturnal epileptiform discharges, are present in a large majority of individuals with autism, even in total absence of clinical seizures *(Chez 2006, El Achkar 2015, Lewine 1999, Munoz-Yunta 2007, Nickels 2008, Sivalingam 2018, Swatzyna 2016, Yasuhara 2010).* The investigation by Chez and colleagues (2006) demonstrated both the importance as well as feasibility of prolonged EEG in children with autism: ***"In addition, this study dispels the myth that children with ASDs cannot participate in prolonged EEG studies or that the studies are too traumatic or technically difficult to do".***
"…current experience in autism suggests that a large percentage of these patients may go on to develop clinical seizures as they go through adolescence and adulthood. […] Treatment of subclinical epileptic spikes may be preventative. The decision to screen for early subclinical EEG abnormalities and offer treatment may be neuroprotective prospectively. In addition, treating subclinical epileptic spikes may also improve cognitive behavior in this population." *(Chez 2006)*

Awake-state interictal epileptiform discharges can cause psychosocial disturbances and transient cognitive impairment by directly interacting with cognitive and behavioral function. Nocturnal interictal discharges may cause fragmented sleep, a well-recognized cause of cognitive and behavioral problems. Research into Landau Kleffner Sydrome disorder, whose clinical presentation often closely mirrors regressive idiopathic autism, shows that nocturnal epileptiform activity can have a significant impact on daytime cognitive function and should not be ignored *(Binnie 1992, Kasteleijn-Nolst 1995, Viscidi 2014)*.

Symptoms and behaviours which are frequently dismissed as 'part of autism', but which may indicate seizure activity include:

- unprovoked outbursts of aggression
- irritability
- crying
- screaming or self-harming
- unusual facial and body movements and postures
- staring spells,
- covering ears with hands
- drooling,
- severe anxiety and panic attacks.

In such cases a video EEG can be helpful for differentiating between seizures and non-epileptic paroxysmal behaviours.

"Despite the multifocal nature of the epileptiform activity in the ASDs, neurosurgical intervention aimed at control has led to a reduction of autistic features and improvement in language skills in 12 of 18 cases."
(Lewine 1999)

"Our results find that compared to the healthy population, a large number of patients with ASD have isolated epileptiform discharges despite never having a seizure. Our findings support the use of EEG in children, adolescents, and young adults with ASD, regardless of gender or age. This is particularly true for those who exhibit aggressive behaviors or those who have failed prior medication attempts with stimulants, antidepressants, and/or antipsychotics."
(Swatzyna 2016)

All types of EEG abnormalities have been reported in patients with autism including:

- epileptiform abnormalities which are focal multifocal, or generalized
- generalized or focal slowing
- excessive fast activity
- the absence of normal wakefulness or sleep patterns.

The epileptiform abnormalities are focal in the majority of cases, and localization varies, with either frontal or temporal/centrotemporal epileptiform discharges tending to be more common. Subclinical epileptiform activity is present especially in the perisylvian regions. However, at least one study reported a predominance of occipital spikes. In patients with epilepsy, generalised tonic-clonic seizures predominate. Epileptic seizure waves most frequently developed from the frontal lobe *(Bolton 2011, El Achkar 2015, Munoz-Yunta 2007, Yasuhara 2010)*.

TREATING SEIZURES AND EPILEPTIFORM DISCHARGES IN THE ABSENCE OF SEIZURES IN AUTISM

Multiple studies have demonstrated that successful treatment of convulsive seizures can lead to a reduction in aberrant behaviours and improvement in psychosocial function in a number of patients. This suggests that some behaviours commonly attributed to autism may in some cases be due to epileptic activity itself.

In addition to clinical seizures, successful treatment of subclinical epileptiform discharges has also been shown to improve cognitive function and autism-related symptoms and behaviours *(Lewine 1999, Wang 2017)*.

Apart from their possible detrimental effects on cognitive and executive function in individuals with autism, abnormal isolated epileptiform discharges (IEDs) have been observed to convert to clinical seizures in over 20% of the sufferers in a 2-year follow up study (Veerappan 2018).

IED group exhibits more intense autistic features, low social functioning, and more severe behavioral problems when compared to non-IED group (P < 0.005). Over the 2-year follow-up, 20% from the IED group exhibited new onset of seizures when compared to 3% from the non-IED group (P = 0.032) indicating that former has an increased chance of developing seizures. … Thus, IED not (the presence or occurrence of) seizures is important with respect to clinical parameters. IED group can further be subdivided into those exhibiting sharp waves and those exhibiting other waves…. Sharp waves are associated with more severe behavioral problems
(Veerappan 2018)

While at present time there are no official guidelines or universally accepted best practices, the results of these studies strongly suggest that identifying EEG abnormalities and **treating subclinical** epileptiform discharges **may be beneficial to the patient**. This approach is of particular importance when there is a history of regression of language or sudden emergence of unexplainable or inconsequent behaviour and/or learning problems.

The following treatments aimed at control of epilepsy and EEG abnormalities have been observed to have led to a reduction of autistic features and improvement in language skills and overall level of functioning

- **AEDs, e.g. valproic acid, levetiracetam, especially their early use**
- **Neurosurgical intervention**
- **Vagus nerve stimulation**
- **Ketogenic diet, modified Atkins diet**
- **Immunomodulatory treatments: high dose steroid therapy, intravenous immunoglobulin (IVIG), plasma exchange; IL-1B antagonists (anakinra); mTOR inhibitors (everolimus)**
- **Adrenocorticotropic hormone (ACTH)**
- **Neurofeedback**

(Altunel 2017, Chez 2006, Couthino 2016, Golla 2014, Frye 2013, Hollander 2001, Jyonouchi 2016, Kasteleijin-Nolst 1995, Kilincaslan 2017, Ko 2016, Kokoszka 2016, Mizuguchi 2018 Pressler 2005, Swatzyna 2016, Wang 2017, Yasuhara 2010).

Future directions: following recent findings of a pathological role played by proinflammatory immune responses in the pathogenesis of epilepsy and neuronal hyperexcitability, novel approaches to address both epilepsy and EEG abnormalities and autism-related impairments have been suggested to include anti-inflammatory and immunomodulatory therapies *(Corradini 2018, Lewis 2018, Mazarati 2017, Missig 2017, 2018)*. Other approaches currently under investigation include bumetanide, monoclonal antibodies, antiglutamatergic drugs and cannabinoids.

"Epileptiform abnormalities are found in a significant subpopulation of children with ASDs. Adequate electrophysiologic monitoring during slow-wave sleep is often requisite to identification of this activity, and such monitoring should be an integral part of the clinical work-up of a child with an ASD, especially if there is a history of regression. MEG and 24-hour EEG are significantly more sensitive than 1-hour EEG and they are the strategies of choice. When epileptiform activity is present, medical therapy designed at ameliorating the epileptiform activity may lead to an improvement in autistic features."
(Lewine 1999)

TREATMENTS ADDRESSING SPECIFIC METABOLIC/MITOCHONDRIAL DISEASE OR DYSFUNCTION

Autism is associated with several metabolic and genetic syndromes in which at least some of the pathophysiology is known, and which are often amenable to treatment. Treating these underlying disorders—for example inborn errors of metabolism—can often lead to reduction in seizures as well as reduction in autism symptoms and improved cognition and functioning.
When a patient is presenting with both autism and seizures, and especially if cognitive and/or motor impairments are also present, it is of crucial importance to always rule out metabolic conditions such as mitochondrial disease and dysfunction and abnormalities in cerebral folate metabolism, disorders of creatine, cholesterol, pyridoxine, biotin, carnitine, γ-aminobutyric acid, purine, pyrimidine, and amino acid metabolism and urea cycle disorders and others.
(Frye 2013, Frye 2015, Guevara-Campos 2015, Novarino 2012, Stockler-Ipsiroglu 2014, Tarailo-Graovac 2016).

See overleaf for our guide to metabolic disorders associated with epilepsy and autism spectrum disorder ➡

"Given that ASD and epilepsy affect one another's behavioral phenotype as well as response to psycho-pharmacological treatment, proper management for epilepsy may in turn reduce autistic symptom severity in these individuals with ASD and epilepsy."
(Ko 2016)

"The reduction in aberrant behaviors observed in this series suggests that some behaviors previously attributed to autism may be associated with intractable epilepsy."
(Kokoszka 2016)

Treatments aimed at control of seizure activity sometimes lead to reduction of autistic features.

The average life expectancy in severe autism is only 39.5 years. Epilepsy is the leading cause of death.

Epilepsy is the leading cause of premature death in individuals with autism.

Subclinical epileptiform activity is present in a large majority of individuals with autism, even in the absence of clinical seizure disorder.

"Given the frequency of seizure disorders in (ASD) population, a high index of clinical suspicion should be maintained for subtle symptoms of seizures."
(Kagan-Kushnir 2005).

Metabolic disorders associated with epilepsy and autism spectrum disorder*

DISORDER	CLINICAL FEATURES	DIAGNOSTIC TESTING
Disorders of energy metabolism		
Mitochondrial disease	Developmental regression, gross motor delay, fatigability, ataxia, and gastrointestinal abnormalities	• Fasting serum lactate, pyruvate, acylcarnitine, amino acids, and urine organic acids
Creatine metabolism disorder	Developmental regression, mental retardation, dyskinesia, and family history of x-linked mental retardation	• Magnetic resonance spectroscopy • Urine and serum creatine and guanidinoacetic acid
Disorders of cholesterol metabolism		
Smith–Lemli–Opitz syndrome	Low birth weight, failure to thrive, poor feeding, eczema, and congenital structural abnormalities of the heart, gastrointestinal tract, genitalia, kidney, limbs, face, and brain	• Blood 7-dehydrocholesterol and cholesterol • DHCR7 sequencing
Disorders of cofactor (vitamin) metabolism		
Cerebral folate deficiency	Ataxia, pyramidal signs, acquired microcephaly, dyskinesias, and visual and hearing loss	• Folate receptor alpha autoantibody • Cerebrospinal fluid 5-methyltetrahydrofolate
Pyridoxine-dependent and pyridoxine-responsive seizures	Mental retardation, breath-holding, aerophagia, and self-injurious behavior	• Pyridoxine trial • Plasma and cerebrospinal fluid pipecolic acid • Urine α-aminoadipic semialdehyde • ALDH7A1 sequencing
Biotinidase deficiency	Developmental delays, seborrheic dermatitis, alopecia, feeding difficulties, vomiting, diarrhea, brain atrophy, and ataxia	• Biotinidase activity • BTD gene sequencing
Carnitine biosynthesis deficiency	Nondysmorphic male–male siblings with autism spectrum disorder	• Plasma and/or urine 6-N-trimethyllysine, 3-hydroxy-6-N-trimethyllysine, and γ-butyrobetaine.
Disorders of γ-aminobutyric acid metabolism		
Succinic semialdehyde dehydrogenase deficiency	Global developmental delay, myoclonus, hallucinations, ataxia, choreoathetosis, and dystonia	• Urine gamma-hydroxybutyric acid
Disorders of pyrimidine and purine metabolism		
Adenylosuccinate lyase deficiency	Global developmental delay, microcephaly, distinct facies, growth retardation, mental retardation, cerebellar vermis hypoplasia, brain atrophy, excessive laughter, and extreme happiness	• Urine and/or cerebrospinal fluid succinyladenosine
Nucleotidase-associated PDD	Hyperactivity, compulsiveness, speech abnormalities, ataxia, abnormal gait, and frequent infections	• Urine uridine
Hyperuricosuric autism	Altered sensory awareness, ataxia, and fine motor deficits	• 24-hour urine urate
Phosphoribosylpyrophosphate synthetase deficiency	Developmental delay and ataxia	• Urine uric and orotic acids • Complete blood count
Disorders of amino acid metabolism		
Phenylketonuria	Global developmental delay, mental retardation, microcephaly, spasticity, ataxia, poor growth, poor skin pigmentation, and aggressive behavior	• Serum phenylalanine
Branched-chain ketoacid dehydrogenase kinase deficiency	Intellectual disability and consanguinity	• Plasma and cerebrospinal fluid branched-chain amino acids
Altered tryptophan metabolism	No specific features besides autism spectrum disorder	• Reduced cellular generation of nicotinamide adenine dinucleotide
Urea cycle disorders		
Urea cycle disorder	Protein intolerance, temperature instability, ataxia, episodic somnolence and lethargy, cyclic vomiting, and psychosis	• Plasma ammonia and amino acids • Urinary orotic acid

* Table reprinted with permission from: Frye R.E. (2015) Metabolic and mitochondrial disorders associated with epilepsy in children with autism spectrum disorder. Epilepsy Behav. Jun;47:147-57. ©2014 The Author. Published by Elsevier Inc.

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Further information on magnetoencephalography MEG: megcommunity.org.

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