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CURRENT AWARENESS SERVICE

Epilepsy and mental illness

This issue's main article by Amitav Parida and Rajat Gupta provides us with a clear and pragmatic overview of the prevalence and importance of the neuropsychiatric co-morbidities of epilepsy. This has been an area that until the past few years had been under-recognised and inadequately managed.

I thought it would be interesting to approach this issue from a different angle, and turn back the clock to when epilepsy was considered a mental disorder, not a neurological one. It also reflects my interest in the psychiatric manifestations of neurological disorders, including epilepsy.

My own journey began in my final year at medical school when I chose a two-month elective in neuropsychiatry at the National Hospital for Nervous Diseases in Queen Square, London (now called 'The National Hospital for Neurology and Neurosurgery). This was rapidly followed by my first pre-registration (allowing me to be 'fully-registered' with the GMC) House Officer post which is broadly equivalent to Foundation Year 1. This was at Charing Cross Hospital in general medicine and neurology and with specific medical responsibilities for the hospital's psychiatric unit and its two consultant psychiatrists. It introduced me to the field of both 'liaison psychiatry' and 'organic psychiatry', both of which I found fascinating and intensely rewarding. I briefly considered a career in psychiatry, but quickly decided paediatrics should be my initial specialism. This took me to Newcastle on a dedicated two and a half year rotation, a concept well ahead of most other large teaching centres at the time. The final six months there included child psychiatry and 'mental handicap' – this latter term was accepted practice in the early 80s, but has been replaced with the term intellectual disability. Finally, in the middle of my consultancy at Alder Hey, I initiated joint clinics with a liaison child psychiatrist to address the specific area of psychogenic, non-epileptic seizures. This was one of the more common examples of non-epileptic attack disorder (NEAD) and one which frequently demands a carefully-choreographed multi-speciality approach for its successful management. Unfortunately, the clinical lead of the Department of Psychological Medicine, a clinical psychologist, determined this was not a priority of the department and this joint clinic was unilaterally abandoned in 2010.

If you Google 'epilepsy and mental illness', one of the first

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results is a series of questions that begin with: 'Is epilepsy a mental illness?' This may be a surprising question for someone in their 20s or 30s, but its basis can be traced back over two centuries when the answer would have been an unequivocal 'yes'. Among the very few diseases that can be traced back to antiquity, none has stimulated human fantasy as much as epilepsy. The many names given to epilepsy reflect the different thinking on the topic over the last 3,000 years. The ancient Greeks believed epilepsy to be a sacred disease with the body being invaded by a god. In the Greco-Roman world, the word 'lunatic' was restricted to epilepsy and was distinguished from a 'maniac' or mad person who was possessed by demons or evil spirits and not gods.

This latter view continued throughout the middle ages, partly influenced by Christian thinking. The Bible includes at least one story of a boy who experienced 'seizures from an evil spirit' (Luke 9: 37-43) or, in a different Gospel (Matthew 17: 15) as simply 'having seizures'. The boy's father had brought him to Jesus for healing; Jesus responded by: 'rebuking the evil spirit' (Luke 9: 42) and with 'the demon coming out of the boy' (Matthew 17: 18). It remains uncertain whether the boy's seizure was a genuine tonic-clonic seizure which was misinterpreted by those telling the story. I will let you decide whether it was non-epileptic and a manifestation of a real demon, and subsequently written in the Gospels as being caused by a demon or evil spirit. This story has been painted by many artists, most notably by Raphael, in a piece he entitled, 'The Transfiguration'. So-called because it depicts an important moment in the disciples' spiritual journey which had occurred at around the same time as the 'seizing boy'.

This belief – that people with epilepsy were possessed or mad – led to them being treated as mentally ill and consequently with contempt, fear and pity, but also social-distancing. This was because of the belief that the hyper-salivation ('frothing at the mouth') possibly contained the evil spirit. It was thought possible to pass the disease on to those close by – somewhat resonant of our current situation with the coronavirus pandemic. This may have initiated or certainly contributed to the stigmatisation of epilepsy, which although considerably eroded in 2020, persists in our developed country and particularly in developing countries.

Up to the latter half of the 19th Century, epilepsy remained an integral part of psychiatry. Many of the long-stay patients in hospitals and institutions for the mentally ill had epilepsy, and were accommodated in the basements of hospitals out of sight and sound of others. There is no information on how many people diagnosed with epilepsy in fact had a primary mental illness, or vice versa; the mis-diagnosis rate would certainly have been higher than in 2020.

Finally, towards the end of the 19th and early 20th centuries, the concept of the 'epileptic personality' also became deeply entrenched. This was the belief that the behaviour and consequently even the seizures themselves came from a constitutional hereditary psychopathic make-up.

The process of distinguishing epilepsy from mental illness began with the development of neurology as a new and independent discipline. This was helped by the development and use of electroencephalography (EEG) in humans by Hans Berger in the late 1920s. The concept of epilepsy as a specific neurological disorder was finally adopted in international classifications of disease in the 1940s and 1950s. In 1960, the World Health Organization (WHO) published a clear distinction between epilepsy and epilepsy with deterioration or psychosis in their 'International Classification of Diseases (ICD)'. The acceptance of this distinction was important as it heralded the overturn of the millennia-old traditional view that epilepsy was a mental disorder. However, it took decades before this distinction permeated into all the psychiatric classifications. It was as if the psychiatrists were in some way reluctant to let epilepsy and its patients out of their grip. This divergence between neurology (including epilepsy) and psychiatry accelerated in the mid to late 20th century but then slowed. At the end of the century and continuing into the early part of the 21st century it began to show some convergence. This included a redefinition of pre, post and interictal psychological manifestations of epilepsy. I think this convergence arose for two reasons. First, because of the arrival of a newer generation of neurologists and super-specialists ('epileptologist'), who took a broader view of

epilepsy. And second, by a significant minority of psychiatrists who took a more active interest in the psychiatric aspects of neurological disorders and which helped to consolidate 'neuropsychiatry'.
'Neuropsychiatry' and a 'neuropsychiatrist' are labels that some might find confusing – it implies a marriage between neurology and psychiatry but whether it is a marriage of convenience or love is unclear.

Neuropsychiatry is generally used synonymously with 'organic psychiatry', but with a broader remit to include those conditions in which psychological and social factors predominate, and specifically the conversion or dissociative disorders. These include NEAD, which is obviously important in the differential diagnosis of epileptic seizures.

Progress in understanding that epilepsy was a neurological disease continued with the discovery of specific anti-epileptic drugs that prevented seizures, but had no similar effect on psychiatric disorders, including the psychoses. Subsequently however, sodium valproate was found years after its licensing for use in epilepsy to be effective in the management of bipolar disorder, another example of convergence between neurology and psychiatry.

It also became more widely accepted that most people with epilepsy have normal mental states and there was no such phenomenon as the 'epileptic personality'. Evidence slowly accumulated that the psychological and psychiatric consequences of having epilepsy were multifactorial and included the existence and site of structural pathologies within the brain. We also discovered the social and psychological stress of living with a chronic, debilitating and stigmatising disease and side-effects of inadequate anti-epileptic drugs. In 1951, the American neurologist and clinical neurophysiologist, Frederic Gibbs, reported a series of 275 patients with 'psychomotor' (essentially temporal lobe) epilepsy in which he found that those with an anterior temporal lobe focus were three times more likely to have a 'severe personality disorder' or a 'psychosis'. He then courageously concluded that, "the sylvian fissure is one of the chief boundaries between neurology and psychiatry". This opens a potential new classification of neuroanatomy based on medical and surgical specialities. For instance, the tentorium could signify the boundary between neurology and neuroradiology. If only because the neuroradiologists can always find abnormalities in the infra-tentorial (posterior fossa) region, and the hypophysial fossa is the jurisdiction of the endocrinologist. But enough of this flight of fantasy…

One cannot overstate the complex interface between neurology and psychiatry, and one which clearly reflects the incredibly intricate structural, electrical and biochemical networks within the brain. Consequently, there will be a significant functional overlap between epilepsy (and other neurological disorders) and psychiatry. However, this is not confined to the psychological and social factors of epilepsy because a spectrum of psychosocial components can be found in all diseases. Some call the medical approach to this, the 'biopsychosocial' approach, and one that should be adopted by all doctors and not just neurologists and psychiatrists. Others would define this as the 'holistic' approach, which is probably easier to understand and appreciate, although not always easy to put into practice. Holism mandates that the patient is treated as a whole, as a person, and not as a collection of symptom and signs.

Professor Richard Appleton
Co-Editor

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The neuropsychiatry of the paediatric epilepsies A practical review

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Introduction and aims

Epilepsy is one of the most common chronic health conditions affecting children. The paediatric epilepsies are a heterogenous group of disorders of varying aetiology and severity [Duchowny et al, 2014]. The traditional focus in the treatment of epilepsy has been to achieve optimal seizure control and, ideally, seizure freedom.

Neuropsychiatric disorders frequently coexist with epilepsy and remain under-recognised and under-treated in clinical practice [Reillt et al, 2014; Ott et al, 2003]. Anti-epileptic drugs (AEDs) may have adverse neuropsychiatric side-effects [Aldenkamp et al, 2016; Brodie et al, 2016]. A number of specific electroclinical epilepsy syndromes and epilepsies are more strongly associated with neuropsychiatric manifestations than others [MacAllister and Schaffer, 2007; Besag et al, 2016(a)].

Neuropsychiatric comorbidities in childhood epilepsy may have a more detrimental effect on a child's health, happiness, educational potential and overall quality of life than the effect of seizures alone [Ross et al, 2020]. Nonetheless, optimising seizure control may also lead to improvement in the severity of co-existing neuropsychiatric problems. A number of studies, albeit primarily in adolescents and adults, have indicated that freedom from seizures, particularly tonic-clonic seizures, is rated as the most important factor in determining their quality of life.

The management of neuropsychiatric comorbidities overlaps many of the traditional boundaries in child health including acute paediatrics, community child health, educational psychology, neuropsychology, child psychiatry and paediatric neurology. It is important for professionals from across specialities to be aware of the neuropsychiatric manifestations of the paediatric epilepsies such that integrated interdisciplinary treatment pathways are available. The aim of this review is to provide a concise framework in the recognition and management of the common neuropsychiatric comorbidities associated with the paediatric epilepsies for clinicians from all backgrounds.

Epidemiology

Epidemiological studies have shown high rates of neuropsychiatric comorbidity in paediatric epilepsy. The old, but still seminal Isle of Wight (UK) study revealed 58% of children with complex lesional epilepsy had the diagnosis of a psychiatric condition compared to 11% of children with physical disability and 7% in healthy controls [Rutter et al, 1976].

The recent CHESS (Children with Epilepsy in Sussex Schools) study of 85 school aged children with epilepsy showed 60% met the criteria for a DSM-IV psychiatric disorder [Reilly et al, 2014]. Only one third of these children had previously been diagnosed with the identified disorder. Learning disability (LD) was present in 40%, attention deficit hyperactivity disorder (ADHD) in 33%, autistic spectrum disorder (ASD) in 33%, developmental coordination disorder (DCD) in 19%, anxiety in 13%, depression in 7% and oppositional defiant disorder in 4% of children.

Learning disability (LD)

Learning disability may be classified as an IQ of less than 70 [Rutter et al, 1976]. The prevalence of LD is highest in children with onset of seizures in the first two years of life and medication refractory epilepsy [Reilly et al, 2014].

LD is most prevalent in children in a number of epileptic encephalopathies including West, Dravet and Lennox-Gastaut syndromes, as well as myoclonic astatic epilepsy and some symptomatic focal epilepsies [MacAllister and Schaffer, 2007; Besag et al, 2016(a)]. Longitudinal epidemiological studies have shown that LD is a significant independent predictor for poor long-term outcome in childhood onset epilepsy. This is determined by increased mortality, seizure refractoriness and reduced ability to lead an independent adult life [Camfield and Camfield, 2007].

In the UK, the diagnosis of LD is typically made after the age of five years when children have started primary school education. However, routine psychometry or performance testing is not usually performed in the UK until year 2 (6-7 years of age). Thus, learning difficulties may be under-recognised in some children, especially if the learning difficulties are relatively subtle.

Behavioural issues such as inattention and frustration may be primarily related to difficulties in learning. Involvement of the special educational needs coordinator (SENCo) and an educational psychologist may be necessary to characterise a child's strengths and difficulties. Specific

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learning difficulties, such as dyspraxia, dyscalculia and dyslexia, may be present in children with epilepsy who do not have overall LD [Sillanpää, 1992]. A specific reading difficulty is particularly associated with childhood epilepsy with centrotemporal spikes (CECTS) [Pinton et al, 2006].

Developmental coordination disorder (DCD) has also been identified as more prevalent in children with epilepsy [Reilly et al, 2015]. DCD may present with delayed pencil skills, poor handwriting and clumsiness. Referral to an occupational therapist should be considered in children with such difficulties.

Autism and epilepsy

Autistic spectrum disorder (ASD) is a pervasive neurodevelopmental disorder. It is characterised by delay in speech and language development, restricted interests and abnormal reciprocal social interaction, which result in a functional impairment to a child [Reilly et al, 2015]. ASD is 3-6 times more common in boys than in girls. Recent studies have suggested an estimated prevalence of 1.5% in developed countries [Basag et al, 2016(a)] . There is a high prevalence of ASD or autistic-like features in specific disorders where epilepsy is present. These are namely Dravet syndrome [Li et al, 2011], PCHD19 genetic epilepsy [Jamal et al, 2010] and tuberous sclerosis complex (particularly when associated with the TSC 2 gene) [Besag et al, 2016(a); Muzykewicz et al, 2007].

The phenotypic spectrum and presentation of ASD is vast. ASD may present in early childhood (2-4 years of age) with early development impairment that predominantly affects speech and social or emotional skills. There is often a characteristic period of developmental regression between 18 to 24 months of age, where there is loss of speech. At the other end of the spectrum, children with normal intellect and speech and language development may present with impaired social interaction when they start attending school [Baumer, 2008].

The interrelationship between ASD, epilepsy and LD is complex. Multiple studies have shown a high prevalence of ASD in children with epilepsy [Besag et al, 2016(a); Reilly et al, 2015; Besag, 2009; Besag, 2018; Besag et al, 2016(b)] . However, it should be noted that in the absence of LD there is minimal evidence of increased risk of epilepsy in ASD [Berg et al, 2012].

There has been significant debate about whether epilepsy itself may cause ASD [Besag, 2009; Berg et al, 2012]. A high prevalence of interictal spikes on EEG in children with ASD has been widely reported in the literature. However, the diagnosis of epilepsy is not made solely on EEG. Many children with ASD and interictal spikes have never experienced an epileptic seizure and do not have a clinical diagnosis of epilepsy [Berg et al, 2012; Chez et al, 2006]. There is no evidence that treating interictal spikes in children with ASD without a diagnosis of epilepsy helps to ameliorate or 'improve' the features of ASD [Tuchman, 2000].

The diagnosis of ASD in the ICD-10/DSM-V criteria mandates that autistic behaviours should not be fully explained by other comorbidities such as epilepsy [Volkmar et al, 1992]. The temporal onset of seizures and features of ASD may give some diagnostic clues.

Children with early onset epileptic encephalopathies such as West and Dravet syndromes, and to a lesser extent, because of its usual age of onset, Lennox-Gastaut syndrome, will typically have seizures in infancy. These predate or coincide with concerns about features of ASD [Besag et al, 2016(a); Li et al, 2011; Kayaalp et al, 2007]. Seizures are frequently drug refractory in this cohort and LD will be present in the majority of children. There is also an association between ASD and structural focal epilepsy, particularly of right temporal lobe origin [Taylor et al, 1999]. In this specific group, the seizures typically precede the onset of autistic features.

Conversely, some children who already have a diagnosis of ASD may then present with seizures. There is often no underlying neurogenetic syndrome identifiable and centrotemporal spikes may be seen on EEG. Seizures are often well controlled with AEDs [Buckley and Holmes, 2016].

In most cases, there are no specific drug treatments for ASD or LD associated with epilepsy. Nonetheless, identification of ASD or LD may allow a child to have additional educational support or may highlight the need to move the child to a specialist school with expertise in maximizing their potential. In a child with pre-existing ASD being investigated for possible epilepsy, it is important to be aware of a high rate of misdiagnosis of epilepsy in this group for two reasons. First, some of the behaviours and automatisms that occur in children with ASD may be misinterpreted as absence or focal seizures. Second, the EEG may show non-specific abnormalities (even spikes) despite the fact that the child has never experienced epileptic seizures [Berg et al, 2012; Chez et al, 2006].

Epileptic conditions which may mimic ASD

It is important to mention two rare epileptic encephalopathy syndromes, Landau-Kleffner syndrome (LKS) and electrical status epilepticus in slow sleep (ESESS). ESESS was previously used interchangeably with continuous slow and spike wave in slow sleep (CSWSS). It is now appropriately renamed epileptic encephalopathy with continuous spike-and-wave during sleep (EECSWS) [Fisher et al, 2017]. Both LKS and EECSWS may manifest with features that are misdiagnosed as ASD [Galanopoulou et al, 2000]. In these disorders there is developmental or cognitive regression driven by the

epileptic encephalopathy that can be mistaken for the regression seen in ASD.

In LKS there is a specific language regression, that is loss of language comprehension (auditory verbal agnosia) and verbal expression (aphasia) [Taylor et al, 1999]. EECSWS is associated with a more global cognitive regression. The regression tends to occur at a later age (5-7 years) compared to ASD (18 months to three years) [Galanopoulou et al, 2000].

The majority of children with these electroclinical syndromes will have clinical seizures (typically focal motor seizures) pre-dating the cognitive regression. It is important to obtain a prolonged sleep EEG. A brain MRI may show a structural focal abnormality driving the epileptic encephalopathy. LKS may also be associated with a pathogenic variant of the GRIN2A gene [Lesca et al, 2013].

Treatment with AEDs (such as clobazam, levetiracetam and sodium valproate) and the corticosteroid prednisolone may reverse the background encephalopathy thus improving a child's developmental and learning potential [Okuyaz et al, 2005; Sánchez Fernándezet al, 2014]. Serial neuropsychological assessments should be considered to assess the response to treatment. Some AEDs such as phenytoin, phenobarbital, carbamazepine and topiramate may worsen the cognitive regression [Veggiotti et al, 2012; Lerman 1986]. Epilepsy surgery should be considered early if there is a unilateral structural pathology and no improvement in the background EEG with medication therapy [Santalucia et al, 2017].

Children with a diagnosis of CECTS may develop cognitive regression as a result of drug treatment with carbamazepine leading to CSWSS [Seidel and Mitchell, 1999]. An urgent sleep EEG should be obtained in such circumstances and if there is evidence of CSWSS, the carbamazepine should be withdrawn and replaced with another AED such as sodium valproate or levetiracetam.

Attention deficit hyperactivity disorder (ADHD)

ADHD is generally regarded as being a neurobehavioral or neurodevelopmental disorder, but in the literature has also been referred to as being a neuropsychiatric disorder. ADHD has been shown in a number of studies to be the most common neurobehavioral or neuropsychiatric comorbidity in children with epilepsy [Reilly et al, 2014; Sillanpää, 1992; Reilly et al, 2014; Sillanpää et al, 2016]. ADHD is generally much more common in boys than girls, but there is no gender predominance in children with ADHD and epilepsy. Twenty thousand school-age children are estimated to have both epilepsy and ADHD in the UK [Besag et al, 2016(c)].

ADHD is characterised by inattentive, hyperactive and mixed subtypes [Tripp et al, 1999]. The inattentive subtype (also referred to as attention deficit disorder [ADD]) was shown to be more common in children with epilepsy in one study [Reilly, 2011]. The ICD-10/DSM-V criteria for a diagnosis of ADHD include that the difficulties must be present in at least two settings, for instance, both at home and at school. It must also cause a significant functional impairment to the child [Hastings et al, 2005]. It is uncommon to give the diagnosis to a child less than six years of age. The diagnosis of ADHD is more challenging in a child with learning disability where it can be difficult to differentiate a poor attention span from difficulty and frustration in understanding lessons. ADHD often co-exists with ASD [Jang et al, 2013]. A final diagnostic challenge is that ADHD may co-exist with childhood-onset absence epilepsy. Consequently, the diagnosis of the absence seizures may be missed because of the earlier diagnosis of ADHD or ADD, but the converse may also be true.

Specific conditions such as tuberous sclerosis complex [Muzykewicz et al, 2007; D'Agati et al, 2009] and electroclinical syndromes (for instance CECTS) have particularly high rates of ADHD [Ross et al, 2020]. In CECTS the seizures are often infrequent and well controlled with medication, with ADHD symptoms predominating [Ross et al, 2020].

The underlying pathogenesis of ADHD in epilepsy is thought to be multifactorial and variable depending on the specific electroclinical syndrome [Besag et al, 2016(c)]. Some children with epilepsy are thought to have the 'classical' ADHD seen in children without epilepsy. Frequent ictal discharges, particularly centrotemporal discharges but also focal and generalised spike and wave discharges, have been postulated to contribute to attentional difficulties. In addition, irreversible damage to important structural brain networks governing attention is thought to play a role in structural focal epilepsies [Hesdorffer et al, 2004].

Post-ictal elevations in mood or even interictal mania or psychosis have been suggested as contributing to low attention [Besag et al, 2016(c)]. Specific AEDs such as benzodiazepines [Sheth et al, 1994], phenobarbital [Aldenkamp et al, 2016; Domizio et al, 1993], topiramate [Aldenkamp et al, 2016] and vigabatrin [Ferrie et al, 1996] have been shown to be associated with attention and concentration difficulties.

Methylphenidate is considered to be the first-line pharmacological agent in the treatment of ADHD in children [Storebø et al, 2015]. The use of methylphenidate and dexamphetamine in children with ADHD and epilepsy had previously been an area of contention. Historical versions of the British National Formulary suggested discontinuation of the medication if epileptic seizures should occur [Besag et al, 2016(c)].

A number of studies have shown that children with epilepsy and ADHD who have epileptiform activity on

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interictal EEG are more likely to have further seizures [Kanazawa, 2014; Holtmann et al, 2003]. However, no association was shown between the use of a stimulant drug and an increased risk of seizures or the unmasking of epilepsy [Gross-Tsur et al, 1997].

Additional studies have demonstrated no increased seizure risk in children with ADHD and epilepsy, treated with atomoxetine [Wernicke et al, 2007]. Atomoxetine is a non-stimulant drug, which is usually used as a second line agent for ADHD when a stimulant has been ineffective. However, in children with autism and ADHD, anxiety symptoms can often be prominent and these may be made worse by a stimulant [Arnold et al, 2006]. Hence, atomoxetine may be used as a first-line treatment in this group.

Depression and anxiety

Affective disorders are more prevalent in children with epilepsy than age-matched controls, affecting a quarter to a third of children with epilepsy [Sillanpää et al, 2016]. Depression and anxiety frequently co-exist. The presentation is similar to that in children without epilepsy. It will often involve changes in observed behaviour, both in and outside school, and decline in educational performance, rather than the child reporting specific cognitive symptoms as seen in adults [Seyfhashemi and Bahadoran, 2013; Goodman et al, 2000; 2003; Reilly et al, 2011; Dunn et al, 2016]. Diagnosis is made on the ICD-10/DSM-V criteria. A number of screening questionnaires can be used in clinical practice to identify early anxiety or depression, or both [Goodman et al, 2000; 2003].

The aetiology of depression/anxiety in epilepsy is thought to result from the complex interplay of predisposing biological factors associated with epilepsy itself and perpetuating psychosocial factors involving adaptation to a chronic health condition. These factors may include inadequate social/emotional support and inability to give a child autonomy in managing their health condition [Reilly et al, 2011].

The higher prevalence of depression or anxiety (or both) amongst girls in childhood has been shown to be less pronounced when there is comorbid epilepsy [Dunn et al, 2016]. Specific electroclinical syndromes or epilepsy aetiologies have not been shown to be disproportionally associated with depression or anxiety [Reilly et al, 2011]. However, higher rates of anxiety and depression have been described in children with learning disability and epilepsy than in those with only epilepsy [Thomé-Souza et al, 2004]. Poor seizure control may precipitate and perpetuate depression and anxiety; higher rates of depression or anxiety are described in children with uncontrolled seizures [Dunn et al, 2016; Berg et al, 2011] .

Phenobarbital, levetiracetam, topiramate and zonisamide have been reported to cause depression [Kanner and Dunn, 2004]. Zonisamide, felbamate and levetiracetam have been implicated in increasing anxiety in some patients [Mula and Sander, 2007; Weintraub et al, 2007]. Nonetheless, data on these adverse effects is largely limited to adult patients, although it must be emphasised that depression in children is generally under-considered and under-diagnosed. There are no clear data that would predict which children are most susceptible to depression.

Lamotrigine, sodium valproate and carbamazepine have all been described to have mood stabilisation, anti-depressant and anxiolytic effects. Depression and anxiety symptoms have been reported to worsen on withdrawal of these AEDs [Ketter et al, 1994].

The National Institute for Health and Care Excellence (NICE) guidelines for depression in childhood suggest children and young people should receive a course of cognitive behavioural therapy (CBT) first. A trial of an anti-depressant should be considered when the symptoms of depression or anxiety are moderate or severe and have not responded to CBT [Murray and Cartwright-Hatton, 2006; McArdle 2007]. Selective serotonin reuptake inhibitors (SSRIs) are generally used as the first-line drug therapy in childhood depression or anxiety. They have been demonstrated to be safe in epilepsy. It should be noted that fluoxetine, a commonly used SSRI, is a CP450 enzyme inhibitor, which may lead to drug interactions with phenytoin, carbamazepine, phenobarbital and sodium valproate [Thomé-Souza et al, 2007].

Psychosis

Psychosis in children with epilepsy is rare and largely restricted to the teenage population [Lax Pericall and Taylor, 2010]. The psychosis may be drug-induced, interictal or post-ictal and has even been described after temporal lobectomy [Macrodimitris et al, 2011; Besag et al, 2016(d)]. There is a strong association between epilepsy and increased risk of psychosis in adult life [Clarke et al, 2012]. The classical association between temporal lobe epilepsy and psychosis in adults has not been described in the paediatric population [Besag et al, 2016(d)]. This may in part be explained by temporal lobe resective surgery for epilepsy being performed much earlier, including in children, than 20 or more years ago. This may be preventing the development of such a psychosis.

Psychosis precipitated by vigabatrin [Ferrie et al, 1996], topiramate [Mula et al, 2003] and levetiracetam [Kossoff et al, 2001] have all been described in the paediatric literature. Slower anti-epileptic dose escalation has been associated with lower rates of neuropsychiatric adverse effects in the adult population [Mula et al, 2003].

Ictal psychosis is the manifestation of psychotic features as part of a seizure itself. It has rarely been described in the paediatric population [Besag et al, 2016(d)]. Post-ictal psychosis is a well-recognised phenomenon of a self-limiting period of psychotic behaviour after a seizure or seizure cluster. The psychosis may appear up to 72 hours after the last seizure has occurred [Kanemoto et al, 2012].

Interictal psychosis refers to psychosis occurring between seizures but having no clear time relationship to them. This has been reported to occur in adults but also infrequently in teenagers and may occur many years following the onset of seizures [Besag et al, 2016(d)].

Reciprocal (also known as alternative psychosis) is the phenomenon of psychosis worsening when seizures are better controlled and improving or resolving when seizures are worse. This is a clinical phenomenon and does not rely on EEG findings. In contrast, the diagnosis of forced normalisation is dependent on EEG findings and refers to the emergence of psychosis with improvement in epileptiform activity on EEG. The true existence of these phenomena is strongly debated for a number of reasons. One is the possibility that the psychosis is being induced by the AED used and is not arising as a direct result of the epileptiform activity or seizure control improving [Besag et al, 2016(d)].

Autoimmune antibody mediated encephalitis (particularly anti-NMDA receptor encephalitis) should always be considered in a child presenting with an acute or subacute onset of psychosis and seizures. The psychosis can be very dramatic. A movement disorder may also develop. The EEG will typically show evidence of a background encephalopathy. The classical delta brush EEG abnormalities described in adults with anti-NMDA receptor encephalitis are less frequently seen in the paediatric population [Haberlandt et al, 2017]. MRI brain scans may be normal, or show temporal lobe hyperintensity, brainstem encephalitis or diffuse white matter abnormalities [Hacohen et al, 2014]. A paraneoplastic cause (particularly ovarian teratoma in females) should always be considered and, where appropriate, sought [Henry et al, 2009].

The diagnosis of anti-NMDA receptor encephalitis is made on the basis of the presenting history, clinical findings and a positive NMDA receptor autoantibody, with the cerebrospinal fluid (CSF) having a better sensitivity than blood [Lee and Lee, 2016]. The treatment is with immunosuppression, which may include corticosteroids, intravenous immunoglobulin, rituximab, or cyclophosphamide, plasma exchange, or a combination of two or more of these therapies [Titulaer et al, 2013]. Supportive treatment with anti-psychotics or AEDs is often required.

Anti-psychotics have been shown to be safe when used in children with epilepsy. However, clozapine has been associated with worsening seizures but is rarely used in paediatric practice [Pacia and Devinsky, 1994].

Drug effects on behaviour

The role of specific AEDs in precipitating neuropsychiatric disorders such as psychosis, depression and anxiety has been covered earlier in this article. A number of AEDs have been associated with more non-specific behavioural and cognitive adverse side effects, where a precise psychiatric diagnosis has not been made. Phenobarbital [Camfield et al, 1979; Vining et al, 1987], phenytoin [Aldenkamp et al, 1993], topiramate [Kang et al, 2007] and zonisamide [Eun et al, 2011] have been associated with worsening cognition in school aged children. Phenobarbital [Wolf and Forsythe, 1978], sodium valproate [Glauser et al, 2010] , gabapentin [Lee et al, 1996], topiramate [Coppola et al, 2008], levetiracetam [de la Loge et al, 2010] and zonisamide [Miyamoto et al, 2000] have all been associated with generalised worsening of a child's behaviour.

Aggressive behaviour is recognised as an adverse effect of AEDs. Levetiracetam, perampanel and topiramate are associated with the highest reported frequency of aggressive behaviour among AEDs, particularly in patients with a previous history of psychiatric or behavioural symptoms [Hansen et al, 2018]. Seething rage, uncontrollable anger and 'fits of fury' with levetiracetam have been described and have been referred to as levetiracetam-induced rage [Molokwu et al, 2015]. This, however, appears to be rare and resolves after discontinuation of the drug. The behavioural side effects with levetiracetam may show improvement with pyridoxine (vitamin B6) supplementation [Alsaadi et al, 2015].

Conversely, some AEDs have been reported to have some positive effects on cognition and behaviour. Lamotrigine has been reported to improve behaviour and cognition [Buchanan, 1995] and levetiracetam to improve cognition [Lagae et al, 2005].

Close monitoring for potential behavioural side effects is recommended when initiating AEDs, particularly levetiracetam, topiramate and perampanel; they should also be introduced more slowly in children with a pre-existing comorbidity such as ADHD, ASD or learning difficulties [Hansen et al, 2018]. There are limited data on the neuropsychiatric side effects of the newer AEDs.

Conclusions and practical approach to diagnosis management

Neuropsychiatric comorbidities are common in children with epilepsy. Their recognition, diagnosis and treatment are important in the holistic clinical care of any child with epilepsy. No specific validated screening questionnaire for neuropsychiatric disorders in paediatric epilepsy currently exists. However, the Strengths and Difficulties Questionnaire (SDQ) and Development and Well Being

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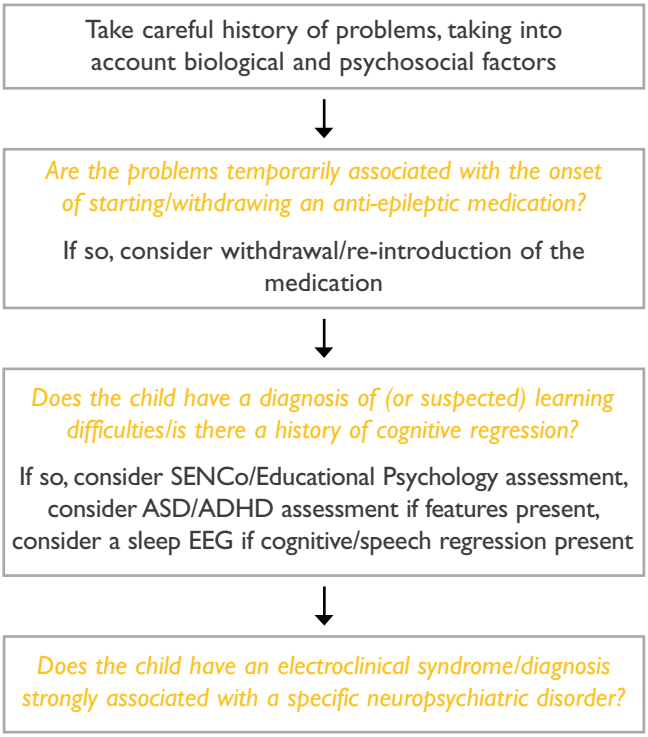
Figure 1. Approach to behavioural problems in a child with epilepsy



Assessment (DAWBA) have shown early promising results in detecting undiagnosed neuropsychiatric co-morbidities in children with epilepsy [Goodman et al, 2000; Bennett et al, 2019].

A structured approach, taking into account biological and psychosocial factors, is required (Figure 1). Determining a temporal relationship between the onset of seizures, neuropsychiatric features and medication changes is important. However, one should never forget to consider or ignore environmental factors (eg. impaired family dynamics, bullying at school, a death from epilepsy of a close or extended family member) because these may cause or contribute to a range of neuropsychiatric problems. Early identification of emerging learning difficulties and cognitive regression is crucial.

Management will frequently require effective inter and multi-specialty collaboration between educational, psychiatric and paediatric services. In most cases, no one individual specialist will be able to deal with all aspects of a neuropsychiatric disorder occurring in a child, particularly in a child with coexisting epilepsy.

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Figure 2. Age at typical presentation of behavioural problems in paediatric epilepsy

Pre-school – autistic spectrum disorder

Primary school – attention deficit hyperactivity disorder / learning disability / autistic spectrum disorder / developmental coordination disorder / depression / anxiety

Secondary school – depression / anxiety / psychosis

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Recently published papers

This section highlights recently published papers. Hopefully this will be very useful to all, helping to keep everyone up to date with the latest developments. It will certainly save you research and reading time, not having to search so many journals.

There are many (often over 300) epilepsy papers published every three months, so what follows has been edited. All animal papers have been excluded and as many review papers as possible have been included. We hope you find the papers of interest in your pursuit to keep abreast of the very latest knowledge.

TANG S, Addis L, Smith A, Topp S D, Pendziwiat M, Mei D, Parker A, Agrawal S, Hughes E, Lascelles K, Williams R E, Fallon P, Robinson R, Cross H J, Hedderly T, Eltze C, Kerr T, Desurkar A, Hussain N, Kinali M, Bagnasco I, Vassallo G, Whitehouse W, Goyal S, Absoud M, EuroEPINOMICS-RES Consortium; Møller R S, Helbig I, Weber Y G, Marini C, Guerrini R, Simpson M A, Pal D K.
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doi: 10.1111/epi.16508.

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Use of Ketogenic Diet Therapy in Infants With Epilepsy: A Systematic Review and Meta-Analysis
Epilepsia. 2020;00:1–21.
doi: 10.1111/epi.16543.

ZHANG L, Zhu X, Peng A, Lai W, He S, Qiu X, Zou X, Chen L.
Predictors of Drug-Resistance in Epilepsy With Auditory Features
Epilepsy Res. 2020 Aug;164:106353
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KAYYALI H, Abdelmoity S, Bansal L, Kaufman C, Smith K, Fecske E, Pawar K, Hall A, Gustafson M, Abdelmoity A, Abdelmoity A
The Efficacy and Safety of Rapid Cycling Vagus Nerve Stimulation in Children With Intractable Epilepsy
Pediatr Neurol. 2020 Apr 13;S0887-8994(20)30119-3.
doi: 10.1016/j.pediatrneurol.2020.04.003.

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Epilepsy and Electroencephalographic Abnormalities in SATB2-Associated Syndrome
Pediatr Neurol. 2020 Apr 13;S0887-8994(20)30122-3.
doi: 10.1016/j.pediatrneurol.2020.04.006.

KONG A N, Fong C Y, Ng C C, Mohamed A R, Khoo T B, Ng R L, Jalaludin M Y, Nadarajaw T.
Association of Common Genetic Variants With Vitamin D Status in Malaysian Children With Epilepsy
Seizure. 2020 Jul;79:103-111.
doi: 10.1016/j.seizure.2020.05.009.

ZHANG Y-Y, Song C-G, Wang X, Jiang Y-L, Zhao J-J, Yuan F, Yang X-A, Yang F, Jiang W.
Clinical Characteristics and Fetal Outcomes in Women With Epilepsy With Planned and Unplanned Pregnancy: A Retrospective Study
Seizure. 2020 Jul;79:97-102.
doi: 10.1016/j.seizure.2020.05.011.ß

SHLOBIN N A and Sander J W.
Towards a Pragmatic Epilepsy Classification: Future Considerations
Seizure. 2020 Jul;79:95-96.
doi: 10.1016/j.seizure.2020.05.002.

KAPOOR D, Sidharth, Sharma S, Patra B, Mukherjee S B, Pemde H K.
Electroclinical Spectrum of Childhood Epilepsy Secondary to Neonatal Hypoglycemic Brain Injury in a Low Resource Setting: A 10-year Experience
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