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Psychiatric and Behavioural Disorders in Children with Epilepsy (ILAE Task Force Report): Behavioural and psychiatric disorders associated with epilepsy syndromes*

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ABSTRACT – The categorisation of the childhood epilepsies into a number of different syndromes has allowed greater insight into the prognosis, not only with regard to seizure control but also in relation to cognitive and behavioural outcome. The role of genetics in determining both the syndrome and the behavioural outcome remains promising, although the promise is still largely unfulfilled. The behavioural/psychiatric outcome of a selection of the large number of childhood epilepsy syndromes is presented. The rate of autism in West syndrome, particularly in children who have tuberous sclerosis with temporal tubers, is high. In Dravet syndrome there is a loss of skills, with an associated increase in behavioural problems. The frequency of both subtle and overt seizures in the Lennox-Gastaut syndrome almost certainly accounts for the apparent poor motivation; however, a marked improvement in seizure control with treatment can also result in behavioural problems, probably as a result of the "release phenomenon". A number of cognitive problems can arise in the so-called "benign" syndrome of epilepsy with centrotemporal spikes (BECTS)

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and the rate of ADHD is high. Autistic features and ADHD have been described in the Landau-Kleffner syndrome and other syndromes associated with electrical status epilepticus of slow-wave sleep (ESES). Early effective treatment may reverse some of these features. There is clear evidence for a behavioural syndrome in relation to juvenile myoclonic epilepsy (JME), in which both clinical descriptions and functional neuroimaging indicate frontal lobe deficits.

Key words: West syndrome, Dravet syndrome, Lennox-Gastaut syndrome, Rolandic, Landau-Kleffner syndrome, juvenile myoclonic epilepsy

There has been an increasing recognition, over recent years, of the importance of the classification of childhood epilepsy into syndromes, not only to provide insight into the treatments that are most likely to be effective and the prognosis of the seizures but also with regard to the likely outcome in terms of cognition and behaviour. Because over 40 epilepsy syndromes and related conditions are listed in the proposed International League Against Epilepsy classification (Engel and International League Against Epilepsy, 2001), it is not possible to discuss the behavioural manifestations of each of these. Furthermore, the quality of behavioural information available is currently still limited. A few of the most frequently occurring and important syndromes will be discussed.

The importance of the behavioural implications of syndrome classification could be considered in two broad categories: first, the behavioural effects of epilepsy syndromes and second, the behavioural associations of childhood syndromes ("behavioural phenotypes") in which epilepsy occurs as a prominent feature. The second category includes a very large number of syndromes and will not be discussed here. However, in view of the extraordinary advances in genetics, particularly with the advent of array comparative genomic hybridization (array CGH), it is appropriate to draw attention to the growing number of genetic defects that are being recognised as being associated with epilepsy, intellectual disability and psychiatric problems. Galizia *et al*. (2012) examined adults with treatment-resistant epilepsy, most of whom had intellectual disability and at least some of whom had psychiatric disorders from childhood. The patients were drawn from two independent London hospitals. They identified copy number variants (CNVs) "judged to be of pathogenic significance" in 13.5% (7/52) and 20% (5/25) of the patients. These were on a variety of chromosomes including chromosomes 15 (four cases), 16 (three cases), 1, 9, 6 and 4. Bartnik *et al*. (2012) also found a large number of CNVs in their study of 102 patients with epilepsy, many of whom had developmental abnormalities. Battaglia and colleagues (2008; 2010) have drawn attention to the inv dup(15) or idic(15) syndrome, the clinical features of which include early central hypotonia, intellectual disability, autistic or autistic-like behaviour and epilepsy; seizures generally start between six months and nine years and a variety of seizure types can occur. Hesdorffer *et al*. (2012) examined familial clustering of epilepsy and behavioural disorders in 308 probands with childhood onset epilepsy. The DSM-oriented scales for affective disorder, anxiety disorder, conduct disorder and oppositional defiant disorder were significantly associated with a family history of unprovoked seizures. They concluded that their results supported the concept that behavioural disorders might be a manifestation of the underlying pathophysiology involved in the epilepsy.

With regard to the genetics of specific epilepsy syndromes, the situation remains that a single genetic defect can be associated with more than one syndrome and more than one genetic defect can be associated with a single syndrome. A discussion of the behavioural associations with specific epilepsy syndromes now follows. Descriptions of each of the syndromes will not be provided, because most of this information is available in a previous review (Besag, 2004).

Search strategy

The Medline/PubMed database was searched from inception until the end of March 2015 using the search terms: epilep$ and (child$ or pediat$ or adolescen$) and (behav$ or psychiat$ or psychol$) and ([name of syndrome]). Abstracts of likely relevance to the topic were examined to select papers for final detailed review. Reference lists of included papers were searched for any further relevant studies. The ILAE website section on epilepsy syndromes was examined for any further information.

West syndrome

The cognitive and behavioural outcome of West syndrome has been reviewed by Guzzetta (2006) and in other previous reviews of the behavioural outcome of epilepsy syndromes (Besag, 2004). Jambaque (1994) reviewed the neuropsychological outcome. Intellectual disability has typically been reported in around 70

to 80%. Riikonen and Amnell (1981) reported that 28% had psychiatric disorders with autism and hyperkinesis in equal numbers. The deterioration in cognition and behaviour appear to coincide with the onset of the severe EEG abnormality of hypsarrhythmia. Against this background, it might be expected that the cognitive and behavioural outcome would depend on prompt treatment. The study by O'Callaghan *et al*. (2011) on 77 infants showed clearly that the earlier the onset of the spasms and the longer the delay to treatment, the worse the outcome in terms of Vineland adaptive behaviour scales at 4 years of age.

There is a marked association between tuberous sclerosis and infantile spasms; the rate of autism in children who have both these conditions appears to be particularly high. For example, Hunt and Dennis (1987) stated that 58% of those who had both West syndrome and tuberous sclerosis remained autistic. When West syndrome occurs in babies with tuberous sclerosis the rate of seizure freedom with vigabatrin is very high. Jambaque *et al*. (2000) showed that when these babies were treated with vigabatrin both the mental age and the behaviour improved. Bolton *et al*. (2002) showed that autism is more likely to occur in children with tuberous sclerosis who had both infantile spasms and temporal lobe tubers, again suggesting that early treatment of the infantile spasms might improve not only cognition but also the psychiatric outcome. Similar conclusions were drawn from the study by Eisermann *et al*. (2003) for the treatment of infantile spasms in Down syndrome and by Bombardieri (2010) for babies who had tuberous sclerosis. There was a significant correlation between treatment lag, cessation of spasms and developmental quotient ($p = 0.003$) and with the score of autistic features ($p = 0.04$). For the group of patients who were treated within two months ($N = 8$), the response to treatment was more rapid ($p = 0.002$), the DQ was higher ($p = 0.004$) and the score of autistic features was lower ($p = 0.006$). All these studies give a clear indication that early treatment is more likely to be effective in terms of controlling the spasms and is also more likely to be associated with a better cognitive and psychiatric outcome.

Dravet syndrome (severe myoclonic epilepsy of infancy)

Brunklaus *et al*. (2011) carried out a study on quality of life and behavioural/psychiatric problems in 163 patients with Dravet syndrome. They screened for psychiatric/behavioural problems using the strengths and difficulties questionnaire (SDQ). The results were as follows: conduct problems 35%, hyperactivity/inattention 66% and peer relationship problems 76%. It should be noted, however, that the SDQ is not a particularly suitable instrument for children with more severe intellectual disability. Acha *et al*. (2014) found significant neurodevelopmental delay in patients with Dravet syndrome in both basic and higher-order cognitive performance. The impairment was greater in verbal abilities than in tasks that required processing visual material. Relative deficits in verbal abilities can influence both behaviour and the strategies used to manage behaviour. Nabbout *et al*. (2011) treated 15 patients with Dravet syndrome using the ketogenic diet; 66% had a decrease in seizure frequency of 75% or more. The authors said that not only was the seizure control improved but hyperactivity and behavioural disturbance also improved. This was a small study with promising results, suggesting that a larger trial would be worthwhile. Genton *et al*. (2011) carried out a long-term outcome study on 24 patients with Dravet syndrome. Five (21%) died. They commented that some patients "*had a major personality disorder, labelled autistic or psychotic*". Only three of the 24 patients lived independently. Because the seizures are often resistant to treatment, polytherapy tends to be used; Casse-Perrot *et al*. (2001) have commented that the polytherapy may contribute to the deterioration in cognition and behaviour. On the other hand, the deterioration in cognition and behaviour seems to coincide with the onset of EEG abnormalities, again raising the question of whether early effective treatment might lead to an improved outcome.

Lennox-Gastaut syndrome

Considering the severity of this syndrome, which involves frequent seizures of multiple types that are generally highly resistant to treatment, the data, both in terms of seizure outcome and behavioural disturbance remain extraordinarily sparse (Arzimanoglou *et al*., 2009; Cross and Neville, 2009; Hancock and Cross, 2009). Most of the studies have been on mixed groups of patients and have not used standardised behavioural measures. Mikati *et al*. (2009) assessed quality of life changes after vagus nerve stimulation in 16 patients with the Lennox-Gastaut syndrome, 11 of whom were children; the total group scored significantly higher in the social domain ($p = 0.039$). It is not surprising that they found that improvement in quality of life was significantly associated with seizure reduction ($p = 0.034$). Similar results were obtained in an earlier study by Majoie *et al*. (2001) on 16 children with "Lennox-like syndrome", who found that there were moderate improvements in mental functioning, behaviour and mood. Boyer and Deschatrette (1980) stated that a diagnosis of primary autism was made

in nine children with the Lennox-Gastaut syndrome. Roger *et al*. (1987) carried out a large long-term study of 338 patients, who were followed into adulthood. They stated that 62.4% had an unfavourable outcome and that 20.4% had fairly rare partial seizures and neurological or psychiatric symptoms. Septien *et al*. (1992) found that two children with the Lennox-Gastaut syndrome had a frontal behavioural syndrome with hypokinesia, distractibility, aggressiveness and alexithymia; after they underwent an anterior two-thirds corpus callosotomy in the early teenage years they improved with regard to frontal-lobe syndrome features within two months of the surgery. Keiffer-Renaux *et al*. (2001) reported that behavioural problems were frequent in the first year of the seizure disorder; these problems were said to have included hypokinesia, with the inability to pursue an activity for more than a few minutes and autistic or psychotic features in some patients. It is highly likely that the hypokinesia described was a direct result of the frequent seizures that commonly occur in this syndrome. Some of the reports of behavioural disturbance when the seizure frequency is significantly decreased probably represent the "release phenomenon"; this situation can occur when someone who has been disabled by severe epilepsy for a long period becomes much more able as a result of successful seizure control but has not yet learned how to use their new-found ability in an acceptable way (Besag, 2001).

Benign childhood epilepsy with centrotemporal spikes (BECTS)/ Rolandic epilepsy

Although this syndrome generally has a good outcome in terms of seizure control by the mid-teenage years, the previous impression that the outcome was also good in terms of behaviour and cognition was not accurate. There are now many papers demonstrating that a number of cognitive deficits and a significant rate of psychiatric disorder, especially ADHD, can occur in association with this syndrome (Heijbel and Bohman, 1975; D'Alessandro *et al*., 1990; Weglage *et al*., 1997; Staden *et al*., 1998; Croona *et al*., 1999; Massa *et al*., 2001; Giordani *et al*., 2006; Northcott *et al*., 2007; Taner *et al*., 2007; Lillywhite *et al*., 2009; Goldberg-Stern *et al*., 2010; Overvliet *et al*., 2011; Sarco *et al*., 2011; Genizi *et al*., 2012; Jurkeviciene *et al*., 2012; Raha *et al*., 2012; Filippini *et al*., 2013). It is also recognised that this syndrome lies on the spectrum with CSWS/Landau-Kleffner syndrome (Gobbi *et al*., 2006; Raha *et al*., 2012). Massa *et al*. (2001) have put forward the persuasive argument that the past statements that the syndrome was benign were based on retrospective studies that excluded children who did not have a benign outcome. They carried out a detailed prospective study on 35 children who fulfilled strict diagnostic criteria for BECTS. They were recruited immediately after the first seizure and were followed up for at least six months after the full normalisation of the EEG. In addition to carrying out a very detailed battery of psychometric tests, they classified educational performance impairments, behavioural disorders and social-familial problems into mild = 1, moderate = 2 or severe = 3. They then divided the 35 children into two groups: Group I with no relevant social-familial problems (score $\leq$2) and Group II who had developed serious difficulties impairing quality of life at home and at school (score $\geq$3). Group II had a poorer outcome on a wide variety of measurements, including educational performance, behavioural disorders, IQ during the course of the epilepsy, recovery IQ, auditory-verbal deficit, visual-spatial deficit and attention deficit. In particular, 10/25 (40%) in Group I had behavioural disorders (all mild, score = 1), whereas 10/10 (100%) in Group II had behavioural disorders (3 mild, 3 moderate and 4 severe). At onset, 4/25 (16%) of Group I had attention deficit compared with 8/10 (80%) of Group II. During the course of the epilepsy 10/25 (40%) of Group I had attention deficit (all mild) whereas 10/10 (100%) of Group II had attention deficit (2 mild, 4 moderate, 4 severe). In the recovery phase 5/25 (20%) in Group I had attention deficit (all mild) compared with 4/10 (40%) in Group II (2 mild, 2 severe). Yung *et al*. (2000) examined the learning and behavioural problems of 78 children with centrotemporal spikes, 56 of whom had a history of clinical seizures compatible with BECTS and 22 of whom had centrotemporal spikes without clinical seizures. Eighteen of the 22 children who did not have clinical seizures were referred for psychiatric or behavioural problems and the other four were referred for suspected seizures that were not confirmed on video EEG monitoring. Three of the children had "atypical clinical features", including language disorder and regression. Eight out of the 78 (10%) had a borderline IQ (70 – 80), 7 (9%) had mild intellectual disability (IQ < 70). Twenty-four (31%) had behavioural problems, including inattention/distractibility, hyperactivity, aggression or oppositional behaviour. Thirteen (17%) had specific learning disability in reading, arithmetic or written expression, according to state of Georgia/South Carolina special education criteria. Forty-four of the 78 had neither behavioural nor learning difficulties. Three of the 78 had developmental or acquired aphasia; all three of these children had BECTS. In the group with BECTS, 12% had intellectual impairment, 14% had behavioural problems and 14% had a specific learning disability. It should be noted that the children without clinical seizures had a greater proportion of problems (36% intellectual impairment, 73% behavioural problems and 23% specific learning disability) but this

is almost certainly because of the referral bias since those without obvious seizures were more likely to be referred because of behavioural/psychiatric problems. Referral bias is a limitation of this study but one of the strengths of the publication is the detailed information provided on a number of the individual cases.

Giordani *et al*. (2006) examined cognition and behaviour in 200 children with BECTS presenting for a trial of antiepileptic medication, implying that this was a selected group. The scores for all seizure groups were within the average range for intellectual and memory functioning. However, the simple partial seizure (focal seizure without impairment of awareness) group performed relatively worse on verbal learning. For those with complex partial (dyscognitive) seizures, parental report suggested greater psychosomatic and learning complaints.

Connelly *et al*. (2006) carried out a detailed neuropsychological common language and quality of life assessment in 30 children with BECTS. They used the Child Behaviour Checklist (CBCL), classifying behaviour into clinically abnormal, borderline clinical or normal, according to established methodology. The competence summary scores were: normal 72%, borderline 7% and abnormal 21% ($p < 0.0005$). The problem behaviour summary scores were: normal 67%, borderline 23% and abnormal 10% ($p = 0.016$) [The normative data for the Child Behaviour Checklist competence summary score are: borderline 3%, abnormal 2%. For problem behaviour, the normative data are borderline 8%, abnormal 10%]. Using the Child Health Questionnaire, the psychosocial summary score on 29 of the children revealed a mean of 41.41 (standard deviation 10.24, z-score -4.63, $p < 0.0005$) [For the Child Health Questionnaire the normative data mean is 50 with a standard deviation of 10].

Filippini *et al*. (2013) examined the longer-term effects of epileptiform discharges during non-rapid-eye-movement (NREM) sleep in 33 children with BECTS who were monitored for at least two years. They showed that the children were at higher risk for residual verbal difficulties and that the abnormal neuropsychological development was significantly correlated with a greater frequency of epileptiform discharges during NREM sleep. This might suggest that allowing such epileptiform discharges to continue long-term might also affect behaviour, although behavioural measures were not reported in this study.

Besseling *et al*. (2014) studied the structural and functional connectivity in BECTS. They found an impaired synergy between structural and functional development, especially in the youngest study subjects, suggesting delayed brain network maturation. The behavioural implications of these findings have yet to be determined.

The Landau-Kleffner syndrome

The acquired aphasia in the Landau-Kleffner syndrome occurs because of the development of verbal agnosia, apparently in association with electrical status epilepticus of slow-wave sleep or continuous spike-waves in slow-wave sleep (ESES/CSWS). It is not surprising that children who lose the ability to understand speech are liable to exhibit behavioural problems. A number of case reports and small series describe behavioural/psychiatric problems, including aggression, sleep disorders, hyperkinesia and autistic regression (Forster *et al*., 1983; White and Sreenivasan, 1987; Hirsch *et al*., 1990; Zivi *et al*., 1990; Beaumanoir, 1992; Lopez-Ibor *et al*., 1997). Several papers have also discussed the relationship between autism, epileptiform discharges and the Landau-Kleffner syndrome (Nass *et al*., 1999; Tuchman, 2000; Deonna and Roulet, 2006; Besag, 2009). This subject has been reviewed by Deonna and Roulet-Perez in their book (2005). Nieuwenhuis and Nicolai (2006) reviewed the pathophysiological mechanisms of the cognitive and behavioural disturbances that can occur in this syndrome. Shinnar *et al*. (2001) prospectively identified 177 children with language regression, some of whom had the Landau-Kleffner syndrome, and stated that 88% met the criteria for autism or had autistic features. Overvliet *et al*. (2010) have reviewed the relationships between nocturnal seizures/epileptiform discharges and language impairment.

Several publications have emphasised the importance of early effective treatment. Medical treatments include steroids, sodium valproate, benzodiazepines, sulthiame and intravenous immunoglobulin. Surgical treatment with multiple subpial transection can be of great value when medical treatment has failed (*Behavioural effects of epilepsy surgery*, p. 68-76). In the series published by Robinson *et al*. (2001), no child who had ESES for more than three years had a normal language outcome. This study, and a number of others, have indicated that the longer the ESES continues, the poorer the outcome in terms of language recovery and consequently the poorer of the outcome is likely to be in terms of behaviour. This implies that the longer the delay in providing early effective treatment, the more likely it will be that there will be long-term cognitive and behavioural problems. As discussed in previous reviews (Besag, 2004), this raises the question of when surgical intervention, in particular multiple subpial transection (Morrell *et al*., 1989), should be considered. Some children recover spontaneously, although there may be some residual language deficit, whereas others have permanent severe language deficits. If surgery is carried out too early, it may have been unnecessary but if it is carried out too late, the child may be left with serious problems that could have been avoided.

Other syndromes involving ESES or CSWS

The International League Against Epilepsy provides a description of a syndrome that involves CSWS or ESES but is not the Landau-Kleffner syndrome. An extract from the definition of "epilepsy with continuous spike-and-waves during slow-sleep (other than LKS)" follows. "*There is a constant and severe deterioration in neuropsychological functions associated with the disorder, and language capacity can be particularly affected. Patients may also show a profound decrease in intellectual level, poor memory, impaired temporospatial orientation, reduced attention span, hyperkinesis, aggressive behaviour, and even psychosis. Motor impairment, in the form of dyspraxia, dystonia, ataxia, or unilateral deficit, has been emphasised as one of the outstanding disturbances occurring in this syndrome. There is a strict association between the pattern of neuropsychological derangement and the location of the interictal focus* (. . .)".

The importance of this syndrome is the recognition that CSWS or ESES can present with a wide variety of deficits, not necessarily involving language – in contrast to the Landau-Kleffner syndrome. The similarity with the Landau-Kleffner syndrome is that CSWS or ESES occurs and may coincide with a marked deterioration in function that is, in at least some cases, reversible with antiepileptic medication or surgery (examples follow). The other characteristic that the two syndromes have in common is that obvious clinical seizures do not necessarily occur; although recognisable seizures are often part of the syndrome, the child may have a deterioration in function without having any current or past clinical seizures. The difference between the two syndromes, as already stated, is that language function is not necessarily involved in the CSWS syndrome.

Because ability may become acutely impaired in this syndrome, as for the Landau-Kleffner syndrome, it is not surprising that many of these children present with behavioural disturbance. Although several papers report behavioural disturbance that resolves with resolution of the CSWS, in most cases very few details of the behaviour itself are provided and, in general, standardised behavioural measures, during the acute phase of the CSWS and after this has resolved, are generally not available. Some of the reports that follow illustrate the variety of neurocognitive deficits that can occur in this syndrome.

Roulet-Perez *et al.* (1993) described an acquired epileptic frontal syndrome in four children with CSWS who had mental and behavioural regression. They commented that the pattern of behavioural and cognitive disturbance was similar to that found in some autistic-like disorders but they also drew attention to the similarity to the features of frontal lobe syndrome, more commonly described in adults. They made the important point that the deficits are potentially reversible and referred to the similarity to the Landau-Kleffner syndrome but with a different area of the brain being affected. Eriksson *et al.* (2003) described a striking case of visual agnosia accompanying occipito-temporal CSWS in an 8-year-old boy with sporadic seizures. There were no focal neurological signs. Visual acuity was intact. An MRI scan was normal. However, EEGs showed ESES/CSWS. Attention and executive functions were intact. There were no memory problems. He had normal global intelligence but major deficits in visual perception. Guzzetta *et al.* (2005) examined the cases of 32 patients with prenatal or perinatal thalamic injuries. Twenty-nine had "major sleep EEG activation". Twelve had CSWS. Behavioural problems were greater in patients with "true CSWS". Improvement in behaviour was in parallel with the disappearance of the CSWS. Aeby *et al.* (2005) assessed the effect of add-on levetiracetam on the EEG, behaviour and cognition of 12 patients with CSWS. In seven of the 12 (58%) the EEG was improved with the levetiracetam. Neuropsychological evaluation showed an improvement in three of the seven; the other four patients could not be tested because of the severity of the cognitive impairment. They commented that behaviour was improved in all seven patients. They also remarked that two patients improved in neuropsychological evaluation despite the lack of EEG improvement. Taner *et al.* (2007) carried out a detailed comparison study between 30 children with CSWS, 42 children with BECTS, 23 children with absence epilepsy and 40 healthy controls. There were high rates of ADHD (43.5-53.3%) and pervasive developmental disorder (43.5-70%) in all the epilepsy groups, in sharp contrast to the control group. The most striking differences were in the high rate of intellectual disability in the CSWS group (33.3%) compared to the other two epilepsy groups: absence epilepsy (4.35%) and BECTS (11.9%). The rates of conduct disorder (27%) and anxiety disorders (30%) were also notably higher in the CSWS group than in the other groups but it should be noted that the overall numbers were small, implying that these differences should be viewed as being of doubtful significance. There were, however, statistically significant differences in all three WISC-R IQ measures (verbal IQ, performance IQ and full-scale IQ) between the CSWS group and both the absence group and the BECTS group. This raises the question of whether the higher rate of some of the psychiatric disorders in the CSWS group might have been accounted for, at least in part, by the lower cognitive ability of this group. Saltik *et al.* (2005) found that a

number of clinical features indicated the development of ESES in a group of 16 children with idiopathic partial epilepsies. These features included an increase in seizure frequency, addition of new types of seizures, appearance of cognitive/behavioural changes or a progression in EEG abnormalities. Behavioural and psychiatric problems occurred in 81% (13/16); these included anxiety, depression, distractibility, hyperactivity, impulsivity and being easily frustrated. After remission of the ESES, three of the 13 patients had an excellent recovery, one was diagnosed as having the Landau-Kleffner syndrome, and nine patients performed better but did not achieve premorbid levels. Nikanorova *et al*. (2009) evaluated the ketogenic diet as treatment in five children (8-13 years of age) with CSWS refractory to conventional antiepileptic drugs and steroids. CSWS resolved in one patient. There was mild decrease in the spike-wave index in another patient. There was no response in the other three patients. The authors noted that, in two patients, there was an improvement in attention and behaviour. Kallay *et al*. (2009) demonstrated that an acquired frontal syndrome in association with CSWS was reversible by hemispherotomy at 5 years of age. Battaglia *et al*. (2009) similarly demonstrated that CSWS with refractory epilepsy from early injury to the thalamus resolved completely with functional hemispherectomy in two children, followed by progressive improvement in both cognition and behaviour. Seegmuller *et al*. (2012) carried out a long-term follow-up study of 10 adolescents and young adults who had had cognitive and behavioural regression with CSWS. The mean follow-up period was 15.6 years (range 8-23 years). None of the patients recovered fully but the marked behavioural disorders resolved in all but one of the 10. Three patients who had had a frontal syndrome during the active phase of CSWS had only mild residual executive and social cognition deficits. The outcome correlated with the duration of the CSWS, emphasising the recommendation that early effective treatment should be implemented.

The prominence of autistic features in association with CSWS has been emphasised by a number of workers (Tuchman, 2000; Deonna and Roulet, 2006). The classification of a specific acquired frontal syndrome with CSWS, as described in some of the reports presented earlier, has also been suggested (Roulet-Perez *et al*., 1993).

It is worth repeating that not all the children with CSWS have clinical seizures. The implication is that if cognition and behaviour deteriorate in a child, even if there is no history of seizures, unless another cause can be found, there is a strong argument for requesting overnight EEG monitoring.

Juvenile myoclonic epilepsy (Janz syndrome)

This has traditionally been considered to be a syndrome with a good outcome, both with regard to seizures (provided antiepileptic treatment is continued) and other aspects, despite the fact that the original publication by Janz and Christian (1957), over 50 years ago, confirmed more recently by Janz (2002), stated that many patients had attractive but unstable, suggestible and unreliable, rather immature personalities, often resulting in an inadequate social adjustment. Janz (2002) has pointed out that these features could be attributed to frontal lobe dysfunction and that neuroimaging studies appear to have confirmed this hypothesis. Risk-taking behaviour has been associated with microstructural alterations within frontal lobes of patients with juvenile myoclonic epilepsy (JME) (Wandschneider *et al*., 2013). Long-term follow up studies, for example the population-based study of Camfield and Camfield (2009), have indicated that some patients have seizures that are resistant to treatment and a number of studies have determined that a considerable proportion of those with JME have psychiatric/personality disorders (Janz and Christian, 1957; Trinka *et al*., 2006; Moschetta *et al*., 2011; de Araujo Filho *et al*., 2013). By definition, this syndrome is not usually considered as presenting before around 12 years of age, although it appears that a proportion of children who have absence seizures subsequently develop JME. It would be of great interest to carry out a prospective study examining psychiatric and personality traits on a very large cohort of children with absence seizures to determine whether those who subsequently develop JME differ, with regard to their psychiatric profile, from those who do not. These data are currently sparse; most of the psychiatric data are on adults or mixed groups with relatively few teenagers. In a small sample of 19 children aged 8-18 years with new-onset JME, Lin *et al*. (2014) prospectively studied the maturational trajectories of brain and cognitive development in comparison with 57 healthy controls. At baseline, the cognitive abilities in the children with JME were similar to or worse than in controls; their cognitive abilities did not reach the level of healthy controls at two-year follow-up across most of the cognitive areas tested. MRI scans revealed significant abnormalities in cortical volume, thickness, and surface area in fronto-parieto-temporal regions. With regard to the personality traits, it might be reasonable to expect that the adult data would be of relevance to teenagers as well; the results from some studies have suggested that there might be grounds for this contention, *e.g*. Iqbal *et al*. (2009), whereas others do not, indicating that these

traits might become more prominent with the duration of the epilepsy (see later). Psychiatric disorders such as psychosis, on the other hand, are likely to present in late adolescence or adulthood, often with no indication of pre-existing childhood or early teenage traits. For these reasons, the adult data on personality disorder will be presented but the adult data on other psychiatric disorders will, in general, not be discussed in this review. It should be noted that not all the papers have stated the age range of the population studied.

Perini *et al*. (1996) reported that the rate of psychiatric disorder in 18 patients with JME was 22%. Devinsky *et al*. (1997) carried out tests of frontal lobe functioning in 15 patients with JME who had a normal IQ; their performance was variable, with some patients showing marked impairment and others none. Concept formation-abstract reasoning and mental flexibility, cognitive speed and planning, and organisation were particularly affected. Gelisse *et al*. (2001) studied a mixed group of teenagers and adults (age range 15-70 years, mean 33 years) and found that 24 patients (15.5%) had persisting seizures despite adequate therapy and lifestyle. Psychiatric problems were strongly associated with seizure resistance: 58.3% in the resistant group compared with 19% in the non-resistant group ($p = 0.0026$). Trinka *et al*. (2006) also studied a mixed group of adults and teenagers (age range 15-63 years). They used the Structured Clinical Interviews for DSM-IV (SCID-I and SCID-II). 33% had one or more psychiatric disorder. Personality disorder was diagnosed in 23%. de Araujo Filho *et al*. (2007) compared the frequency of psychiatric disorders in 100 patients with JME compared with 100 healthy matched controls. They also used the DSM-IV SCID-I and SCID-II. Psychiatric disorders were diagnosed in 49 patients with JME. Anxiety disorder was diagnosed in 23 patients and mood disorder was diagnosed in 19 patients. Personality disorders were diagnosed in 17. The majority of these had cluster B personalities with the characteristics of impulsivity, humour reactivity, emotional instability and difficulty accepting social rules, factors that are remarkably similar to the original description by Janz and Christian (1957).

Plattner *et al*. (2007) used the Youth Self Report (YSR) and the Weinberger Adjustment Inventory (WAI) in 25 of 38 patients who agreed to participate and completed the assessments. The YSR revealed that JME patients had twice the amount of psychiatric symptoms compared to age-matched norms. Psychopathological symptoms increased with the duration of the JME. The WAI revealed decreased self-restraint; the longer the duration of the JME the less the self-control.

Iqbal *et al*. (2009) compared a group of eight sibling pairs, one of whom had JME and the other of whom did not, with 16 matched controls. The group of JME patients and their siblings differed significantly from controls on measures of phonemic and semantic verbal fluency and also scored significantly higher on the Dysexecutive Questionnaire, indicating that they were much more likely to have features associated with executive dysfunction. The authors interpreted these results as suggesting that both the patients and their siblings might have similar underlying dysfunction of cortical and subcortical structures responsible for these functions. It is interesting to compare these results with those of other studies, for example that of Plattner *et al*. (2007), that indicated that measures of frontal lobe dysfunction appeared to increase with the duration of the JME.

Pulsipher *et al*. (2009) compared 20 children with recent-onset JME with 51 healthy controls and 12 children with BECTS, using quantitative magnetic resonance imaging (MRI) and subtests from the Delis-Kaplan Executive Function System (D-KEFS) and the Behaviour Rating Inventory of Executive Function (BRIEF). They found that executive functions were impaired in the JME patients compared both to the controls and to the children with BECTS. The patients with JME had significantly smaller thalamic volumes and more frontal cerebrospinal fluid than controls and BECTS subjects.

de Araujo Filho *et al*. (2009b) carried out magnetic resonance spectroscopy studies comparing 16 JME patients who had cluster B personality disorders (see earlier) with 41 JME patients who had no psychiatric disorder and with 30 healthy controls. A significant reduction of the N-acetyl-aspartate/creatinine ratio was observed mainly in the left frontal lobe in the group of JME patients who had the personality disorder. The same group (de Araujo Filho *et al*., 2009a) carried out a volumetric MRI study in 16 JME patients with cluster B personality disorder compared with 38 patients without any psychiatric disorder and 30 matched healthy controls. Significant reductions were observed in the posterior region of the corpus callosum in the JME group with personality disorder relative to the other groups.

Guaranha *et al*. (2011) studied 65 consecutive JME patients, 45 of whom (61.5%) achieved good seizure control and 25 of whom (38.5%) became seizure free. They compared these with the remainder who had moderate or poor seizure control. Those with persistent seizures presented at a younger age at epilepsy onset (12.6 ± 3.33 years compared with 15.4 ± 5.47 years, $p = 0.015$) and had a higher prevalence of personality disorders (25% compared with 4%, $p = 0.029$) together with higher scores on the State-Trait Anxiety Inventory (45.9 ± 11.31 compared with 3.66 ± 11.43, $p = 0.011$).

Moschetta *et al*. (2011) examined personality traits in a mixed group of adults and teenagers, most of whom

were adults (mean age 26.57 years, standard deviation 8.38) and 42 matched controls. They used the Temperament and Character Inventory (TCI). The JME patients had significantly higher scores on Novelty Seeking (p = 0.001) and Harm Avoidance (p = 0.002) and significantly lower scores on Self-Directedness (p = 0.001). They concluded that patients with JME had a higher expression of impulsive personality traits. The same group, Moschetta and Valente (2012), evaluated their 42 patients and a control group using the Digit Span tests (forwards and backwards), Stroop-Color Word Test, Trail Making Test, Wisconsin Card-Sorting Test, Matching Familiar Figures Test and Word Fluency Test. The JME patients showed specific deficits in working memory, inhibitory control, concept formation, goal maintenance, mental flexibility and verbal fluency. Of the whole group of JME patients, 83% had moderate or severe executive dysfunction. Attention and executive impairment was correlated with a higher frequency of seizures and the presence of psychiatric disorders. Executive dysfunction correlated with a longer duration of epilepsy.

There is now a large body of evidence confirming the original observations of Janz and Christian (1957) that certain personality traits are much more common in patients with JME and that these reflect both structural and functional frontal lobe deficits. At what age these are present and to what extent other factors, such as duration and severity of the epilepsy, play a role remain subjects that require further investigation.

Conclusions

Although there is great variability within each of the childhood epilepsy syndromes, there is a growing body of evidence indicating that the identification of the epilepsy syndrome can be of prognostic value not only in terms of seizure control but also in providing an indication of the likely behavioural and cognitive outcome. This knowledge empowers clinicians and families, helping them to gain a greater understanding of the child as well as assisting in the planning of management and resources. □

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TEST YOURSELF

(1) Why is the classification of epilepsy into the appropriate syndrome of relevance with regard to behavioural/psychiatric disturbance in children with epilepsy?

(2) For children with a history of West syndrome and tuberous sclerosis complex, what additional anatomical abnormality is associated with the risk of developing autism?

(3) In which epilepsy syndrome is there considerable evidence for frontal lobe dysfunction, on the basis of both clinical findings and neuroimaging?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The Epicentre".