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Psychiatric and Behavioural Disorders in Children with Epilepsy (ILAE Task Force Report): Epilepsy and Autism*

Frank Besag [1], Albert Aldenkamp [2], Rochelle Caplan [3], David W. Dunn [4], Giuseppe Gobbi [5], Matti Sillanpää [6]

[1] Mid Beds Clinic, East London NHS Foundation Trust, Bedford, UK
[2] Department of Research and Development, Epilepsy Center Kempenhaeghe, Heeze; MHENS School of Mental Health & Neuroscience, Maastricht University, Maastricht, The Netherlands
[3] Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, USA
[4] Riley Hospital Child and Adolescent Psychiatry Clinics, Indiana University School of Medicine, Indianapolis USA
[5] Institute of Neurological Sciences of Bologna, Child Neurology Unit, Bologna, Italy
[6] Depts. Public Health and Child Neurology, University of Turku, Turku, Finland

ABSTRACT – A high proportion of children with epilepsy have autism spectrum disorder. Although estimates vary, depending both on the population studied and the definitions used, a figure of around 20% has typically been reported. Autism can have a major impact on the life of the child and family. Despite the importance of this comorbidity and although many studies have been performed, a full understanding of the possible links between epilepsy and autism remains elusive. In a minority of cases, for example in the Landau-Kleffner syndrome, the autistic features can be the result of the epilepsy itself. However, there has been a failure to demonstrate that the epilepsy itself plays a major role in most cases. The current evidence seems to point to a common underlying predisposing factor. The discovery of a growing number of genetic defects leading to both conditions would support this explanation of the link.

Key words: autism, ESES, CSWS, epileptiform, Landau-Kleffner

The rate of epilepsy in people with autism is high and the rate of autism in people with epilepsy is also high (Tuchman and Rapin, 2002; Amiet *et al.*, 2008; Mouridsen *et al.*, 2011). The association between epilepsy and autism has been the subject of much debate and much controversy (Besag, 2009; Spence and Schneider, 2009). Particular attention should be drawn to the papers by Tuchman and co-workers (see later), in which the subject of epilepsy and autism has been examined extensively. There is still no clear consensus with regard to the cause of the association between the two conditions, although many possible mechanisms have been proposed.

Correspondence:
Professor Frank M C Besag
FRCP FRCPsych FRCPCH
Consultant Neuropsychiatrist
Mid Beds Clinic
24 Grove Place
Bedford MK40 3JJ
<frank.besag@elft.nhs.uk>

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Search strategy

In addition to studies already known to the authors, 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 (autism or autistic). 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.

Epidemiology

The prevalence of epilepsy in childhood is around 4-7 per 1,000 (Sillanpää, 1992) and the prevalence of autism spectrum disorder (ASD) is approximately 1% (Baird *et al.*, 2006b). Estimates of the prevalence of epilepsy in autism range widely, from approximately 2 to 40% (Woolfenden *et al.*, 2012), depending not only on the group of subjects studied but also on the criteria and ascertainment used both for the diagnosis of epilepsy and, particularly, the diagnosis of autism/ASD. Furthermore, the prevalence will depend on the age at which the subjects are studied. There are two peaks of onset of epilepsy associated with autism, the first in infancy and the second in the teenage years. This implies that the childhood prevalence is likely to be lower than the prevalence in the late teenage years. Some studies quote point prevalence and others quote lifetime prevalence; the latter will clearly be higher. The rate of misdiagnosis of epilepsy is high, typically around 20-25% (Jeavons, 1983; Uldall *et al.*, 2006). The diagnosis of autism is subjective, since there is no laboratory test for the condition. Interviews, questionnaires and observational instruments are all subject to error. Most of the studies on the prevalence of autism and epilepsy have not been prospective and have been on selected samples, rather than being population studies. The prevalence of autism also depends very much on the level of intellectual ability (Amiet *et al.*, 2008).

Steffenburg *et al.* (1995) carried out a population study in Goteborg, Sweden, on cohorts of children aged 6-9 years and 10-13 years. Ninety-eight children met the criteria for intellectual disability (mental retardation) and active epilepsy. Twenty-four subjects (27%) had "autistic disorder" and a further 10 (11%) had "an autistic-like condition". Of the 90 children examined, 53 (57%) had at least one additional psychiatric diagnosis, the most common being ADHD. A subsequent study by the same group (Steffenburg *et al.*, 1996) showed that the prevalence of autism increased with age, up to 10 years. At 10 years, the prevalence of autism alone was 8%, of autism with severe mental retardation but no cerebral palsy 27% and autism with severe mental retardation and cerebral palsy 67%.

Clarke *et al.* (2005) based a diagnosis of autism on the autism screening questionnaire (ASQ) in a tertiary care clinic. Of the 97 ASQ questionnaires that were properly completed, 32% fulfilled the criteria for ASD. The children in this study were aged 2-18 years (mean age 12.7 years). However, the questionnaire return rate was only one-third, implying that the results might not have been typical of the whole sample of children attending the clinic. Danielsson *et al.* (2005) carried out a further study on the population of individuals identified with epilepsy born from 1962 to 1984 in Goteborg. They found that 30% of 120 individuals with autistic disorder or "autistic-like condition" had epilepsy at some point in their lives. By the time of this study, six (5%) of the 120 individuals had died and six (5%) had parents who did not want to participate. The remaining 108 subjects (77 male and 31 female, mean age at study 25.5 years, range 17-40 years) were included. Amiet *et al.* (2008) reviewed all data available from published reports from 1963 to 2006 on autism and epilepsy. They carried out meta-analyses and found that the pooled prevalence of epilepsy was 21.5% in autistic subjects with intellectual disability compared to 8% in those without intellectual disability. The male to female ratio of autism with epilepsy was approximately 2:1 in contrast to the male to female ratio of autism without epilepsy which was 3.5:1. Epilepsy was more likely to occur in girls with autism ($p<0.001$). Turk *et al.* (2009) compared two groups of 60 children, aged 7-17 years, with autism spectrum disorder: one with epilepsy (ASD + epilepsy) and the other without (ASD only). The male to female ratio was 6.5:1 in the ASD-only group but only 2:1 in the ASD + epilepsy group. The group with ASD + epilepsy were more likely to have had a later diagnosis of ASD and, in contrast to what might have been expected, were no more likely to be aloof and passive than the ASD-only group. As might have been predicted, the ASD + epilepsy group had more motor difficulties, developmental delays and challenging behaviours, in keeping with previous findings. Although the investigators endeavoured to recruit all children with autism in a given geographical area, the groups were not very well matched, implying that the results cannot confidently be generalised to other populations.

Berg *et al.* (2011) carried out a community-based, prospective, long-term, follow-up study of children enrolled when first diagnosed with epilepsy by paediatric neurologists in the state of Connecticut from 1993 to 1997. Parents were interviewed at five and nine years after the initial recruitment into the study. For the majority of the children (489/613), an interview was carried out at both these times. In addition, medical and other records were scrutinised. It should be noted, however, that no standard autism screening instrument was used, nor were the children examined

personally to determine whether they had autism. Twenty-eight were classified as definitely or probably having ASD, 26 by parental interview and two through medical records only. One of the children had Rett syndrome and all of the 28 had ASD before the onset of epilepsy. In another 24 children the diagnosis (although not necessarily the initial onset of symptoms) of ASD was identified after the children had been recognised as having epilepsy. There were a further 28 children who were identified by the parent or from the medical records as having possible ASD that were excluded on further scrutiny. A further 21 children had autism-spectrum-disorder-like features but did not have definite or possible ASD. The overall prevalence of ASD was 5% (95% confidence interval 3.2-6.9%). In those with an estimated IQ of 80 or greater, the prevalence was 2.2% (95% confidence interval 0.8-3.6%) compared with 13.8% (95% confidence interval 8-19.5%) in those who had an IQ of less than 80. In the bivariate analysis, male gender, early age of onset, IQ less than 80 and West syndrome were all associated with ASD. The same parameters, apart from West syndrome, were all associated with autistic-like features. On the basis of multiple logistic regression, the following characteristics were correlated with ASD in 27 of these children with this diagnosis (excluding the one child with Rett syndrome): a history of West syndrome, prevalence ratio 3.4, 95% confidence interval 1.36-8.65, p= 0.009, intellectual impairment, prevalence ratio 5.08, 95% confidence interval 2.15-12.0, p= 0.0002 and male sex, prevalence ratio 2.22, 95% confidence interval 0.97-5.07, p= 0.06. The following factors were independently associated with ASD in children with no history of West syndrome: intellectual impairment, prevalence ratio 4.46, 95% confidence interval 1.93-11.25, p= 0.0006 and male sex, prevalence ratio 3.71, 95% confidence interval 1.24-11.1, p= 0.02. The authors concluded that West syndrome appeared to have a strong and specific association with ASD. Apart from this association, the main risk factors for ASD in children with epilepsy seemed to be the same as in the general population, although there did appear to be a small increased risk of this disorder associated with childhood-onset epilepsy in the absence of cognitive impairment. However, it should be noted that the numbers, when stratified, were quite small and the confidence interval for ASD occurring in those with an IQ of more than 80 was 0.8-3.6%; this implies that, although the prevalence was 2.2%, which is higher than the most recent estimates of autism prevalence in whole population studies, the confidence interval overlaps with the figure for autism in the general population.

Matsuo *et al.* (2010) studied 519 patients with epilepsy, aged 2-43 years (median 11 years), followed up at the paediatric department of a children's hospital. All of these patients had the first seizure before 18 years of age. Seventy-nine patients (15.2%) had ASD, which included autism, Asperger syndrome and pervasive developmental disorder not otherwise specified (PDD-NOS). The most frequent age of onset of seizures was 4 years. The epilepsy onset was before 10 years of age in 85%. ASD was detected after the onset of epilepsy in 47%. The authors pointed out that eight of these 29 cases had been overlooked for more than five years; most of these had high-functioning ASD. The most frequent seizure type was complex partial (dyscognitive) seizures (68%). Paroxysmal EEG abnormalities in the frontal area were recorded in about half of the cases. They concluded that complex partial (dyscognitive) seizures with frontal paroxysms occurring from 1 to 9 years of age seemed to be characteristic of epilepsy associated with ASD. They also drew attention to the fact that their study did not show a second peak of epilepsy onset in teenagers with ASD but this was because the clinics were mainly for children of less than 15 years of age. The male to female ratio of idiopathic ASD was 3 to 1 and of secondary ASD was 2.4 to 1. They stated that this was consistent with other studies suggesting that epilepsy might be more prevalent in females with ASD than in males with ASD because these ratios are lower than the male to female ratio of autism quoted for the general population.

Bolton (2011) carried out a long-term follow-up study of individuals who were diagnosed with autism in childhood. The study was performed when the subjects were at least 21 years of age. Of this group of 150 individuals, 22% had developed epilepsy, the majority after 10 years of age. However, it should be noted that those with a history of infantile spasms or those with severe or profound intellectual disability (mental retardation) were excluded. The group with epilepsy was compared to those in the same clinic population who did not develop epilepsy. Both verbal and non-verbal ability were lower in the epilepsy group. As in other studies, the gender ratio was more equal in those with epilepsy (39% female) than in those without epilepsy (24% female).

Jokiranta *et al.* (2014) identified cases of autism spectrum disorder through the Finnish Prenatal Study of Autism and Autism Spectrum Disorders, which included data on 4,705 children. They examined associations between epilepsy and various types of autism spectrum disorder, including childhood autism, Asperger syndrome and pervasive developmental disorders (not otherwise specified). Each case was matched to four controls. They found that epilepsy was associated with autism spectrum disorder in all of the autism spectrum disorder groups, after adjusting for covariates. However, the association was stronger in the group with intellectual disability, especially females.

Woolfenden *et al.* (2012) carried out a systematic review of two outcomes in autism spectrum disorder: epilepsy and mortality. They found 16 studies in which the percentage of those with autism who had developed epilepsy was measured after at least 12 months of observation. In two of the studies, for which the age at follow-up was under 12 years, the majority of subjects did not have intellectual disability and the estimate of the percentage having epilepsy at follow-up was 6.1% (95% confidence interval 3.8–9.0%). In nine of the studies, the majority of subjects did have intellectual disability and the age at follow-up was 12 years or more; the pooled estimate of the percentage having epilepsy at follow-up was 23.7% (95% confidence interval 17.5–30.5%). It is interesting to note that these figures are very comparable with the previous analysis by Amiet *et al.* (2008), namely 8% and 21.5%, respectively (see earlier). Woolfenden *et al.* also examined the effect of gender; three papers provided this data: 3–10% of females had epilepsy compared to 13–29% of males.

Causes of autism in children with epilepsy

This subject has been discussed by a number of authors, notably Tuchman and co-workers (Tuchman *et al.*, 2010; Tuchman and Cuccaro, 2011; Cuccaro *et al.*, 2012; Tuchman, 2013). As previously discussed (Besag, 2009), the cause of the link between epilepsy and autism might be framed in the following three questions.

– Can epilepsy result in autistic features?
– Can autism cause epilepsy?
– Could there be underlying causes or conditions that predispose both to autism and epilepsy?

These questions will be discussed in turn.

Can epilepsy result in autistic features?

There are many anecdotal reports of this, demonstrated clearly by the resolution or reduction of autistic features when the epilepsy, manifesting as seizures and/or epileptiform abnormalities, is treated successfully – see later. One of the reasons that there has been such an intense interest in the possibility that epilepsy might play a role in the causation of autism is the finding that 15-40% of children with autism regress, *i.e.* lose skills, within the first three years of life, raising the question of whether some subtle manifestation of epilepsy might be playing a role (Baird *et al.*, 2008). Although the rate of epileptiform abnormality in the EEG of subjects with autism is high, there seems to be no association with regression, as demonstrated by Chez *et al.* (2006). They carried out a retrospective review of 24-hour ambulatory EEG data from 889 patients with autism spectrum disorder and found that 540 (60.7%) had abnormal epileptiform activity in sleep. The epileptiform discharges were most frequently localised over the right temporal region. Eighty of 176 patients treated with valproic acid had normalisation of the EEG and an additional 30 showed improvement on the EEG. As discussed in the paper on epilepsy syndromes (see later), Roulet-Perez *et al.* (1993) described an acquired epileptic frontal syndrome in four children with continuous spike waves in slow-wave sleep (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. Deonna and Roulet (2006) have stated that it is disappointing that after a period of 10-20 years during which there has been a hope of finding epilepsy as a possible cause of autism there has been a growing absence of evidence of a direct causal link. Tharp (2004) reviewed the data and concluded that there was no justification to support the use of antiepileptic medication or surgery in children with pervasive developmental disorders, *i.e.* that there is no evidence that treatment to eliminate EEG spikes would have a therapeutic effect on the behavioural abnormalities of autism. Baird *et al.* (2006a) carried out an audit of sleep EEGs in 64 children (18-48 months) with autism, none of whom had a history suggestive of epilepsy. Thirty-nine had regressive autism. Twenty showed some epileptiform abnormality. Although the authors found that there was no statistically significant difference in epileptiform activity in those who showed regression compared with those who did not, it should be noted that the percentage of abnormal EEGs was higher (38.5%) in those who had set-back compared with those who did not (20%) and, although the overall difference was not statistically significant (p=0.07), the p value was not far above 0.05, raising the possibility that larger numbers might have revealed a statistically significant difference.

There are major methodological difficulties in endeavouring to assess the role of epileptiform discharges in autistic regression. A daytime EEG may not pick up abnormalities that are clinically significant. Twenty-four-hour monitoring or, at least, sleep monitoring is recommended. Furthermore, if the regression takes place over a short period of time and the EEG is carried out after the period of regression, it would not be surprising if the EEG abnormality were largely "burnt out" by that stage, resulting in a false negative result. This area, which has been one of great controversy, remains open to debate.

Can autism cause epilepsy?

The second possibility is that autism might cause epilepsy. No reasonable hypothesis appears to have been put forward to suggest causality in this direction.

Could there be underlying causes or conditions that predispose both to autism and epilepsy?

The third possibility is that there is an underlying disorder or abnormality leading both to epilepsy and to autism (Brooks-Kayal, 2010; Tuchman and Cuccaro, 2011). The finding that the majority of children with epilepsy who have autism are also in the intellectual disability range (IQ less than 70) offers strong supportive evidence to this suggestion. However, it should be noted that, as indicated earlier, there appears to be a small increase in epilepsy in those who have autism but do not have intellectual disability (Amiet *et al.*, 2008). More recent genetic work suggests that a number of gene defects might be associated both with epilepsy and autism. This issue has been discussed in some detail by Tuchman and Cuccaro (2011). Particular attention should be drawn to the review by Betancur (2011), which has the thought-provoking title *Etiological heterogeneity in autism spectrum disorders: more than 100 genetic and genomic disorders and still counting*. In that review, data is provided on 103 disease genes and 44 genomic loci reported in subjects with autism spectrum disorder or autistic behaviour. She points out that these genes and loci have all been causally implicated in intellectual disability, indicating that these two conditions share a common genetic basis. Furthermore, she has made the important point that the findings illustrate that autism is not a single condition. She reports that the most common single gene mutation in subjects with autism spectrum disorders is Fragile X syndrome (FMR1), present in about 2% of cases. A number of other monogenetic disorders in which ASD can occur include tuberous sclerosis (TSC1, TSC2), neurofibromatosis (NF1), Angelman syndrome (UBE3A), Rett syndrome (MECP2) and PTEN mutations associated with macrocephaly and autism. Rare mutations identified in synaptic genes include NLGN3, NLGN4X, SHANK3 and SHANK. A large number of other genetic disorders are included in that review. Particular attention has been drawn to copy number variants (CNVs). These can include microdeletions and microduplications with variable expressivity and/or incomplete penetrance. Those associated with neurodevelopmental disorders include 1q21.1, 15q13.3, 16p13.11, 16p11.2 and 22q11.2.

What conclusions can be drawn about the cause of autism? The first conclusion should be that the search for a single cause is unlikely to be successful, regardless of whether the subjects have epilepsy or not, since autism, as already stated, appears to represent a number of different conditions with common clinical characteristics. There are likely to be multiple causes but identifying at least some of these might be helpful in management.

The management of children with epilepsy and autism

The management of the child with epilepsy and autism basically consists of managing each of these conditions as they would be managed on their own, with certain notable exceptions. Rarely, a child may lose skills because of electrical status epilepticus of slow wave sleep (ESES)/continuous spike-waves in slow-wave sleep (CSWS). As stated in previous reviews, although the Landau-Kleffner syndrome of acquired epileptic aphasia is a rare condition, it provides an interesting model in this context, since it is reported that 20-30% of these children do not have obvious seizures (Caraballo *et al.*, 2014). Despite this, antiepileptic treatment with medication or with surgery such as multiple subpial transection (Morrell *et al.*, 1989) can be highly effective if implemented early. ESES/CSWS does not always present with regression of language skills; it may present with loss of other skills. Again, treatment to abolish the epileptiform abnormality may result in partial or substantial return of the lost skills. Apart from these important exceptions, standard management for both epilepsy and autism spectrum disorder should be implemented. Notwithstanding these comments, Robinson (2012) has pointed out that there are several reports of reductions in emotional lability, aggression, impulsivity and self-injurious behaviour with a number of antiepileptic drugs including carbamazepine (Gillberg, 1991), valproic acid (Nass and Petrucha, 1990; Plioplys, 1994; Childs and Blair, 1997), divalproex sodium (Hollander *et al.*, 2006), lamotrigine (Uvebrant and Bauziene, 1994) and topiramate (Hardan *et al.*, 2004). However, most of these reports are single cases or open trials. Although the study by Hollander *et al.* (2006) was a double-blind, placebo-controlled trial of divalproex sodium against placebo, the number of participants with autism spectrum disorder (13) was small and the duration of the trial (eight weeks) was relatively short. They reported a statistically significant group difference in improvement in repetitive behaviours (p= 0.037) and a large effect size (1.616). They acknowledged that this was a preliminary study. It should be noted that carbamazepine and sodium valproate/divalproex sodium are well-established mood-levelling drugs and it is consequently quite likely that any beneficial effect was through the mood-levelling properties rather than the antiepileptic effects. Topiramate is an antiepileptic

drug with multiple modes of action; it is not surprising that it has been reported as showing both deleterious and beneficial effects on mood in various studies. Although the main role of antiepileptic drugs in children with autism and epilepsy is to control the seizures, in those who have mood disorders, choosing a medication that also has mood-levelling properties may be of benefit. Whether any additional benefit is derived from suppression of epileptiform discharges remains very much open to debate, as discussed elsewhere (Deonna and Roulet, 2006; Besag, 2009).

Both epilepsy and autism are associated with higher rates of coexisting psychiatric/behavioural problems. Viscidi *et al*. (2014) examined the association between epilepsy, autism spectrum disorder and maladaptive behaviours in 139 children. These were the children from the group of 2,645 subjects with autism spectrum disorder from the Simons Simplex Collection, of whom 139 additionally had epilepsy. The children with autism spectrum disorder who also had epilepsy had more autism symptoms and more maladaptive behaviours than those without epilepsy. However, they found that, after adjusting for IQ, only hyperactivity symptoms remained statistically significantly increased (13% higher) in the group of children with epilepsy. In the children who also had intellectual disability, the children with epilepsy had significantly more irritability (20% higher) and hyperactivity (24% higher) symptoms.

Future research

The area of genetics research has expanded to an extraordinary degree over recent years; this is true for genetics research into autism as it is into many other conditions. The results are complex but tantalising. Whether they will give precise guidance on management except in a small minority of cases remains to be seen.

Despite the disappointment expressed by Deonna and Roulet (2006), a large-scale prospective study in which 24-hour EEG, or at least an overnight/sleep EEG is performed in children as soon as any sign of regression becomes evident, might still be worthwhile. The evidence so far seems to indicate that such a study would identify only a very small number of children with epilepsy or epileptiform discharges, including electrical status epilepticus of slow-wave sleep, as the cause for the autism. However, if the clinical features of these children can be characterised, this could imply that, at least for this small subgroup, prompt and effective treatment might prevent further regression and allow some return of function.

Research into specific disorders in which autism is frequent, such as tuberous sclerosis complex, Rett syndrome and Fragile X syndrome, although interesting, have so far not yielded results that can be applied more generally to the management of autism. Nevertheless, continued research in these areas would appear to be worthwhile. An area of increasing interest is the role of neuronal antibodies in causing epilepsy and a number of psychiatric/psychological changes (Irani *et al*., 2011; Vincent *et al*., 2011). The role of neuronal antibodies in the complex relationships between epilepsy and autism is yet to be elucidated.

At present it must be concluded that, despite extensive research, there are still many unanswered questions regarding the relationships between epilepsy and autism. □

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TEST YOURSELF

(1) What is the approximate prevalence of autism in young people with epilepsy by the end of the teenage years?

(2) What disease complex is associated with a high rate of infantile spasms and autism?

(3) What is the most common relationship between epilepsy and autism: epilepsy causing the autism, autism causing the epilepsy or some underlying factor predisposing to both disorders?

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".