Autism and epilepsy

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Abstract

The link between epilepsy and autism has been established in several epidemiological studies. Although results vary, meta-analyses have suggested that the rate of epilepsy in autism is between 20 and 30%. It is considerably less in populations of children with autism who do not have intellectual disability, in whom around 6-8% are reported to have epilepsy. The reason for the coexistence of epilepsy and autism remains unclear. It seems that the epilepsy itself is probably the cause of the autism in only a very small minority of cases. In most cases an underlying predisposition is probably responsible for both conditions. A number of genetically-determined conditions have been implicated in this regard, of which tuberous sclerosis is one of the most interesting examples. With a few exceptions, the management of individuals who have both autism and epilepsy is similar to those who have either of these conditions on its own.

Introduction

Several epidemiological studies have established a clear link between epilepsy and autism (1-6). Epilepsy typically occurs in about 20% of people with autism (4), and autism is one of the most common psychiatric disorders in children with epilepsy (6,7). The reasons for the link between the two conditions have been the subject of debate over several years and has been discussed in detail in recent reviews (8-11). What are the possible reasons for such a link? The logical possibilities can be explored by endeavouring to find answers to the following questions. Does autism cause epilepsy? Does epilepsy cause autism? Are there underlying factors that predispose both to autism and epilepsy? Are different mechanisms responsible for the link between the two conditions in different people?

Epidemiology

The current author has recently summarised the literature on the epidemiology of epilepsy and autism (12). The prevalence of childhood epilepsy is around 4–7 per 1000 (13) and the prevalence of ASD is approximately 1% (14). Wolfenden et al. (4) carried out a systematic review on outcomes of children with autism. They estimated from two studies of children with autism for whom the age of follow-up was under 12, and in whom the majority did not have intellectual disability (mental retardation), that the rate of epilepsy was 6.1% (95% confidence interval 3.8%–9.0%); in nine studies in which the majority of subjects did have intellectual disability and the age at follow-up was 12 years or more, the pooled percentage estimates of those having epilepsy at follow-up was 23.7% (95% confidence interval 17.5–30.5%). These figures are similar to an earlier analysis by Amiet et al. (1). The age of onset of epilepsy in autism appears to have two peaks: either the epilepsy onset is in the first year of life or it is before the end of the teenage years. This implies that early childhood studies would reveal a lower prevalence than those examining subjects in the late teenage years.

Does autism cause epilepsy?

No plausible mechanism has been proposed that might explain how autism could cause epilepsy. It could, of course, be argued that a person with autism is more at risk of having an accident that could cause a brain injury resulting in epilepsy. Not only would such cases be exceptionally rare but the cause of the epilepsy would also be obvious.

Does epilepsy cause autism?

Prolonged seizure activity of the type that results in unconsciousness ("convulsive status epilepticus") lasting much longer than 20 minutes can sometimes cause permanent brain damage (15,16). This can be followed by both intellectual impairment and, in some cases, autism. However, such a sequence of events would, again, be both obvious and rare.

The main interest in epilepsy as a possible cause of autism has been exploring whether the autism might be the result of subtle seizure activity. The concept of subtle manifestations of epilepsy has been discussed in greater detail by the current author (17). Some specific examples of how subtle seizure activity might result in autistic features follow.

(i) Nonconvulsive Status Epilepticus

Nonconvulsive status epilepticus is usually considered to be a state in which subtle seizures (i.e. not involving convulsions, stiffening or any other obvious movements) occur so frequently that the person is in a constant altered state of consciousness.

Very frequent absence seizures or nonconvulsive status epilepticus may mimic an autistic-like state because of the very limited interaction between the individual and the world around him or her. It might seem that nonconvulsive status epilepticus would be such an obvious condition that the chances of mistaking it for autism would be negligible but this is not the case. Nonconvulsive status epilepticus can be missed. If the nonconvulsive status epilepticus is generalised then an EEG should enable the diagnosis to be made promptly. Temporal lobe nonconvulsive status epilepticus, in which the epileptiform discharges are much more localised, may be more difficult to diagnose but is probably very uncommon. The situation that must alert the clinician to the possibility of nonconvulsive status epilepticus is unexplained loss of skills. It has been suggested that, if the nonconvulsive status epilepticus is of very long duration (probably weeks or months), permanent cognitive damage might occur. Because a proportion of children, perhaps around 25% with autism, have a history of unexplained loss of skills under three years of age (18), there has been great interest in exploring the possibility that the autism in this group of children may have been caused by epilepsy. This issue will be discussed at the end of the next section (see later).

(ii) Electrical status epilepticus of slow-wave sleep (ESES) or continuous spike-waves in slow-wave sleep (CSWS)

The other situation in which epilepsy can be the cause of loss of skills is electrical status epilepticus of slow wave sleep (ESES), defined as more than 85% of slow-wave sleep being occupied by epileptiform spike-wave discharges. An alternative term is continuous spike-waves during slow-wave sleep (CSWS). The classical model for this situation is the Landau-Kleffner syndrome of acquired epileptic aphasia (19), in which a child with apparently normal early language development loses the ability to understand speech and consequently, because they cannot understand their own speech either, may become mute. The loss of speech ability appears to coincide with the ESES. These children are often described as having autistic features (20). If the ESES is treated with medication (21) or surgery (22), before permanent damage occurs, the child can at least partly recover speech and the autistic features tend to resolve because the child is able to interact again. Against the background of this model, attempts have been made to discover whether the loss of skills in autism has coincided with overnight epileptiform discharges in the brain. Although these endeavours have not proved to be successful, it is notable that the study by Baird et al., (23) while failing to prove any statistically significant relationship with overnight epileptiform discharges and autism, nevertheless revealed a trend towards the presence of such discharges with autism (see later). The concept of this model is very powerful because the implication is that if the ESES is treated early enough the speech may return and the autistic features resolve but if the treatment is left too late, the damage can be permanent. ESES is thought to be rare, implying that autistic features from this source are also likely to be rare but this situation opens the possibility of treating and resolving autistic features, in marked contrast to the situation for classical autism, in which the condition is pervasive, both across situations and across time.

The research studies that have been performed have failed to show any clear link between regression in autism and epileptiform discharges (3,24). However, such studies are subject to methodological difficulties and the possibility remains that a small subset of children in whom autism is diagnosed and who undergo regression do so because of frequent epileptiform discharges. It is interesting, in this context, to note that Baird et al., (23) in keeping with other studies, in a study of children with autism but with no diagnosis of epilepsy, failed to find any statistically significant difference between epileptiform discharges in sleep EEGs in those who underwent regression and those who did not. However, the percentage of abnormal EEGs was higher (38.5%) in those who regressed compared with those who did not (20%) and, although the overall difference was not statistically significant, the p value was 0.07, suggesting that larger numbers might have revealed a significant difference.

There is a strong argument for recommending that any child who loses skills for no apparent reason deserves energetic investigation and, if no other cause can be found, this investigation should include EEG monitoring, initially daytime EEG monitoring followed, if necessary, by overnight EEG monitoring. Daytime EEG monitoring will determine whether the child is in generalised nonconvulsive status epilepticus and overnight monitoring will determine whether the child is having ESES.

Although the cases discussed in this and the previous section probably represent a tiny minority of children who present with loss of skills and autistic features, it is important to draw attention to them because of the possibility of resolving the autistic features by treating the epilepsy, i.e. by abolishing the daytime epileptiform discharges of nonconvulsive status epilepticus or the nocturnal epileptiform discharges of ESES, effectively with medication or surgery.

(iii) Other epilepsy syndromes associated with autistic features

The literature on the behavioural effects of epilepsy syndromes has been reviewed by the current author (20). Autistic features have been described in association with some of the epilepsy syndromes in a number of publications. However, the diagnostic criteria for autism have generally not been stated and it seems likely that the authors have misinterpreted the lack of social interaction due to severe epilepsy as being a manifestation of autism. For example, the Lennox-Gastaut syndrome is characterised by severe, difficult-to-treat epilepsy with several different seizure types, notably frequent atypical absence seizures. As already stated, a child who is having frequent absence seizures is unlikely to be able to interact satisfactorily and may appear to be "autistic". However, the situation is quite different from classical autism. Not only is this condition potentially treatable (although, in practice, the Lennox-Gastaut syndrome is often resistant to treatment) but also the autistic features are likely to be variable as the frequency of the atypical absence seizures varies.

Are there underlying factors that predispose both to autism and to epilepsy?

There is a strong link between intellectual disability and epilepsy: the lower the IQ the higher the risk of epilepsy. Using current criteria for autism spectrum disorder (ASD), around 50% of those with this disorder will have an abnormally low IQ, i.e. less than 70. Consequently, the expected rate of epilepsy would be proportionately high. This raises the question of whether the rate of epilepsy in people with autism who do not have intellectual disability is also high. Some studies suggest that it is. For example, in the meta-analyses of Amiet et al., (1) based on published reports from 1963 to 2006 on autism and epilepsy, the pooled prevalence of epilepsy was 21.5% in those with intellectual disability compared to 8% in those without intellectual disability. The male: female ratio of autism with epilepsy was approximately 2:1 in contrast to the male: female ratio of autism without epilepsy which was 3.5:1. Epilepsy was more likely to occur in girls with autism ($p < 0.001$).

Many genetically-determined conditions have been identified in which both autism and epilepsy occur at a high frequency. This subject has been reviewed by Tuchman and co-workers (10). A number of these conditions are listed in the genetics paper in this issue. Although these conditions also tend to be associated with intellectual disability, the suggestion is that the latter does not necessarily account for the high frequency of epilepsy. Tuberous sclerosis, which has been linked to defects in the hamartin and tuberin genes in chromosomes 9 and 16, respectively, is a particularly

interesting example of a genetically-determined syndrome in which the autism appears to be linked to the epilepsy. In this syndrome, a defect in cell-growth regulation results in hamartomas that can occur in multiple sites of the body, including the brain and the skin. The skin lesions constitute the characteristic facial fibroangiomas and the brain lesions can result in epilepsy. Bolton and co-workers (25) have shown that children with this condition who have a severe form of epilepsy known as West syndrome (infantile spasms) and who also have hamartomas (tubers) in the temporal lobe are especially liable to develop autism. The exact mechanism is not known but might provide further insight into the links between epilepsy and autism. It is also interesting to note that the seizures in West syndrome due to tuberous sclerosis respond remarkably well to the antiepileptic drug vigabatrin. This is an exceptional case of a genetic syndrome associated with autism leading to a specific recommendation for antiepileptic treatment.

Are different mechanisms responsible for the link between the two conditions in different people?

The evidence already presented has indicated that different mechanisms can, indeed, be responsible for the link between autism and epilepsy in different people. However, it is quite possible that, in addition to the small number of people in whom the epilepsy itself might lead to autistic features and the larger number in whom genetic defects underlie both conditions, there may be other mechanisms linking epilepsy and autism. It would be inappropriate to speculate or to draw conclusions from anecdotal reports if there were good evidence supporting mechanisms for the link in the majority of cases. However, in the absence of such evidence, it might be considered acceptable to draw on anecdote and speculation, with the aim of guiding future research.

Anecdote and speculation

The current author has seen a number of patients in whom frequent epileptiform discharges, not necessarily amounting to nonconvulsive status epilepticus or ESES, have been associated with autistic features. When these epileptiform discharges have been treated successfully, the ability of the individuals has improved markedly: however, although they have become much less markedly autistic, they have, nevertheless, retained clear-cut features of autism. This might suggest that if a child is unable to interact satisfactorily because of frequent epileptiform discharges during a critical developmental period, they might have difficulty learning such social-interaction skills at a later stage, after the critical developmental period, and might consequently remain on the autism spectrum. If this hypothesis is correct, it again emphasises the importance of early effective treatment for frequent epileptiform discharges.

There is a growing interest in the role of previously-unknown, specific mechanisms that can result in acquired brain damage. In particular, the importance of neuronal receptor antibodies as a cause of both seizures and other neurological deficits has become increasingly evident in recent years. The most frequently-reported cases are those of voltage-gated potassium-channel-complex antibodies and NMDA antibodies, although many other antibodies are implicated (26,27). If individuals with encephalitis from neuronal antibodies are treated with immunosuppressive/immunomodulatory therapy promptly and effectively, the seizures can be cured and the neurological deficits, including intellectual disability, can be minimised. Whether neuronal antibodies play any role in the causation of some cases of autism and are responsible for the link between epilepsy and autism in such subjects remains to be seen. Perhaps individuals with a genetic predisposition are particularly liable to specific damage from such antibodies; this could account for the tendency for autism to run in families.

Treatment of epilepsy in someone who has autism spectrum disorder

The key principles of epilepsy treatment are, with the rare exceptions discussed earlier, much the same regardless of whether the individual also has autism or not. The mainstay of treatment is antiepileptic medication. In general, medications that tend to improve mood and are not generally associated with behavioural deterioration should be chosen in preference. Antiepileptic drugs such as lamotrigine,

carbamazepine and valproate tend to have mood-levelling effects and, for this reason, tend to be favoured. Although pregabalin and gabapentin are said to be effective in treating anxiety, there appears to be no current evidence of anxiolytic effects in people with autism.

Because there have been some reports of improvement in behaviour when children with autism were treated with antiepileptic medication (28), it might be tempting to suggest that subtle epilepsy was being treated. However, a more plausible explanation is that the antiepileptic drugs have improved behaviour through their mood-levelling properties.

There has been concern that certain psychotropic drugs might exacerbate seizures. Most of this concern has been based on myth and not on evidence. Low-dose risperidone is often used in people with autism to decrease anxiety and consequently improve behaviour. There is no evidence that, in low doses, this drug exacerbates seizures (29). ADHD is a common comorbidity of autism (see paper on autism and ADHD in this issue). There is now good evidence to indicate that methylphenidate does not exacerbate seizures (30).

Concluding comments

The links between epilepsy and autism remain a subject of controversy. It appears that, although epilepsy might cause autism in a minority of subjects, this is not the main reason for the comorbidity. There is growing evidence for a genetic predisposition underlying both conditions but this might not be the entire explanation either. With certain notable exceptions, good management of the autism and good management of the epilepsy remain much the same, regardless of whether the conditions occur together or not. However, if the child has both conditions, the need for skilled multidisciplinary, multiagency management is all the more important.

GP comment.

What I have learned from the paper?

1. I enjoyed reading the paper which is well-written, concise and very informative.

2. There is a well-established link between autism and epilepsy and I learnt that epilepsy occurs in about 1 in 5 children with autism, whereas it is much less common if the child doesn't have intellectual disability.

3. There exists a genetic predisposition for both the conditions.

4. It is important to establish the cause of loss of skills in a child who presents with ASD features. Investigating possible subtle seizure activity by ambulatory EEG recording followed by appropriate treatment of epilepsy may help to relieve the autistic features, although this seems to occur in a minority of children.

5. When coexistent, both autism and epilepsy should be managed the same way as you would manage each condition separately but with appropriate multidisciplinary and multiagency input. However, I feel the service provision to meet the multiple needs of the child and the family is not always well-coordinated.

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