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Current controversies in the relationships between autism and epilepsy

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ABSTRACT

The controversies that have arisen in endeavoring to establish the nature of the relationships between autism and epilepsy might be summarized in a few simple questions, most of which do not yet have clear, complete answers. Does epilepsy cause autism? Does autism cause epilepsy? Are there underlying brain mechanisms that predispose to both conditions? What is the role of genetics in this regard? What is the importance of prenatal, perinatal, and postnatal environmental factors? Do any of the proposed relationships between autism and epilepsy provide insight into useful management or treatment? Is the prognosis of either autism or epilepsy different when the other condition is also present? What is the role of additional comorbidities, such as intellectual impairment or attention deficit hyperactivity disorder, in the relationship between the two conditions and in influencing treatment choices? From the evidence currently available, it would appear that epilepsy can rarely be the cause of autistic features but is not the cause of autism in most cases. There is currently no credible mechanism for suggesting that autism might cause epilepsy. There is strong evidence for an underlying predisposition for both conditions, particularly arising from genetic investigations. However, many issues remain unresolved. Considering the amount of research that has been published in this area, it is surprising that so few definitive answers have been established. The papers in this issue's special section provide additional insights into the relationships between autism and epilepsy; while they do not provide answers to all the questions, they represent considerable progress in this area and, at the very least, give some strong indication of what research might, in the future, provide such answers.

Introduction

The relationship between epilepsy and autism is the subject of ongoing debate [1]. Questions that have arisen in this debate are not only tantalizing from the scientific point of view but are also challenging from the practical point of view because the answers might have a profound effect on the management of patients. If the risk factors for an individual with autism developing epilepsy are known, steps can be taken to ensure that the epilepsy is recognized promptly and managed properly. In some cases, it might even be possible to prevent the epilepsy from developing. For example, knowing that there is a high risk of an association between certain metabolic disorders and autism could lead to early recognition and treatment of such disorders, which might, in some cases, prevent the development of epilepsy.

Articles in this special section address several of the most fundamental questions in the science and treatment of individuals with autism and epilepsy. These questions have persisted since the initial description of autism, and the answers are continuously evolving, along with the definition of autism itself. In the years following Kanner's [2] first description of autism in 1943, the diagnostic criteria were narrow, and awareness of autism was limited. The prevalence of autism in that period of time was quoted as being a few per 10,000 [3]. In recent years, the importance, in terms of practical management, of diagnosing milder autistic features has become increasingly recognized, with the result that the diagnostic criteria are now broader and prevalence of "autism spectrum disorder" (ASD) has recently been reported as being greater than 1% [4]. Using the previous narrow diagnostic criteria of severe or "Kanner" autism led to a much higher associated prevalence of comorbidity such as intellectual impairment and epilepsy. The broader diagnostic criteria of "autism spectrum disorder", which now include high-functioning autism/Asperger syndrome [5], imply that the rates of intellectual disability and epilepsy will be lower. Most papers do not take account of this changing situation, quoting the results of older studies with narrower diagnostic criteria alongside the results of more recent studies with the broader diagnostic criteria, as if the comorbidity rate would be the same. There is, consequently, considerable uncertainty about the answers to such simple questions as: "what is the rate of epilepsy in people with autism spectrum disorder?" Papers on the relationships between autism and epilepsy need to be read not only with a critical eye on the science but also with an understanding of the diagnostic criteria that were used at that time and in that particular study.

Some of the specific questions addressed by contributors to this special section follow.

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Does epilepsy cause autism?

This might be considered the most fundamental question regarding the relationship between autism and epilepsy. It is acknowledged that, in rare cases, the epilepsy itself might be responsible for autistic features. For example, in the Landau–Kleffner syndrome of acquired epileptic aphasia [6], the marked deterioration in social communication has been described as being autistic [7], but it appears to be the direct result of the epilepsy. If the epilepsy is treated promptly and effectively, the "autistic features" might improve or even resolve in at least some cases. The Landau–Kleffner syndrome and other syndromes in which the epilepsy itself seems to be directly responsible for the autistic features are rare. The debate does not stop at this point, however. The aim of several studies has been to determine whether epileptiform abnormalities, not necessarily presenting as obvious seizures, nor presenting with syndromes such as the Landau–Kleffner syndrome, might be responsible for the "autistic regression" that occurs in approximately a third of children with (narrowly defined) autism under 36 months of age [8]. The results of these studies are conflicting and inconclusive. These topics are covered in more detail in several papers in this special section.

An area of particular interest has been the association of epileptiform discharges and autism. Several studies have shown that such discharges are far more frequent in people with autism [9–11], even if they do not have a diagnosis of epilepsy, than in the general population [12,13]. The number of interictal epileptiform discharges recorded is greater if prolonged EEGs, including overnight recordings, are performed. It is interesting to note the frequent occurrence of nocturnal epileptiform discharges and autism alongside the very high rate of sleep disturbance (estimated as 40% to 80%) in this condition, as emphasized in Accardo and Malow (this issue).

If epileptiform discharges are indeed higher in individuals with autism, are such discharges associated with autistic regression? Some studies have claimed to have found such an association [14,15], and others have not [9,11,16]. However, the results need to be scrutinized carefully. For example, Baird et al. [17] carried out sleep EEGs on 64 children with autism, none of whom had a diagnosis of epilepsy. No statistically significant difference in epileptiform discharges was found between 39 of these children who had regressed and the remainder who had not regressed. However, there was a trend towards greater numbers of epileptiform discharges in those who had regressed, suggesting that if larger numbers had been examined, the result might have been statistically significant. There is another major methodological issue that could affect the outcome of such studies. If frequent epileptiform discharges cause regression, such as appears to occur, for example, in the cases of Landau–Kleffner syndrome and West syndrome, and if the EEG investigations are carried out too late, the epileptiform discharges may no longer be present and, consequently, will not be detected. This provides a strong argument for carrying out prospective studies on large populations, ensuring that comprehensive EEG investigations, including at least a sleep EEG and preferably an overnight EEG, are carried out on any child who regresses, at the time of the regression, not at some later time when the damage may have been done and the epileptiform discharges may have resolved ("burnt-out cases"). Such studies would not be easy to perform but might provide the best way of establishing the relevance of epileptiform discharges to the regression that occurs under three years of age in about a third of children with autism.

Does autism cause epilepsy?

There does not appear to be any credible mechanism for suggesting that autism causes epilepsy. Some have argued that autism could be said to cause epilepsy on the grounds that, in a large proportion of individuals, autism is associated with other comorbid brain dysfunction, notably intellectual impairment, which is also associated with epilepsy. However, this coexistence of autism and epilepsy is association, not causation.

Are there underlying brain mechanisms that predispose to both conditions?

The answer to this question, in many cases, is undoubtedly yes. Several metabolic and mitochondrial disorders underlie both conditions (Frye, this issue). Many genetic defects have also been identified as causing both conditions as further described in several papers in this special section. The paper by Frye raises important questions with regard to the importance of mitochondrial dysfunction. He points to a recent meta-analysis that established that 5% of children with ASD meet the criteria for mitochondrial disease but as many as 30% may manifest mitochondrial dysfunction. His review has also drawn attention to the finding that treatments for mitochondrial disease reportedly improve ASD symptoms. These findings have implications for how individuals with ASD might be both investigated and treated. This is another area of autism research that requires much more attention so that specific guidelines for investigation and treatment can be provided.

What is the role of genetics in determining conditions that underlie both autism and epilepsy?

The remarkable advances in genetics over the recent years have confirmed that many genetically determined disorders increase risk of both autism and epilepsy. Much attention has rightly been given to obvious examples such as tuberous sclerosis, which results from defects in the hamartin gene on chromosome 9 or the tuberin gene on chromosome 16, causing defects in cell growth regulation. The manifestations of tuberous sclerosis affect many body systems, but it is the cerebral malformations ("tubers") that are associated with both epilepsy and, particularly if they occur in temporal lobes in West syndrome, autism. Not only do these findings raise more questions with regard to the nature of autism, they also open another avenue of treatment. Drugs such as sirolimus (rapamycin) and everolimus that limit the cell growth might actually have a role to play in the prevention of both the epilepsy and the autism if administered early; however, much more research is required before clinical recommendations can be made in this regard.

Many of the metabolic conditions referred to in the previous section are the result of identified genetic disorders. In addition, several genetic disorders have been identified that cause intellectual impairment and are associated with both autism and epilepsy. These are referred to in several papers in this issue, notably in papers 2, 6, and 8.

As pointed out by Blackmon (this issue), advances in chromosomal microarray analysis (CMA) have made the detection of small chromosomal variations possible. This has changed the role of chromosomal testing fundamentally. In the past, clinicians would examine a patient, perhaps with dysmorphic features, autism, epilepsy, and intellectual impairment, and express the view that it was highly likely that a chromosomal abnormality was responsible, only to find that the investigation techniques at that time revealed no such abnormality. It could be said that the reverse is true now. Chromosomal microarray analysis often yields unsuspected abnormalities, the significance of many of which is currently difficult to interpret. Several of the genetic/chromosomal abnormalities that have been associated with both ASD and epilepsy have been listed in two of the papers in this special issue and are covered in previous reviews [18]. These include the copy number variants (CNVs) listed by Blackmon: 1q21 deletions, 7q11.23 duplications, 15q11.1-q13.3 duplications, 16p11.2 deletions, 7q11.23 duplications, 15q11.1-q13.3 duplications, 16p11.2 deletions, 18q12.1 duplications, and 22q11.2 deletions. A number of the genetic abnormalities associated with ASD and epilepsy are listed by Paciorkowski et al. (this issue). Blackmon (this issue) has reviewed the genetic/