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Management of epilepsy in children with autism

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Summary
Epilepsy is a major cause of morbidity in autism. The diagnosis and management of epilepsy in autism is complicated by a high prevalence of co-morbid neurodevelopmental disorders and co-medication. The prevalence of epilepsy is highest in those autistic children with cognitive, motor and receptive language difficulties. The underlying pathophysiology of Autism, its high rate of paroxysmal electroencephalographic abnormalities and its association with epilepsy is debated. Suggestions regarding the appropriate investigation and management of autistic children presenting with possible epilepsy are outlined.

Practice points

- The prevalence of epilepsy in autism is up to 42%
- Risk factors for epilepsy include the presence of cognitive deficits, motor disabilities and severe language disorder
- All seizure types have been recorded
- There are a number of epileptic syndromes that demonstrate an association with autism
- Behavioural deterioration may be multifactorial
- There is no evidence that an epileptiform EEG or epilepsy is causal of autistic regression <2 years
- An EEG/prolonged sleep EEG recording should be performed if a clinical diagnosis of epilepsy is suspected or if regression occurs after the age of language acquisition
- An experienced paediatrician with an interest in epilepsy or a paediatric neurologist should be consulted prior to starting anti-epileptic medication
- Appropriate management is based upon the identification of epilepsy, co-morbidities and interaction of co-medication

Future research

- Controlled trials are needed to look at the true benefit of treatment of concomitant epileptiform EEG and epilepsy in autistic children with regression

Introduction

Autism is a behaviourally defined disorder associated with qualitative impairments in social interaction, communication, speech and language skills, play and imagination

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appropriate to developmental age, and restricted repetitive and stereotyped behaviours or sequences of behaviour, interests and activities or routines that are difficult to change or modify.[1] In many cases, learning difficulties are also present, ranging from mild to severe and profound.[1] Diagnostic characteristics usually emerge before the age of 3 years.

Autism is found in 13 per 10 000 population,[2] and there is a perception that the prevalence of autism is increasing.[3] Certainly, there is heightened awareness of and concern about the prevalence of this order.[2] There is as yet, however, no proof that this is a true increase rather then an increase in awareness of the condition.

Autism is not a disease but a syndrome with multiple non-genetic and genetic causes. The main associated conditions with autism are chromosome anomalies, monogenic syndrome (including fragile X syndrome), neurocutaneous syndromes, epileptic encephalopathies, neurometabolic diseases and dystrophinopathies. Genetic inheritance has been shown to play an important role in the development of autism, rates of 6% in dizygotic twins and up to 60% in monozygotic siblings being reported.[4] Diagnosable medical conditions together currently account for fewer than 10–20% of cases of autism.[5]

Epilepsy in autism: an overview

Epilepsy is a significant cause of morbidity in the autistic population. The prevalence rate of childhood epilepsy is 0.4–1%, compared with up to 42% in autism.[6,7] The frequency of epilepsy in autism, regardless of IQ, is also higher than that of children with non-autistic severe mental retardation.[8] Epilepsy most commonly occurs in autistic children before the age of 5 years and again after 10 years of age.[9]

A number of risk factors—impaired cognition, motor disabilities and severe language disorders—are associated with the development of seizures in autism. Around 70% of autistic children will have an IQ below 70. Severe learning difficulties and autism are significantly associated with epilepsy.[6] Seizures are particularly common in those children with a combination of significant cognitive delay and motor deficits.[6] When cognitive and motor disabilities are excluded, the risk of epilepsy decreases to 6%.[6] An additional risk factor is the degree of receptive language defect.[6]

More children are being diagnosed with autism; therefore paediatricians must be aware of its close association with epilepsy. One of the questions we must address is whether or not these patients represent a growing subpopulation of children with epilepsy. If so, do they require specific medical management? To answer this, we need first to examine the relationship between autism and epilepsy.

Pathophysiology

The high proportion of epilepsy in autism indicates that autism and epilepsy share a common basis. There is no consensus on the underlying neuropathophysiology of the autistic spectrum disorders and its overlap with epilepsy,[10] but there is evidence from autopsies and from neuroimaging that they do have neuropathological features in common.

There is extensive literature describing subtle prenatal neuronal maldevelopment in the cerebellum, limbic system and neocortex.[11] Magnetic resonance imaging and positron emission tomography scans also implicate the amygdyla (emotion, behaviour), thalamus, frontal and temporal lobe, including the hippocampus.[12] The hippocampus, which is important in auditory and language processing, is commonly involved in epileptogenesis. Indeed, hippocampal sclerosis is the most widely studied pathological lesion underlying partial epilepsy. Abnormalities in neurotransmitters (serotoninergic, cholinergic, glutamatergic, gabaergic) have been described as one of the possible reasons for the increased rates of epilepsy in autism.

Many of the genetic syndromes linked with autism, for example tuberous sclerosis, Angelman syndrome and Rett syndrome, are also associated with an increased risk of epilepsy (Table 1). A strong genetic basis is usually accepted as a primary causative agent between epilepsy and autism, even if a genetic syndrome has not been identified. This is demonstrated by the frequent duplications and inversions in the 15q11–q13 chromosomal region that has been reported in both several epileptic disorders and autism.[13]

Although there is an increased incidence of autism in a number of epileptic syndromes (Table 2), there is as yet no evidence to suggest that autism is an epileptic encephalopathy[13] or indeed that the effects of seizures on the symptoms of autism are, except in rare circumstances, causal.

Types of epilepsy in the autistic child

There is a close association between autism and temporal lobe dysfunction, with electroencephalograph (EEG) abnormalities recorded most commonly over the temporal region.[14] All seizure types and EEG abnormalities have been reported (rolandic, focal with loss of awareness, atypical absences, myoclonic, generalised tonic clonic, infantile spasms), and reports of the most common type of epilepsy in these children vary with the population being studied.[6,13]

Table 1 Some genetic syndromes associated with epilepsy and autism.

Genetic disorder	Genetic mutations
Tuberous sclerosis	*TSC1* gene 9q34, *TSC2* gene 16p13.3
Prader–Willi syndrome	Chromosome 15q11.2–q13
Angelman syndrome	Chromosome 15q11–q13
Fragile X syndrome	*FMR1* gene
Rett syndrome	*CDKL5* and *MECP2* genes
Phenylketonuria	*PAH* gene at 12q22–q24.1
X-linked infantile spasm	*ARX* gene
Down's syndrome	Chromosome 21
Velo-cardio-facial syndrome	Chromosome 22q11 deletion
Williams syndrome	Chromosome 7 deletions
X-linked lissencephaly with abnormal genitalia	*ARX* gene
Neurofibromatosis type 1	Chromosome 17