EEG abnormalities, epilepsy and regression in autism: A review

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Abstract

Autism is associated with a high frequency of epileptiform EEG abnormalities (prevalence range 10.3–72.4%) and epilepsy (prevalence range 0–44.5%). A significant subgroup of autistic children (20–49%) experience autistic regression. The relationship among EEG abnormalities, epilepsy, and regression in autistic patients is not yet well understood. In this review, the current knowledge of the relationship is summarized. The evidence from clinical studies does not support the view that EEG abnormalities play a role in autistic regression. The majority of studies also failed to find any significant relationship between epilepsy and autistic regression. However, some results indicated that the higher the prevalence of epilepsy in the sample, the greater the probability of there being a significant association between epilepsy and autistic regression. Further research on the topic is needed.

Abbreviations & units:
ASD – autism spectrum disorders
EEG – electroencephalography, electroencephalographic
LKS – Landau-Kleffner syndrome
MEG – magnetoencephalography

INTRODUCTION

The incidence of epilepsy in children with autism was first noted in Kanner's landmark article (Kanner, 1943). In the group of autistic children described by Kanner, one patient had epileptic seizures and EEG abnormalities. Rutter was the first to note, in the early 70's (Rutter, 1970), that a high frequency of seizures indicated some degree of organic involvement (Volkmar, 1998). However, more than 20 years later, Gillberg wrote "It is quite surprising the way the connection between autism and epilepsy, documented from Kanner's early writings on autism, has attracted extremely limited scientific attention" (Gillberg, 1992).

Attitudes have changed dramatically during the past 15 years and the days of neglect are gone. Together with a general focus on the neurobiology of autism, many studies on autism and epilepsy and/or EEG abnormalities have emerged. Early development and early diagnostics of autism have also become major areas of research in the past decade (Stone *et al.* 1999; Robins *et al.* 2001; Oslejskova *et al.* 2007a), and this new research has directed attention toward the phenomenon of autistic regression. In our article, we will review a possible relationship between autistic regression and EEG abnormalities on the one hand, and between epilepsy and autistic regression on the other hand.

REVIEW

EEG ABNORMALITIES

The first EEG study in autism reported EEG abnormalities in 58% of the autistic children studied (White *et al*. 1964); later research focused on epileptiform EEG abnormalities.

It was demonstrated that magnetoencephalography (MEG) and sleep EEG were more sensitive for correctly detecting epileptiform EEG abnormalities in autism than wake EEGs (Lewine *et al*. 1999; Hrdlicka *et al*. 2004a). Lewine *et al*. compared MEG, 24-hour EEGs, and 1-hour EEGs in a subgroup of their sample, which consisted of children with regressive autism and Landau-Kleffner syndrome (LKS). Of these 29 children, 45% had epileptiform activity on the 1-hour EEG, 72% showed epileptiform abnormalities on the 24-hour EEG, and 90% showed epileptiform abnormalities on MEG. These numbers indicate that MEG was significantly more sensitive to epileptiform pathophysiology than either the 1-hour ($p < 0.01$) or 24-hour ($p < 0.05$) EEG. In a previous study, in which 43 of 77 autistic children had both sleep and wake EEGs available for review (Hrdlicka *et al*. 2004a), we found sleep EEGs were more likely to detect epileptiform abnormalities than wake EEGs (39.5% vs. 23.3%, $p < 0.001$).

A recent review included 13 EEG studies from the years 1966–2003 (Kagan-Kushnir *et al*. 2005); a quality evaluation of the studies revealed that none of the studies received a "good" quality rating, three were rated "fair," and the other ten were rated "poor." In examining the prevalence of epileptiform abnormalities in all patients, irrespective of clinical seizure history, wide variants in prevalence rates were obtained, ranging from 10.3% to 72.4%. When only the "fair" studies were considered, the rates ranged from 38.3% to 60.8%. Eight of the 13 studies examined the prevalence rate of epileptiform abnormalities in patients with no clinical history of seizures and it was found to range from 6.1% to 31% (Kagan-Kushnir *et al*.2005). However, epileptiform abnormalities also exist in normal children and have a prevalence range of 1.5–5% (Trevathan, 2004).

The focus of spike discharges has been reported to be mainly in the centro-temporal or temporal (Olsson *et al*.1988; Rossi *et al*. 1995; Tuchman & Rapin, 1997), frontal (Kawasaki *et al*. 1997; Hashimoto *et al*. 2001; Komarek *et al*. 2002), or rarely in the occipital (Nass *et al*. 1998) regions.

The clinical utility of electroencephalography in autism remains limited. EEG abnormalities were not found to be associated with clinical severity of autism (Hrdlicka *et al*. 2004b). Although, some authors have suggested that the EEG is an important tool in differential diagnostics between autism and Landau-Kleffner syndrome. Two of four completed studies have also supported this suggestion. Shevell *et al*. (2001) found one possible case of LKS in a sample of 50 children with autism spectrum disorders (2%). Battaglia & Carey (2006) also found one LKS case in a sample of 85 children with pervasive developmental disorder (1.1%). The other two studies were negative (Challman *et al*. 2003; Kosinovsky *et al*. 2005).

EPILEPSY

Epilepsy is the most common neurological comorbidity in autism. The prevalence of epilepsy reported in autism has varied across studies depending on the age distribution of the sample, the degree of mental retardation, and the type of language disorder (Volkmar *et al*. 2005). There are two recent reviews on the topic. In the first review, a meta-analysis included 12 studies and found the median rate of epilepsy to be 16.7%. The range of prevalence was 0–26.4% (Volkmar *et al*. 2005). In the second review, 25 studies from the years 1966–2003 were analyzed (Kagan-Kushnir *et al*. 2005). In the quality evaluation of the studies, eight of the studies were "good," eight were "fair," and nine were "poor." The prevalence of seizures in these studies varied widely from 0 to 44.5%, with the highest cluster of estimates ranging from 20%–30%. Examining only the "good" studies, prevalence estimates showed a similar range (0–39.2%). Female gender, severity of cognitive impairment, verbal auditory agnosia, motor impairment, a history of autistic regression, and a family history of epilepsy were all found to be risk factors for seizures (Kagan-Kushnir *et al*. 2005).

The onset of epilepsy in autism has two peaks: one before 5 years of age and one after 10–12 years of age, with most cases presenting after 10 years of age (Volkmar *et al*. 2005). All types of epilepsy have been associated with autism (Gillberg, 1991; Volkmar *et al*. 2005).

REGRESSION

Autistic regression could be defined as a severe developmental downturn in verbal and nonverbal communication, sociability, play, and sometimes cognition. Regression can occur in children with entirely normal development prior to regression onset, as well as in children who had previously showed mild signs of autism. The average onset of regression is consistently described across studies as between 14 and 24 months of age (Ozonoff *et al*. 2005). Incidence reaches a peak at around 18 months. Prevalence rates of regression in the autistic population vary between 20% and 49%. (Bernabei *et al*. 2007). The etiology of regression still remains unknown. A line of research has hypothesized a relationship between regression and vaccinations (e.g., Wakefield *et al*. 1998; Wakefield, 1999; Geier & Geier, 2006), however, this idea has been rejected by academic psychiatry because of a lack of evidence (e.g., Rutter, 2005; Volkmar *et al*. 2005).

The phenomenon of autistic regression has been known since the early history of autism. However, only

Table 1: Relationship of EEG abnormalities and autistic regression

Study	Dg	N	Age±SD or range (years)	Regres. rate (%)	Epi EEG abn. (%)	Epilepsy excluded	Relationship found
Kurita et al. (1992)	A	196	7.4±3.6	26	28	NO	NO
Rossi et al. (1995)	ASD	106	12.4	25; 36; 41	19; 24	NO	NO
Tuchman, Rapin (1997)	ASD	585	5.8	34	21	YES	YES
Hrdlicka et al. (2004a)	ASD	77	9.1±5.3	26	38	NO	NO
Canitano et al. (2005)	A	46	7.8±2.7	52	22; 35	NO	NO
Baird et al. (2006)	A	64	2-4	61	31	YES	NO
Oslejskova et al. (2007b)	ASD	205	10	35	48	NO	YES
Giannotti et al. (2008)	A	104	2.3-7.1	33	41	NO	NO

Dg – diagnosis; N – number of patients; SD – standard deviation; Regres. – regression; Epi EEG abn. – epileptiform EEG abnormalities; A – autism; ASD – autism spectrum disorders.

Table 2: Relationship of epilepsy and autistic regression

Study	Dg	N	Age±SD or range (years)	Regres. rate (%)	Epilepsy (%)	Relationship found
Tuchman et al. (1991)	A	302	5.2	33	14	NO
Rossi et al. (1995)	ASD	106	12.4	25; 36; 41	24	NO
Tuchman, Rapin (1997)	ASD	585	5.8	21	11	NO
Kobayashi, Murata (1998)	A	179	21.9±3.2	30	20	YES
Fombonne et al. (2004)	A	180	7.6	24	16	NO
Hrdlicka et al. (2004)	ASD	77	9.1±5.3	26	22	YES
Canitano et al. (2005)	A	46	7.8±2.7	52	13	NO
Oslejskova et al. (2007b)	ASD	205	10	35	31	YES
Ming et al. (2008)	ASD	160	6	28	14	NO
Hansen et al. (2008)	ASD	333	3.7	41	12	NO
Baird et al. (2008)	ASD	255	9-14	22	18	NO
Giannotti et al. (2008)	A	104	2.3-7.1	33	19	YES

Dg – diagnosis; N – number of patients; SD – standard deviation; Regres. – regression; A – autism; ASD – autism spectrum disorders

after the availability of videotapes, which documented infant behaviors, was it possible to clearly observe that some children with autism spectrum disorders (ASD) did truly lose skills (Lord *et al*. 2004). Werner & Dawson (2005) compared three groups of children: (i) autistic children with reported history of regression, (ii) autistic children without reported history of regression, and (iii) typically developing children. They used home videotapes of the first and second birthday parties of 56 children. Analyses revealed that infants with ASD with regression were similar to typical infants at 12 months of age, but, in contrast, much more similar to infants without regression at 24 months of age. This was seen as validation of the existence of early autistic regression. Another study reported 56 children with ASD (with or without autistic regression) and 14 typically developing children, all of whom had been documented on home videotapes. Results indicated a substantial concordance between parental reports and observer codes for onset and loss of expressive language, but minimal concordance for loss in non-language domains (Goldberg *et al*. 2008).

EEG ABNORMALITIES AND AUTISTIC REGRESSION

Our analysis included only studies that involved autistic children with and without regression, i.e. clinically non-selected samples. We excluded studies involving only children with regression (e.g., Lewine *et al*. 1999), or only children with EEG abnormalities (e.g., Nass *et al*. 1998). A summary of our findings are presented in Table 1.

A majority of the studies (6 of 8 studies) did not find any significant relationship between EEG abnormalities and autistic regression. Only two studies were positive (Tuchman & Rapin, 1997; Oslejskova *et al*. 2007b). Of

all the studies, Tuchman & Rapin (1997) had the largest sample (585 children) but only part of the sample had EEGs available (i.e. sleep EEGs; only sleep EEGs were performed in this study). Among 392 children having sleep EEGs available, the EEG was epileptiform in 68% of the 57 epileptic children and in 15% of the 335 non-epileptic children. To assess the relationship between regression and an epileptiform EEG, the authors removed patients with epilepsy from the analysis. Among 335 children without epilepsy, the proportion of children with epileptiform sleep EEG data and autistic regression was almost twice as high: 19% with regression compared with 10% without regression (p = 0.02). However, readers of the Tuchman & Rapin (1997) study should note that the overall rate of epilepsy in the autistic sample was quite low (11%), as was the rate of epileptiform EEG abnormalities in non-epileptic autistic patients (15%). In comparison, other studies listed in our summary gave higher rates of epileptiform abnormalities in non-epileptic autistic children, 19% (Rossi *et al*. 1995) and 22% (Canitano *et al*. 2005). The overall rate of epileptiform EEG abnormalities in the whole sample (21%) was also very low, where other comparable studies were in the range of 28–48% (Kurita *et al*. 1992; Hrdlicka *et al*. 2004; Baird *et al*. 2006, Oslejskova *et al*. 2007b; Giannotti *et al*. 2008).

Oslejskova *et al*. (2007b) performed a retrospective study involving 205 autistic children and found a positive association between epileptiform EEG abnormalities and autistic regression (p = 0.040). Unlike Tuchman & Rapin (1997), they did not exclude patients with epilepsy from the analysis. Furthermore, the rate of epileptiform abnormalities in their study was very high (48%) in contrast to Tuchman & Rapin (1997) although they did not exclusively use sleep EEG recording as did Tuchman & Rapin.

A study by Giannotti *et al*. (2008) can be viewed in two ways. The first one is negative, and it is included in Table 1. If all epileptiform EEG abnormalities were taken into account, the association with autistic regression is non-significant. On the other hand, if only frequent EEG epileptiform activity (i.e. at least 2 spikes per minute or 5–10 seconds/burst of spikes) was taken into account then the association was significant (p < 0.05).

EPILEPSY AND AUTISTIC REGRESSION

We included only studies in the analysis that involved autistic children with and without regression, i.e. clinically non-selected samples. We excluded studies involving only children with regression (e.g., Shinnar *et al*., 2001). A summary of our findings are presented in Table 2.

A majority of studies (8 of 12 studies) did not find any significant relationship between epilepsy and autistic regression. However, four studies were positive (Kobayashi & Murata, 1998, Hrdlicka *et al*. 2004a, Oslejskova *et al*.2007b, and Giannotti *et al*. 2008). All four studies had a relatively high prevalence of epilepsy, with a position in the upper half of the list of twelve studies. The prevalence range of epilepsy in the positive studies ranged from 19% (Giannotti *et al*. 2008) to 31% (Oslejskova *et al*. 2007b), whereas the median of epilepsy prevalence from all 12 studies in this review was 17%. This result is almost identical to the median value of 16.7% reported by Volkmar *et al*. (2005); it's also worth noting that while the median values are similar the results were achieved with a completely different set of studies.

Based on this analysis, it seems likely that the higher the prevalence of epilepsy in a sample, the greater the probability of a significant association between epilepsy and autistic regression in the sample.

There is another factor that could play a contributing role. Amiet *et al*. (2008) published a meta-analysis of published reports (1963-2006) on autism and epilepsy. Ten of 23 identified studies provided sufficient data on epilepsy and mental retardation in autistic patients and were included into the meta-analysis. The authors found significantly more autistic patients with mental retardation having epilepsy (p < 0.001). Unfortunately, only a small number of the studies listed in our review provided clear data on mental retardation in the sample. We can only hypothesize that higher rates of mental retardation associated with higher rates of epilepsy could have contributed to the positive results seen in some studies.

CONCLUSIONS

Evidence from clinical studies does not support the view that EEG abnormalities play a role in autistic regression. The majority of studies failed to show any significant relationship between epilepsy and autistic regression. However, some results indicate that the higher the prevalence of epilepsy in a sample, the greater the probability of seeing a significant association between epilepsy and autistic regression. Further research on the topic is needed.

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