Epilepsy in Autism is Associated with Intellectual Disability and Gender: Evidence from a Meta-Analysis

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Background: The association between epilepsy and autism is consistently reported, with a wide range of prevalence rates. This may be attributed to the heterogeneity of the samples with respect to age, comorbidity, sex, and intellectual disability (ID). We aimed to compare the prevalence of epilepsy 1) among autistic patients with ID versus autistic patients without ID and 2) among male versus female autistic patients.

Methods: We reviewed all data available from published reports (1963–2006) on autism and epilepsy and conducted a meta-analysis of 10 and 14 studies, respectively, to assess the relative risk (RR) of epilepsy in autism according to ID and gender. The pooled groups included 2112 (627 with IQ $\geq$ 70, 1485 with IQ $<$ 70) and 1530 (1191 male, 339 female) patients, respectively.

Results: There was a strong discrepancy in relative risk (RR) according to IQ, with more autistic patients with ID having epilepsy (RR = .555; 95% confidence interval [CI]: .42–.73; $p < .001$). The pooled prevalence of epilepsy was 21.5% in autistic subjects with ID versus 8% in autistic subjects without ID. There was a strong discrepancy in RR according to sex, favoring comorbidity of epilepsy in autistic girls (RR = .549; 95% CI: .45–.66; $p < .001$). The male:female ratio of autism comorbid with epilepsy was close to 2:1 whereas the male:female ratio of autism without epilepsy was 3.5:1.

Conclusions: The results of this meta-analysis indicate that risk for epilepsy in autism is a function of ID severity and distinguishes autism associated with epilepsy as a subgroup of autism by its male-female ratio.

Autism, defined in DSM-IV as a pervasive developmental disorder involving profound deficits in social relatedness, communication impairments, repetitive behaviors, and restricted interests with onset prior to 3 years old, is a behavioral syndrome. An association between autism and epilepsy has been consistently reported (1,2) and is included in DSM-IV (3), although it is not among the diagnostic criteria. Although the prevalence of epilepsy in autism clearly exceeds that of the general population (about .5%–1%) (4), reported prevalence rates of seizures in this condition range from 5% to 40% (2), and several studies have not reported such an association (5). This variability has been attributed to the heterogeneity of samples with respect to age, sex, comorbidity, subtype of pervasive developmental disorder (PDD), intellectual disability (ID), or causes (6,7). It may also result from the criteria used to diagnose epilepsy. Early childhood and adolescence have been reported to be the peak periods for seizure onset in studies of adolescents and adults presenting the highest rates of prevalence (1). The risk

of epilepsy also varies according to subtype within the autistic spectrum: autism, Asperger syndrome, Rett syndrome, childhood disintegrative disorder (CDD), and PDD not otherwise specified. The lowest prevalence rate (4%) occurs in Asperger syndrome (8) and the highest (77%) occurs in CDD (9). Moreover, individuals with "complex" autism (as opposed to essential autism), that is, with additional neurologic impairments, such as cerebral palsy, microcephaly, or identified neurodevelopmental disorders with dysmorphic signs, are at a higher risk for seizures (2,6).

In the general population, one of the major risk factors for seizures is intellectual disability (10). An overall cognitive deficit is not a defining feature of autism. However, like epilepsy, intellectual disability is still considered to be intrinsically associated with autism, although there is a trend toward reporting less than 50% of ID in autistic subjects in recent studies (11). Early studies showed that the likelihood of epilepsy was negatively correlated with IQ (12,13). More recently, some studies have found a greater rate of seizures in individuals with intellectual disability (9,14,15).

To clarify the relationship between epilepsy and autism, the aim of this study was to use a meta-analytic method to assess whether the association of epilepsy with autism is mediated by intellectual disability. Given that 1) autism is less prevalent in females, with a reported male:female ratio of 4:1 (16), 2) autistic females are generally more severely mentally disabled than autistic males (17), and 3) epilepsy might be more prevalent in autistic females (17–20), we used a similar method to assess whether the association of epilepsy with autism is mediated by gender.

Methods and Materials

Identification and Selection of Relevant Reports

We performed a computerized search of the Medline database (PubMed version) for appropriate articles published from January 1963 through November 2006. The key words used were *epilepsy/seizures* and *autism/pervasive developmental disorder*. The reference lists of all identified reports, studies, and reviews

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in the field were screened. All potentially pertinent articles for inclusion were reviewed by the titles and abstracts.

To be included in the analyses, studies had to fulfill the following criteria: 1) they had to involve subjects with a diagnosis of autism and/or PDD, 2) they had to be published in an English-language scientific journal, and 3) they had to report epilepsy as a function of IQ or according to gender. When detailed data were not available, we asked the authors of the articles to provide us with their data so we could include their samples in the meta-analysis.

Reviews, comments, and case report articles were excluded. Also, because some disorders related to autism are comorbid with epilepsy, we excluded articles in which the entire study population presented with a comorbid Axis III disorder (e.g., tuberous sclerosis, fragile X, Down syndrome, Rett syndrome). The Medline search yielded 513 articles. We excluded 112 reviews, 71 case reports, 91 studies focused on Axis III comorbidity and 190 articles that were not relevant. After an individual review of the remaining titles and abstracts, we found 49 articles indicating the prevalence of epilepsy among patients with autistic disorder. In the remaining sample, a comorbid Axis III disorder was identified in some patients in the following studies (Table 1): Olsson *et al*. (5), Ritvo *et al*. (21), Tuchman *et al*. (18), Wong (22), Elia *et al*. (19), Nordin and Gillberg (23), Kielinen *et al*. (24), Cederlund and Gillberg (8), Danielsson *et al*. (20).

Study Criteria and Hypothesis

The primary aim of the meta-analysis was to compare the prevalence of epilepsy among autistic patients with and without intellectual disability. We hypothesized that the more severe intellectual disability, the more prevalent epilepsy should be.

Epilepsy is defined by the International League Against Epilepsy (ILAE) (25) as a chronic neurologic condition characterized by recurrent spontaneous epileptic seizures. This definition has not always been used in reported studies. Consequently, it was not possible to use a single common criterion for the definition of epilepsy across selected studies for the meta-analysis. Therefore we used the definition given in each report (Table 1). The common definition of intellectual disability is based on IQ levels. Intellectual disability was defined by an IQ $\leq$ 70. However, several instruments are available to assess IQ in youths, although the severity of language impairments may interfere with IQ testing, and some instruments, which represent the vast majority of those used in the studies examined here, underestimate autistic intelligence (11). Table 1 reports the instrument used to assess IQ in each study. The secondary aim of the meta-analysis was to compare the male-female ratio among autistic patients with comorbid epilepsy to the male:female ratio among autistic patients without epilepsy. We hypothesized that epilepsy was more prevalent in female than male autistic subjects.

Statistical Analysis

The statistical analyses were performed using EasyMA software (26). We used relative risk (RR) as a parameter of incidence with a fixed effect model. The pooled estimate of the overall RR was calculated using the inverse variance–weighted RR for each study. A chi-square association and chi-square heterogeneity tests were performed, and *p* value for significance was set at .05. The RRs with the corresponding 95% confidence interval (CI) were presented in the analysis.

Regarding intellectual disability, several analyses were performed. An initial analysis was performed in which all studies

were included and comparisons made between epilepsy in autistic subjects with ID (IQ $\leq$ 70) and without ID (IQ $>$ 70). We then repeated the analysis, grouping studies according to the year of publication (before or after 1994) to assess whether changes in the definition of autism and PDD had influenced the data. Finally, we conducted another analysis on a subset of studies that described the prevalence of epilepsy among autistic patients in accordance with the level of ID (IQ $\leq$ 50 vs. 50 $<$ IQ $\leq$ 70; then IQ $\leq$ 50 vs. IQ $>$ 70). If there were no subjects with IQ $>$ 70 or with IQ $<$ 70 in a study, the study could not be included in the statistical analysis because no single RR could be calculated because of a cell with a zero value.

Results

Selected Characteristics of Trials

Among the 49 articles selected from the Medline database search and taking into account the authors' responses (*n* = 3) for studies that did not provide sufficient detail in the publication, we retained 23 studies in total (the remaining 26 studies are listed in Supplement 1). Eighteen met our criteria for inclusion in the intellectual disability analysis, and 14 met our criteria for the gender analysis. Summary information on the studies is given in Table 1. Only 10 studies were included in the statistical analysis regarding epilepsy according to ID because 8 studies included only patients in one subgroup (most of them being studies with only subjects with ID), leading to cells with 0 patients (Table 1).

Seven studies reported sufficiently detailed data to be included in the analysis regarding levels of ID. All the available studies were included in the analysis regarding epilepsy according to gender.

The dates of publication of the studies ranged from 1976 to 2005. Because of modifications to the diagnostic criteria for autism over the years, the population studied may be heterogeneous. To assess confounding bias regarding autism criteria, we also performed our analysis separately for the studies published before and after the publication of the DSM-IV (1994) (discussed later). Also, many studies included subjects with autistic disorder, whereas others used autistic spectrum disorder as an inclusion criterion. Similarly, the definition of epilepsy was heterogeneous across studies, with eight studies using the international classification of the ILAE and five using a less stringent definition (more than one seizure) or questionable definition (antiepileptic intake, "epileptiform" anomalies on electroencephalogram [EEG]). The others did not specify how the diagnosis of epilepsy was determined (Table 1). Finally, all studies except one defined ID as an IQ below 70. The Tuchman *et al*. study (18) defined ID as an IQ $<$ 80. In this analysis, for the sake of simplicity, we acted as if the cut-off were 70. One study considered mild intellectual disability as 55 $<$ IQ $\leq$ 70 and, for the sake of simplicity, we acted as if the cut-off were 50 instead of 55 (27).

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There was significant heterogeneity (*p* = .001) between studies, because one of them reported more epilepsy in autistic patients without ID (5). More epilepsy was found in autistic patients with ID than in those without ID in two studies (13,24). However, combining the 10 studies (*n* = 2112), there was a strong and significant reduction in RR, with more epilepsy in

Table 1. Main Characteristics of the 23 Studies Included in the Meta-Analysis

Study	M:F Ratio	Age (Years) M (SD) or Range	PDD Diagnosis	Axis III	IQ < 70	≥ 70	Instruments Used to Measure IQ	Definition of Epilepsy
Bartak and Rutter, 1976 (12)	ns	≤17	Autism	ns	47	17	Merrill-Palmer; WISC	ns
Tsai *et al.*, 1981 (28)	78/24	6.58	Autism	ns	ns	ns	ns	ns
Jacobson and Janicki, 1983 (13)	ns	0–adult	Autism	ns	706	384	ns	ns
Olsson *et al.*, 1988 (5)	39/13	4–11	Infantile autism (DSM-III), autistic-like conditions	ns	46	6	ns	> 1 seizure
Volkmar and Nelson, 1990 (42)	150/42	14.1 (7.18)	Infantile autism (DSM-III)	ns	159	27	ns	ns
Ritvo *et al.*, 1990 (21)	184/49	3–27	Autism (DSM-III)	37	ns	ns	ns	ns
Tuchman *et al.*, 1991 (18)	228/74	6.33	Autistic spectrum disorder (DSM-III-R)	ns	222[a]	68[a]	ns	ILAE
Wong, 1993 (22)	128/17	8.17	Infantile autism (DSM-III)	1	ns	ns	ns	ILAE
Giovanardi Rossi *et al.*, 1995 (14)	90/16	12.41	Autistic disturbance (DSM-III-R)	0	106	0	WPPSI, WISC, WAIS	ILAE
Elia *et al.*, 1995 (19)	34/29	14.95 (5.13)	Infantile autism (DSM-III-R)	19	63	0	WPPSI, WISC, WAIS	ILAE
Nordin and Gillberg, 1996 (23)	18/9	9.78	Autistic disorder, autistic-like conditions, autism spectrum disorder-NOS (DSM-III-R)	4	24	3	ns	Seizures and/or antiepileptic treatment
Kurita, 1997 (43)	13/3	3–12	Asperger syndrome, high-functioning atypical autism (ICD-10)	ns	0	42	Stanford-Binet, WISC-R	ns
Mouridsen *et al.*, 1999 (9)	27/12	28.6 (7.9)	Infantile autism (ICD-8, 10)	ns	28	11	Leiter International Performance Scale, WAIS, Vineland	≥ 1 convulsion or antiepileptic treatment after convulsion
Giovanardi Rossi *et al.*, 2000 (44)	53/7	17.16	Autistic disorder (DSM-III-R, IV)	0	60	0	Stanford-Binet, WPPSI, WISC-R, WAIS	ILAE
Parmeggiani *et al.*, 2002 (45)	20/1	17.08	Autistic disorder (DSM-IV)	0	21	0	Stanford-Binet IIIR, WPPSI, WISC-R, WAIS	ns
Kielinen *et al.*, 2004 (24)	ns	8.9	Autistic disorder (DSM-IV)	ns	96	91	WPPSI, WISC-R, WAIS	ILAE
Cederlund and Gillberg, 2004 (8)	100/0	11.25 (3.10)	Asperger syndrome (ICD-10, DSM-IV)	ns	0	100	WISC-R, WISC III, WAIS	ns
Hrdlicka *et al.*, 2004 (15)	61/16	9.1 (5.3)	PDD (ICD-10, DSM-IV)	0	55	14	Gesell Developmental Scale, Stanford-Binet IV	ns
Pavone *et al.*, 2004 (27)	57/15	9.04	Autism (DSM-III, -IV, CARS)	0	54	0	ns	ns
Hughes and Melyn, 2005 (46)	69/9	.5–21	Autistic disorder (DSM-IV)	ns	ns	ns	ns	Seizures
Danielsson *et al.*, 2005 (20)	77/31	25.5	Autistic disorder (DSM-IV), autistic-like conditions	23	102	6	WAIS-R, Vineland Adaptive Behavior Scale	ILAE
Canitano *et al.*, 2005 (47)	34/12	7.8 (2.7)	Autistic disorder (DSM-IV)	0	46	0	WISC-R, Raven Progressive Matrices, Leiter test	ILAE
Gabis *et al.*, 2005 (48)	43/13	1–14	PDD (DSM-IV)	ns	ns	ns	ns	> 1 unprovoked seizure and/or epileptiform EEG

CARS, Childhood Autism Rating Scale; EEG, electroencephalogram; ILAE, International League Against Epilepsy; M:F, Male/Female; NOS, not otherwise specified; ns, not specified; PDD, pervasive developmental disorder; WAIS-R, Wechsler Adult Intelligence Scale—Revised ; WISC, Weschler Intelligence Scale for Children; WISC-R, WISC—Revised; WPPSI, Wechsler Preschool and Primary Scale of Intelligence.

[a]IQ score distribution is different: IQ < 80, IQ ≥ 80.

autistic patients with ID (Figure 1: pooled RR = .555; 95% CI: .42–.73; $p <$ .001). The pooled prevalence of epilepsy was 21.4% in autistic subjects with ID ($n = 1485$) versus 8% in autistic subjects without ID ($n = 627$).

To confirm that the date of publication was not a confounding bias, the same analysis was conducted separately for the studies published before and after 1994, resulting in similar results

(pooled RR = .578; 95% CI: .42–.80; $p <$ .001; and .493; 95% CI: .29–.84; $p <$ .001, respectively).

Figure 2 reports the frequency of comorbid epilepsy in subjects with autism as a function of IQ. The more severe the ID, the more prevalent is epilepsy. However, this increased RR is only significant when comparing autistic subjects with an IQ ≥ 70 versus autistic subjects with an IQ < 50 (RR = .537; 95% CI:
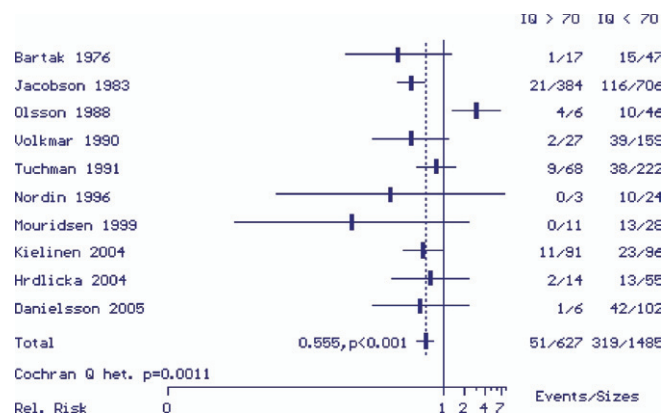
Figure 1. Relative (Rel.) risk of epilepsy in persons with autism according to intellectual disability: individual series and combined analysis. Q het., Q heterogeneity.

Figure 3. Relative (Rel.) risk of epilepsy in persons with autism according to sex: individual series and combined analysis. Q het., Q heterogeneity.

Discussion

Epilepsy in Autism Is Associated with Intellectual Disability and Sex

.37–.77; $p < .001$). No significant difference was reported when comparing autistic subjects with an IQ ≥ 70 versus autistic subjects with an $50 < IQ < 70$ (RR = 1.298; 95% CI: .80–2.10; $p = .29$). The pooled population included in this secondary analysis was smaller because of the limited reporting of epilepsy as a function of IQ (215 subjects with IQ ≥ 70, 306 subjects with $50 < IQ < 70$ and 398 subjects with IQ < 50).

Epilepsy in Autism Is Associated with Sex

There was no significant heterogeneity ($p = .55$) between studies in this case. More epilepsy was found in female than male autistic patients in four studies (5,18,20,28). However, combining the 14 studies ($n = 1530$), there was a strong and significant reduction in RR favoring comorbidity of epilepsy in autistic girls (Figure 3: pooled RR = .549; 95% CI: .45–.66; $p < .001$). The pooled prevalence of epilepsy was of 34.5% in female versus 18.5% in males. Thus the male:female ratio of autism comorbid with epilepsy was close to 2:1, whereas the male:female ratio of autism without epilepsy was close to 3.5:1.
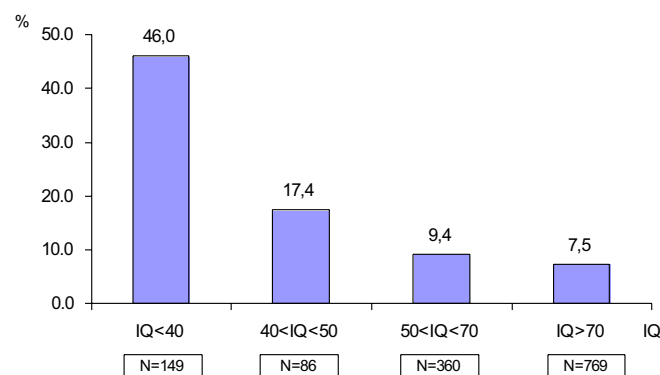

Figure 2. Frequencies of comorbid epilepsy in subjects with autism as a function of IQ. Data from Bartak and Rutter (12), Jacobson *et al.* (13), Olsson *et al.* (5), Volkmar *et al.* (42), Tuchman *et al.* (18), Giovanardi Rossi *et al.* (14), Elia *et al.* (19), Nordin and Gillberg (23), Kurita *et al.* (43), Mouridsen *et al.* (9), Giovanardi Rossi *et al.* (42), Parmeggiani *et al.* (45), Kielinen *et al.* (24), Pavone *et al.* (27), Hrdlicka *et al.* (15), Cederlund and Gillberg (8), and Danielson *et al.* (20).
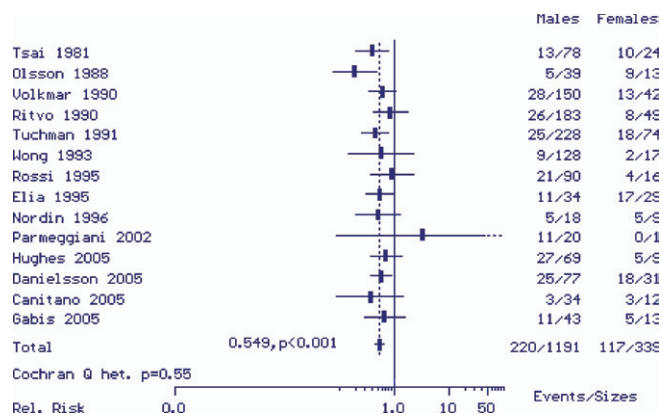
The results of this systematic review of studies published between 1963 and November 2006 point to a difference in the risk for epilepsy in autism related to intellectual disability and to sex. Moreover, our study reports that 1) the more severe the ID, the more prevalent epilepsy is and 2) the greater part of the statistical association between epilepsy and ID in autism relates to moderate and severe ID. The risk of epilepsy was found to be significantly higher for autistic subjects with intellectual disability and only one study had an opposite result (5), probably because of the patients' age. Indeed, in that study, only one of the patients had reached puberty, whereas the other studies reported results in older patients.

Our meta-analysis provided a pooled prevalence rate of epilepsy in autistic patients with ID of 21.4%. However, it is known that epilepsy occurs more frequently in people with an ID than in the general population. The prevalence rate of epilepsy in persons with ID reported in the literature varies from 16.1% to more than 50% and increases with the severity of the ID (10). In contrast, the pooled prevalence rate of epilepsy in autistic subjects without ID was about 8% in the current meta-analysis. On one hand, this prevalence is clearly inferior to that found in ID without autism. This may be explained by an overestimation of ID by instruments used to measure autistic intelligence. On the other hand, this prevalence is higher than the prevalence rate of epilepsy in the general population. The latter discrepancy suggests that epilepsy in autism cannot be considered as only being mediated by ID. However, it should be emphasized that most of the studies examined here did not separate essential autism from complex autism. In this regard, Mottron (unpublished data, 29). found a prevalence of epilepsy of 5.4% in a population of 220 subjects with PDD who had an IQ above 50 (autistic disorder: 92; autistic spectrum: 75; pervasive developmental disorder—not otherwise specified: 58). When restricted to participants with an IQ > 70, the prevalence was 5.31%, and it dropped to 3.33% (5/149) in individuals with IQ $\geq$ 85. Importantly, the prevalence for the entire PDD group was only 1.3% when complex autism was excluded.

Regarding our second hypothesis, the risk for epilepsy was found to be significantly higher for females. In this meta-analysis, the male:female ratio for autistic subjects with epilepsy was estimated at about 2:1, whereas it was about 3.5:1 for autistic

subjects without epilepsy. This could reflect the known circumstance that females with autism tend to be more severely mentally disabled: the more severe the ID, the lower the male:female ratio (17). Unfortunately, not enough information was reported in the studies used in the meta-analysis to determine the risk for epilepsy as a function of gender with a regressive model on IQ.

The Diversity of Epileptic Syndromes May Contribute to This Association in Different Ways

Various seizure types and epileptic syndromes have been described in association with autism. Moreover, epileptic anomalies are frequently observed on the EEGs of autistic patients despite an absence of seizures, suggesting at least a low epileptic threshold. The relationship between autism and epilepsy is complex, and their association may have different origins. Casanova (30) suggested that altered internal organization of minicolumns in the cortex of autistic individuals may be associated with a defect in inhibitory local circuit projection. A defect in these γ-aminobutyric acid (GABA)ergic fibers may correlate with the increased prevalence of seizures in autism. It may also be true that autism and epilepsy share a genetic or neurodevelopmental cause, at least in the case of secondary autism (e.g., tuberous sclerosis). Epilepsy by itself may induce the development of autistic symptoms (31). Two examples can illustrate this point: 1) When the epileptic focus is located in a critical brain area, mainly temporofrontal locations, autistic regression may occur with substantial improvement after medication or even surgical treatment (32,33). 2) Several epileptic encephalopathies are associated with intellectual disability, autistic traits, or both, probably through a specific developmental impact. This is especially true of West syndrome (34–36). Finally, an accidental association between autism and epilepsy cannot be ruled out in some cases, considering the high frequency of epilepsy in the general population. Taken together, these results raise questions about the commonly reported hypothesis that the association between epilepsy and autism reflects common pathophysiologic mechanisms (1).

Regarding this meta-analysis, one should consider that the pooled results of the studies included are extremely disparate concerning information about epilepsy. Indeed, some of them classify epilepsy on a syndromal basis, whereas others describe only seizure types. In other studies, the criteria used for the diagnosis of epilepsy or the terms used to describe seizure types are not accepted by the ILAE. Sometimes seizures are not described. Moreover, data concerning EEG are also variable from one study to another with respect to the description of EEG anomalies and the conditions of EEG recordings (most often on awakening, during sleep deprivation, or, rarely, during sleep). Despite a general positive impact on cognitive development after efficient treatment of severe epilepsy, we cannot exclude that for some individuals, the same medication may have a negative impact on IQ. Finally, neuroimaging data are not always available. All these restrictions make it difficult to conduct an extensive and in-depth analysis of the data collected here from a neurologic point of view.

However, the global results of these meta-analyses remain, in our opinion, of great interest. Indeed, it proves that there are two clear risk factors for epilepsy in autism—intellectual disability and female sex—and leads us to examine the relations between autism and epilepsy on an individual basis, specific to each situation encountered. Still more important, as we now discuss, it questions the link between epilepsy and primary autism.

Clinical Implications Concerning the Identification of Subgroups of Autism

The concept of "syndromal autism" or "complex autism" is used to qualify individuals for whom autism is associated with significant dysmorphology, microcephaly, or an identified neurodevelopmental syndrome, whereas the terms "pure," "primary," or "essential" autism should be limited to autistic individuals without these associations, whatever their level of mental functioning (37). Recently, Judith Miles's group reported the prognostic value of the distinction between complex autism and essential autism in a consecutive sample of 260 individuals. Complex autism was significantly associated with a higher female-to-male ratio, lower IQ, more seizures and abnormal EEGs, more brain abnormalities on magnetic resonance imaging, and less sib recurrence and relatives with autism (6). The latter result is noteworthy because it points toward a distinction between essential autism (with a familial aggregation) and complex autism (in which the associated neurologic or genetic syndrome is not associated with familial aggregation to the same extent). Considering Miles's report and the results of our meta-analysis, epilepsy should be included in the subgroup of syndromal or complex autism, warranting a multidisciplinary approach for management and etiologic search. Along the same lines, the Davies *et al.* (38) epidemiologic survey of mental health problems in children with epilepsy showed that only complicated epilepsy was associated with PDD (prevalence = 16%). Complicated epilepsy was defined as epilepsy comorbid with one or more of the following: severe learning difficulties; cerebral palsy; any stiffness or deformity of the foot, leg, fingers, arms or back; any muscle disease or weakness; a condition present since birth such as clubfoot or cleft palate; any difficulty with coordination; or speech or language problems (38).

The identification of epileptic autistic individuals as a subgroup within autistic spectrum may help to identify new candidate genes associated with autism. Major advances have recently been made in our understanding of the genetic bases of epilepsies, particularly regarding genes that encode subunits of ion channels or neurotransmitter receptors involved in monogenic idiopathic epilepsies (39). Genes coding for subunits of voltage-gated sodium channels or of $GABA_A$ receptors are also implicated in some epileptic encephalopathies with intellectual disability and behavioral problems (such as Dravet syndrome) (39), which may represent phenocopies of autism (40), given that the phenotype-genotype relationship is often weak.

Recently, Beaudet (41) pointed out that children with identifiable genetic abnormalities are often in the syndromal autism group and are more likely to be female. He suggested that mixed epigenetic and genetic and mixed de novo models may be relevant to autism, estimating that only half of the de novo mutations have been detected so far. The fact that comorbid epilepsy or lack thereof distinguishes two autism subgroups by their sex ratio suggests that seizures (and their possible causes) may be one of the factors, along with severe ID, dysmorphic signs, microcephaly, and others, that may contribute to better subtyping of the autistic phenotype.

Conclusion

These meta-analyses permitted us to identify two clear risk factors for epilepsy in autism: intellectual disability and female gender. Considering that epilepsy in autism is a function of ID severity and presents a specific male:female ratio, we propose inclusion of comorbid epilepsy in the subgroup of syndromal or

complex autism, rather than, as currently reported in DSM-IV, as a phenotypic trait of essential autism. This could help clinicians to manage autistic individuals with epilepsy more effectively and lead to a better understanding of a genetic predisposition to autism.

Supplementary material cited in this article is available online.

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