THE SAHLGRENSKA ACADEMY

The importance of Epilepsy in Autism Spectrum Disorder

Degree Project in Medicine

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Programme in Medicine

Gothenburg, Sweden 2017

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ABSTRACT

Background: Studies report high prevalence of epilepsy in autism spectrum disorder (ASD) and vice versa. However, few studies have examined if the association alters the phenotypical expression.

Objectives: (1) To describe the impact of epilepsy on ASD symptomatology and (2) to investigate whether symptomatic expression of ASD in individuals with epilepsy differs from individuals with ASD but without epilepsy.

Methods: The data came from The Child and Adolescent Twin Study (CATSS) a longitudinal Swedish study in which parents of twins are interviewed about the somatic and mental health of their children. The present study included 26,863 twins that were classified into different groups depending on the presence and level of ASD symptomatology, and the presence of epilepsy. Two-way ANOVAs with Bonferroni correction was used to compare mean values and variation within the groups and then a ranking of the symptoms was conducted.

Results: More subjects (7.4%) with epilepsy screened positive for ASD (p-value<0.001) compared to 0.9% in the general population, and 6.1% of all subjects with ASD had epilepsy (p-value<0.001) compared to 0.8% of the general population. The presence of epilepsy was associated with significantly elevated difficulties within the language domain in individuals with ASD (p-value = 0.004). Stereotyped and repetitive behavior and social interaction difficulties in individuals with ASD were largely unaffected by the presence of epilepsy. Individuals who had Epilepsy with or without ASD more frequently had problems with language and social interaction symptoms while individuals with ASD without epilepsy more frequently endorsed symptoms of stereotyped and repetitive behavior.

Discussion and conclusion: This study confirms that Epilepsy and ASD often coexist. The association tends to increase language difficulties. Moreover, symptoms of ASD seem to display a somewhat different profile conditioned on the presence of epilepsy. This may have meaningful implications in diagnostic, treatment and follow up settings for children with ASD with or without epilepsy.

Keywords: Autism, Autism spectrum disorder, Epilepsy.

ABBREVIATIONS

ASD: Autism Spectrum disorder

CATSS: Child and Adolescent Study in Sweden (CATSS)

A-TAC: The Autism, Tics, ADHD and other Comorbidities inventory

CI: Confidence interval

EP: Epilepsy

ADHD: Attention-Deficit hyperactivity disorder

DS: Down Syndrome

NPR: The Swedish National Patient Register

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders

INTRODUCTION

AUTISM SPECTRUM DISORDER

Autism Spectrum Disorder (ASD) is an umbrella term for a group of neurodevelopmental disorders characterized by abnormalities in social interaction, reciprocal communication and by restricted and stereotyped range of interests and activities. The diagnostic criteria stated in the DSM-V and ICD-10 require that these impairments be present from early childhood, or when the capacities of the individual are exceeded by the surrounding demands, and cause clinically significant deficits in social, occupational or other important areas of functioning in a way that is below the expected for the general developmental level. (1, 2). The accepted prevalence today is 1% in children and adults (3, 4) with a higher prevalence in males than in females (ratio 1.3-16 : 1.0, depending on cognitive functioning) in European studies. (5).

In ASD, social communication and interaction deficits can, for example, include hardships with social reciprocity like initiating, responding or engaging in a back-and-forth conversation. Common non-verbal communication problems also include a lack of eye contact and difficulties in interpreting body language. The stereotyped repetitive behaviour can include a strong preoccupation with objects or figures and a strict adherence to routines and insistence of sameness. In addition, the diagnostic criteria also include that individuals might experience sensory abnormalities like hypo- or hyper- sensibility to temperature, sounds or smells (2).

It is important to note that autism symptomatology exists on a spectrum where one individual may have an exceedingly hard time to cope with basic day to day functioning while for another individual the symptoms might only be noticeable in stressful situations. Recent research also shows that the symptoms follow a waxing and waning course over the life span (6, 7). Individuals with ASD most often have additional medical conditions such as intellectual disability, epilepsy, language impairment, tics, developmental coordination disorder and attention-deficit hyperactivity disorder (ADHD) (8). ASD can be conceptualized as the extreme end of a dimensionally distributed trait, and genetic epidemiology suggests that there is little

etiological (genetic or environmental) demarcation between narrowly defined ASD and autistic-like traits in the general population (9-11).

The aetiology of the ASD is highly heterogenous and includes genetic and environmental factors that most likely interplay. Twin and family studies consistently report an overwhelming evidence for the importance of genetic factors in the development of ASD with a higher concordance estimates for monozygotic twins compared to dizygotic twins and heritability figures around 0.70 (12-15).

Molecular genetic studies show that different types of genetic variations from single gene modification to whole chromosomal aberrations can co-occur with ASD. The genetic variations can be de novo or inherited. Monogenic disorders that often co-occur with ASD are for instance Tuberous sclerosis (TSC1, TSC2), Fragile X Syndrome (FXS), Neurofibromatosis, and Rett Syndrome (MECP2) (16-19).
Furthermore, some Copy Number Variants (CNV), which are chromosomal microdeletions or microduplications larger than 1 kb, have been found to be related to ASD. Around 234 De Novo CNV loci have been identified to be associated with ASD risk and these do also correlate with the presence of intellectual disability (20). The most common CNV is the duplication of 15q11-q13 also called the "Chromosome 15 phenotype" (21). Other CNV related to ASD are 1q21.1 deletions, 7q11.23 duplications,16p11.2 deletions, 18q12.1 duplications and 22q11.2 deletions (22, 23). Additionally, there is a big number of rare penetrant genes mutations attributed to be associated with ASD such as the genes SHANK1, SHANK2, SHANK3, NLGN3 and NLGN4 (24, 25).

Epidemiological studies have suggested several environmental factors associated with ASD although it is unclear if they are truly in the causal pathway. These environmental factors include toxic exposure (26), teratogens like Valproic acid (27), thalidomide (28) and misoprostol (29), perinatal insult and prenatal infections such as rubella (30) and cytomegalovirus (31). Although these different genetic and environmental factors might have large effects on the brain to explain the aetiology of autism, one generally accepted hypothesis suggests an abnormal synaptic plasticity and failure of neuronal synaptic homeostasis

which might result in altered balance between excitation and inhibition in sensory, mnemonic, social and emotional neural systems could contribute to ASD symptoms in many patients (32-34).

EPILEPSY

Epilepsy is a family of neurological conditions characterised by two or more unprovoked seizures occurred more than 24 hours apart and are caused by a primary pre-dispositional cerebral dysfunction (35). Prevalence rates differ in developed countries from developing countries. Rates being highest in rural areas of developing countries (15.4 per 1,000 in rural and 10.3 per 1,000 in urban area) compared to 5.8 per 1,000 in developed countries (36). The difference between countries is therefore evident, ranging from 35 per 100,000 in Finland (37) and Iceland (38) to 124 per 100,000 in Chile (39). Studies show a peak of cases in children under one year old and in early adolescent years (40). Gender differences can be found but they are often statistically insignificant, with a higher number of affected males in the general adult population and a slightly higher number of females observed in children (41, 42).

Epilepsy can be classified both by the type and by the cause of the seizures. There are two types of seizures, the generalised and the partial seizures. In *Partial seizures,* there is evidence of partial or focal onset. The first clinical signs of the seizure called the "aura" corresponds to the functional neuronal activation in cortex (43). This sign can be, for example, a shaking in the arm or leg, contrary to the generalised seizures which involves the whole body. In the *generalised seizures*, there is no evidence of an anatomic location and no clinical evidence of focal onset. Clinically, there are three generalised seizure subtypes. These are **generalised convulsive seizures** with predominantly *atonic,* characterised by a brief lapse in muscle tone resulting in the fall of the patient without any convulsion, *tonic,* in which there is no clonic jerking, can be convulsive or not, *clonic,* which makes the patient lose consciousness with jerking in many parts of the body, *or tonic-clonic* the "grand mal" seizure, in which there is a tonic and then a clonic phase. **Generalised non convulsive seizures** are characterised by absence seizure or "petit mal" which is a brief loss of

consciousness and **myoclonic seizures**; these are brief contraction of muscle or group of muscles **(43).** Based on the aetiology**,** epileptic seizures are categorised in **symptomatic**, secondary to a known cause such as brain tumour, **idiopathic**, presumed to be of genetic origin and with no other apparent cause, and **cryptogenic** which is neurologically symptomatic with an unknown underlying abnormality (44, 45).

EPILEPSY AND ASD

Seizures among children with ASD as well as other psychiatric disorders in children with previous infantile spasms have been reported since the early 1970s (46-48). Up to 25% of individuals diagnosed with ASD later developed epileptic seizures in a retrospective follow up study carried out in Japan in 2006 (49). Other studies have come up with different figures ranging from 5% to 38.3% (50). The onset of seizures are observed either before the age of 5 or in early adolescence (51). The probability of ASD in children with epilepsy ranges between 5-37% (52, 53). Studies have shown that individuals with both ASD and epilepsy are to a larger extent than what could be expected by chance alone, accompanied by intellectual disability. Furthermore, the male : female ratio in ASD is reduced when seizures are present, going from 3.5:1 to 2:1(54-58). A recent Danish study examined the presence of ASD and epilepsy in a siblings-control study which showed that siblings of children with ASD were more likely to develop seizures and vice versa suggesting that ASD and epilepsy share etiological underpinnings (59).

There are a few examples of cases in which children seemingly first develop epilepsy and later develop ASD. These include Infantile spasms (48), Lennox-Gastaut Syndrome (60) and Landau-Kleffner Syndrome (61). Due to the wide range of ASD symptoms, it is difficult to specify which aspect of ASD symptomatology that is mostly associated with epilepsy. There have been efforts to classify types of epileptic seizures that most often occur in the children with ASD. Steffenburg et al. found complex partial, absence, myoclonic and tonic-clonic seizures to be the most common seizures in 98 children with ASD or autistic-like condition in a study done in Gothenburg in 1996 (62). Conflicting results have been reported

from an American study in 1991 in which generalised tonic-clonic and absence seizures were most common (58).

Tuberous sclerosis, Rett syndrome and Fragile X are some of the genetic disorders presenting ASD and epilepsy as some of their symptoms (63). Furthermore, recent genetic studies have established some genetic modifications that often are related to the association between epilepsy and ASD. In their 2015 review, Bo Hoon Lee et. al made a biological classification of the gene modifications involved in the ASD and epilepsy association. The classification consists of at least four pathways involved in neuronal development and function. These are **Transcriptional Regulation** involving the genes FOXG1, MECP2 and MEF2C (causing Rett syndrome), **Cellular Growth** with the genes PTEN, TSC1 and TSC2 (causing tuberous sclerosis); **Synaptic Channels** involving the SCN2 gene and **Synaptic Structure** involving CASK, CDKL5, FMR1 (causing Fragile X syndrome) and SHANK3 (64). In addition to those single gene mutations, there are disorders caused by large chromosomal duplications or deletions. These are for example Duplication of the maternally inherited chromosome 15q11-13 Syndrome (65), Trisomy 21 or Down Syndrome (DS) where 5-9% of the DS patients have ASD symptoms (66) and 8-13% have different types of epileptic seizures (67). Deletion of 22q13.3 that contains the SHANK 3 gene causes the Phelan-Mc Dermid Syndrome characterized by developmental delay, autistic behaviour and seizures (68). Recent studies also show that the severity of the seizures and the ASD symptoms depend on the affected genomic region (69) with 15q11.2 and 16p11.2 deletions and 16p13.11 duplication mostly associated with ASD (70). The inhibitory/excitatory changes in the hippocampus due to early seizures/epilepsy or genetic mutations may increase the risk of ASD, but many questions on the pathophysiology of ASD and epilepsy are yet to be answered (63).

The antiepileptic drug Levetiracetam has been used to treat subclinical epileptiform discharges in children with ASD aged 4 to 6 years in a recent study that showed significant improvement of ASD symptoms (71), though previous studies had showed from no effect (72) to negative effects of the drug (73).

Phenotypic differences in individuals with ASD and epilepsy, and individuals with ASD have been noted in two different studies. In a study made in 2008 in London Turk et al. found out that individuals with both ASD and epilepsy had more motoric and developmental difficulties while the individuals with only ASD were more captivated by objects and had less eye-contact (74). A recent study made in South Korea showed that individuals with both ASD and epilepsy had more impairment in social awareness and communication and suggested that epilepsy may be producing or increasing ASD symptoms (75).

Considering the heterogenous expression of ASD, autism-like traits and the clinical manifestations of epilepsy, it is plausible that clinicians may fail to detect ASD in the presence of epilepsy or vice versa, especially in less obvious cases of seizures like absence and simple partial seizures. It is still unclear whether epilepsy contributes to the ASD symptomatology and the importance of intellectual disability in the association between ASD and epilepsy.

AIM

The aim of this study is to understand the impact of epilepsy on the ASD symptomatology and to investigate whether symptomatic expression of ASD in individuals with epilepsy differs from the individuals without seizures.

MATERIAL AND METHODS

Subjects

The subjects were recruited from the ongoing Child and Adolescent Study in Sweden (CATSS) which emanates from the Swedish Twin Register, specifically the CATSS 9/12. The Child and Adolescent Study in Sweden (CATSS) is a longitudinal epidemiological study that targets all twins born in Sweden since the first of July1992. The CATSS study started in 2004 and assesses somatic and mental disorders in twins. The twins are assessed at age 9 (those born from the 1st of July 1992 to the 21st of June 1994 were assessed at the age of 12) via parental telephone interview containing a multitude of questionnaires. The interviews are effectuated by an interview company and the questions have been the same since the start of the study.

In The CATSS 9/12, which was used for the present study, parents of 9 or 12-year-old twins are interviewed regarding their children's mental health. This interview focuses on neuropsychiatric disorders and is called "The Autism, Tics, ADHD and other Comorbidities inventory (A-TAC)" (76-79).

Furthermore, the CATSS is linked to the Swedish National Patient Register (NPR) which contains data on all inpatient care since 1973 and also includes data about outpatient care since 2001 (80).

Measures

The A-TAC is a fully structured parental telephone interview which consists of 96 questions targeting virtually all common child and adolescent psychiatric problem constellation. The A-TAC has been fully evaluated for reliability and validity in different studies over the years and is reported to have an excellent interrater reliability (76-79, 81). Among these studies is the 2005 study where a cross examination study was made in which the individuals who screened positive for the different disorders included were clinically

examined (76). Later, a validation study was done by clinicians that were blind to previous diagnoses by interviewing previously clinically diagnosed children (79).

All the questions in the A-TAC interview are coded as 0 = "no", 0.5 = "yes, to some extent" and 1 = "yes". The questions are based on the DSM-IV (82) and clinical experience. Out of the 96 questions, 17 pertains to an ASD-domain. The 17 questions in the ASD-domain are subdivided into three modules: Language, consisting of five questions, Social interaction, consisting of six questions and Flexibility, which consists of six questions and refers to the stereotypical and repetitive behaviour described within ASD. The ASD-scale thus ranges from 0-17 with Cronbach's alpha of 0.86. The corresponding alpha value for the language score is 0.66 and 0.77 and 0.70 for social interaction and flexibility respectively (78).
In this study, two cut-offs were used. First, a cut-off of ≥8.5 in the ASD-score which yields a prevalence of 1% and has a sensitivity of 0.71 and a specificity of 0.95 when validated in a case, control and community sample (79). Thus, this cut-off can be conceptualized as a clinical proxy for ASD. Finally, a low cut-off for ASD (≥4.5) with a higher sensitivity (0.96) but a lower specificity (0.88) was used to indicate subthreshold traits not reaching up to the diagnostic level (79).

Epilepsy diagnoses were obtained from the NPR, we included all diagnosis subsumed under the ICD-10 classification G.40 (e.g. localization-related, generalized idiopathic, juvenile myoclonic-epilepsy) (1). Although no formal validation exists for the epilepsy codes in the NPR, other validation studies of autism, tic disorders and psychotic disorders have been conducted which all indicates high validity of the reported conditions (3, 83, 84). Furthermore, in a recent CATSS study, parental questions about epilepsy reported a 73% agreement between parental reported epilepsy and register based (NPR), which rendered a kappa-value of 0.640 (85).

Definitions

At the time of our study 27,092 twins had undergone the CATSS 9/12 interview, out of which 26,863 twins (49.2% females) were eligible for inclusion.

Six groups were created based on whether the twins had epilepsy (EP) or not and on how much they scored on the ASD interview. The six groups were Group 1: No EP and a ASD-score <4.5, Group 2: EP and a ASD-score <4.5, Group 3: No EP and a ASD score of 4.5-8, Group 4: EP and a ASD score of 4.5-8, Group 5: No EP and a ASD-score ≥8.5, Group 6: EP and an ASD-score >8.5 **(Table 1)**.

Groups 1 -2; 3 -4; and, finally 5-6 groups were contrasted against each other on the following four continuous variables: A. ASD-score, B. language-score, C. social-interaction score, and the D. flexibility-score (**Figure 1-4).**

Statistical analysis

The mode of analysis Chi-square analysis was also used to compare the distributions. A two-way analysis of variance (ANOVA) was used to compare sample means and the variation within sample means. In addition to counteract for multiple comparisons we used Bonferroni correction.

In interest to provide clinically relevant information about phenotypic differences, the 17 questions constituting the ASD-score were ranked according to the number of individuals who had endorsed the items. The percentage of "YES = 1 point" scores were used to rank the questions separately in three mutually exclusive groups: A group with individuals with EP only, a group with individuals with ASD ≥8.5 only, and a group with individuals with both ASD ≥8.5and EP. The ranking was done by number 1 (No.1) as the highest percentage of YES responses up to No. 17 as the lowest percentage. A comparison was later made considering which of the ASD domain had the highest symptoms in the 3 groups. **(Table 3).**

ETHICS

The parents of the twins in the CATSS study are informed in writing about the study and are protected by the informed consent process. They are also given the opportunity to discontinue at any time. The CATSS study has ethical approval from the Karolinska Institute Ethical review board: No. 02-289 and 2010 / 507-31 / 1.

RESULTS

Diagnosis of ASD and epilepsy

We had 27,092 twins in this study out of which 229 had rare brain or chromosomic disorder and were therefore excluded from the study. Among the eligible 26,863 individuals, 13,205 were females and 13,658 were males. In the whole population, 0.8% of the individuals had epilepsy, 2.5% of the individuals screened positive for ASD low cut-off, and 1.0% of the individuals screened positive for ASD high cut-off.

Among the 219 individuals with epilepsy, 9.1% screened positive for ASD low cut-off and 7.4% screened positive for ASD high cut-off, which also means that 16.4% (36 of 219) of children with epilepsy had ASD symptoms. In the general population without epilepsy only 2.4% screened positive for ASD low cut-off and 0.9% screened positive for ASD high cut-off. Among the 663 individuals with ASD-score between 4.5-8 (ASD low cut-off), 3% had epilepsy and among the 262 individuals with ASD-score ≥8.5 (ASD high cut-off) 6.1% had epilepsy. Furthermore, 0.8% of the general population with ASD score under 4.5 had epilepsy **(Table 1 and 2).**

Table 1. The Study groups

	Frequency	Percent
(1) No EP nor ASD	25,684	95.6
(2) EP present without ASD	179	0.7
(3) ASD low cut-off without EP	643	2.4
(4) ASD low cut-off AND EP present	20	0.1
(5) ASD high cut-off without EP	246	0.9
(6) ASD high cut-off AND EP present	16	0.1
Total	26,788	99.7

EP: Epilepsy, ASD high cut-off: ASD-score >= 8.5, ASD low cut-off is ASD-score between 4.5-8, No ASD: ASD score < 4.5.

Table 2. DISTRIBUTION OF EPILEPSY AMONG CHILDREN BY ASD CUTOFFS*

	EP absent	EP present	Total
ASD high cut-off absent	26,327	199	26,526
ASD high cut-off present **	246	16	262
ASD low cut-off absent	26,001	199	26,200
ASD low cut-off present **	643	20	663

* Missing data in 4 individuals.
** Pearson chi-square calculated, P- value <0.001.
EP: Epilepsy, ASD high cut-off: ASD-score >= 8.5, ASD low cut-off is ASD-score between 4.5-8.
0.8% of ASD high cut-off absent have epilepsy; 6.1% of all with ASD high cut-off have epilepsy, and 7.4% of all with epilepsy have ASD high cut-off; 0.8% of ASD low cut-off absent have epilepsy and 3.0% of all with ASD low cut-off have epilepsy, and 9.1% of all with epilepsy have ASD low cut-off.

Importance of epilepsy in ASD symptomatology

In the groups with individuals who screened negative for ASD (ASD – score under 4.5) the group without epilepsy was contrasted to the group with epilepsy (group 1 against group 2 in **Table 1**). On the ASD-score variable, the group with epilepsy displayed higher scores with a mean of 0.97 (95% CI 0.81-1.14) than the group without epilepsy 0.55 (95% CI 0.54-0.56), p-value < 0.001 (**Figure 1**). The same tendency of higher

scores in individuals with epilepsy than in the individuals without epilepsy was also noted on the language-score, social interaction-score and flexibility-score variables with p-values <0.001, <0.001 and 0.05 respectively. (**Figures 2, 3 and 4**).

In the groups with ASD low cut-off (groups 3 and 4 in **Table 1**), a slight increase of the ASD symptomatology was observed in the groups with epilepsy, especially on the language and social interaction scales. In the ASD variable, the group with epilepsy displayed slightly higher scores with mean of 6.33 (95% CI 5.74-6.91) than the group without epilepsy 5.76 (95% CI 5.68-5.84), p-value = 0.065 (**Figure 1),** whereas there were little to no difference on the language, social interaction and flexibility scores, with p-value 0.235, 0.001 and 1.00. respectively. **(Figures 2, 3 and 4)**.

In the individuals with ASD high cut-off (ASD score >=8.5, groups 5 against 6 in **Table 1**), not much differences could be discerned between the individuals with epilepsy and the individuals without epilepsy were observed except on the language level. On the ASD-score variable, the group with epilepsy displayed a mean of 11.06 (95% CI 9.88-12.25) and the group without epilepsy 10.74 (95% CI 10.48-10.99), p-value =1. The language score, social interaction score and the flexibility score variables had p-values 0.004, 1.00 and 1.00 respectively. (**Figures 2, 3 and 4**).

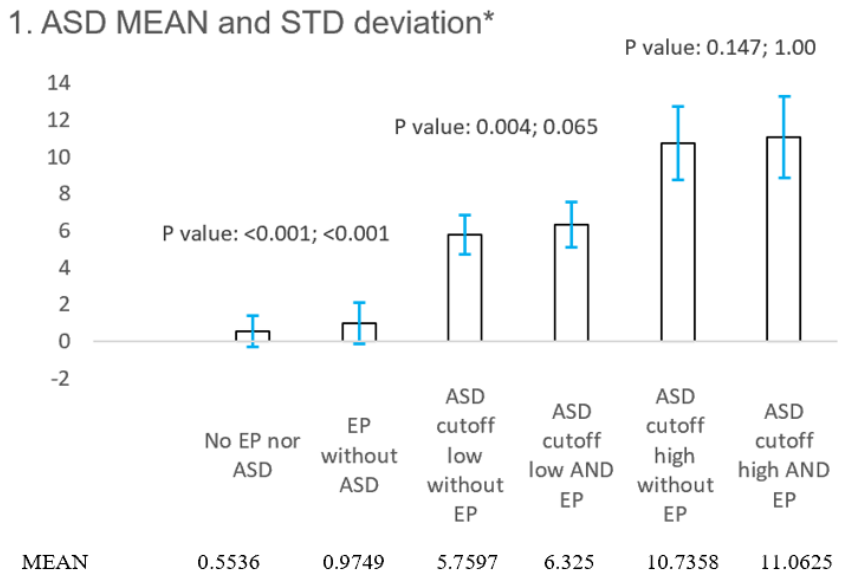

Figure 1. Importance of epilepsy in ASD symptomatology. Comparing different groups' means by considering all the ASD symptom domains.
*ANOVA LSD post hoc test; Bonferroni corrected.
Y-axis: mean of the total points on the A-TAC
STD: Standard deviation of the mean.

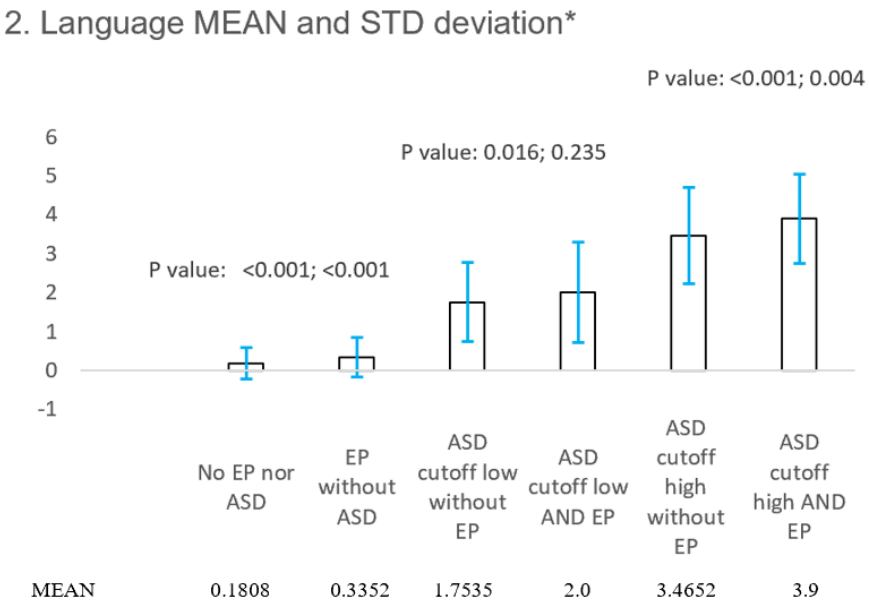

Figure 2. Importance of epilepsy in ASD symptomatology. Comparing different groups' means by considering the language domain.
*ANOVA LSD post hoc test; Bonferroni corrected.
Y-axis: mean of the points on "Language" on the A-TAC
STD: Standard deviation of the mean.

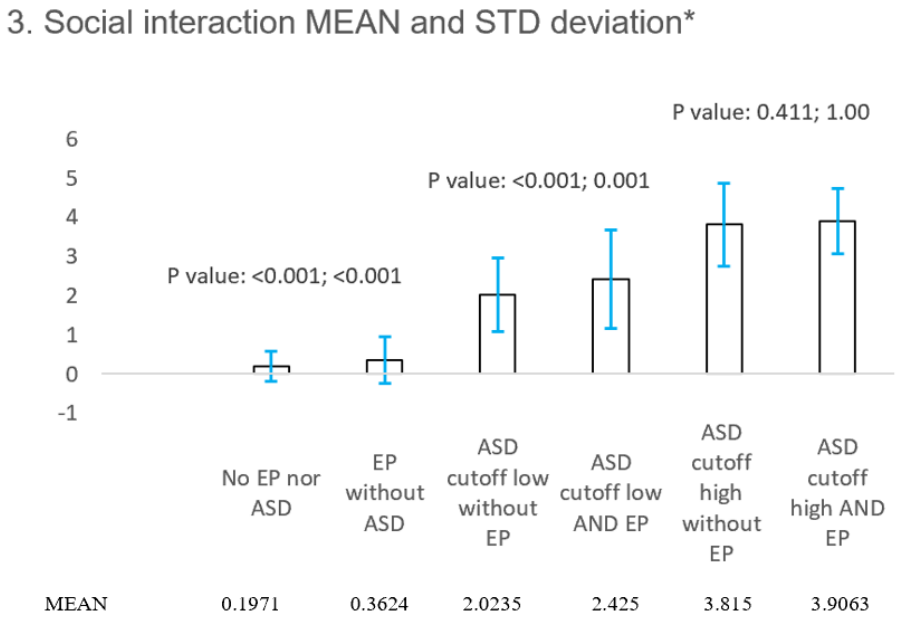

Figure 3. Importance of epilepsy in ASD symptomatology. Comparing different groups' means by considering the social interaction domain.
*ANOVA LSD post hoc test; Bonferroni corrected.
Y-axis: mean of the points on "Social interaction" on the A-TAC
STD: Standard deviation of the mean.

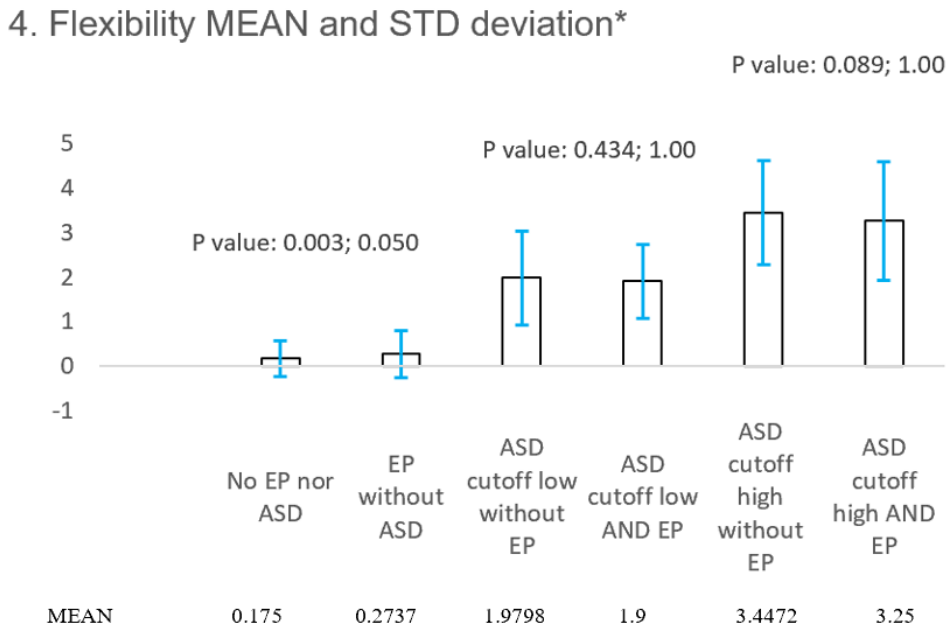

Figure 4. Importance of epilepsy in ASD symptomatology. Comparing different groups' means by considering the Flexibility domain.
*ANOVA LSD post hoc test and Bonferroni corrected.
Y-axis: mean of the points on "Flexibility" on the A-TAC.

STD: Standard deviation of the mean.

Differences in ASD symptom patterns

Individuals with only ASD ranked highest on the flexibility level while individuals who had Epilepsy ranked highest on the language and social interaction levels as did the individuals who have Epilepsy and ASD (**Table 3**).

Table 3. The screening questions and how they were answered by the different groups with ranking

		EP (N=179)	*RANKING*	ASD_H (N=246)	*RANKING*	ASD_H & EP (N=16)	*RANKING*
Questions about language	1.	8.4%	***No. 1***	54.1%	*No. 8*	75.0%	*No. 3*
	2.	0.0%	*No. 17*	34.6%	*No. 16*	81.3%	***No. 1***
	3.	1.7%	*No. 7*	51.7%	*No. 9*	50.0%	*No. 10*
	4.	0.0%	*No. 17*	49.6%	*No. 11*	75.0%	*No. 3*
	5.	1.1%	*No. 9*	41.2%	*No. 14*	8.3%	*No. 17*
	6.	4.6%	*No. 3*	65.4%	*No. 6*	56.3%	*No. 8*
Questions about social interaction	7.	0.6%	*No. 11*	38.6%	*No. 15*	43.8%	*No. 13*
	8.	1.7%	*No. 7*	69.5%	*No. 3*	81.3%	***No. 1***
	9.	0.6%	*No. 11*	24.4%	*No. 17*	50.0%	*No. 10*
	10.	0.6%	*No. 11*	51.6%	*No. 10*	75.0%	*No. 3*
	11.	2.3%	*No. 6*	66.3%	*No. 4*	56.3%	*No. 8*
	12.	7.8%	*No. 2*	60.6%	*No. 7*	25.0%	*No. 16*
Questions about flexibility	13.	3.9%	*No. 4*	72.4%	***No. 1***	75.0%	*No. 3*
	14.	0.6%	*No. 11*	45.9%	*No. 12*	43.8%	*No. 13*
	15.	0.6%	*No. 11*	45.1%	*No. 13*	43.8%	*No. 13*

	16.	1.1%	*No. 9*	65.4%	*No. 5*	50.0%	*No. 10*
	17.	3.4%	*No. 5*	69.9%	*No. 2*	68.8%	*No. 7*

DISCUSSION WITH CONCLUSIONS AND IMPLICATIONS

This study confirms that ASD is overrepresented in the individuals with epilepsy and that the risk of epileptic seizures is higher in individuals with ASD as previous studies had shown in the past. We could see a slight increase of ASD symptomatology, which possibly could be attributed to the presence of epilepsy, in the language and social interaction domains. It was also noted that symptoms of stereotyped and repetitive behaviour were not affected by the presence of epilepsy in any of the groups in our data. Furthermore, the ASD phenotype was different depending on whether the children had ASD and epilepsy or only ASD. In individuals with ASD and epilepsy, symptoms on the language and social interaction scales were most common, while flexibility symptoms were most common in children with only ASD symptoms.

Earlier studies have shown an increase of epileptic seizures in children with ASD and an increase of ASD symptoms in children who had seizures in early childhood (46-51). In this study, it was observed that the epilepsy prevalence increases with the presence of higher ASD symptoms; 3.0% of children with low cut-off ASD symptoms had epilepsy while 6.1% of children with high cut-off ASD symptoms had epilepsy. Likewise, 16.4% of children with epilepsy endorse one of the two cut-offs (9.1% had low cut-off ASD score, and 7.4% had high cut-off ASD score), compared to 2.4 % and 0, 9% respectively, of the sample without epilepsy. However, children included in this dataset had not yet reached 12 years, which presume low epilepsy figures since literatures show a peak of epilepsy incidence during teenage years (40). Although coexistence of autism and epilepsy is well documented, there is no ASD screening done in children with

epilepsy nor epilepsy screening in children with ASD diagnosis. Investigations are only done once there is presence of symptoms which often delays the beginning of treatment measures.

A study in South Korea in 2016 on the effects of epilepsy on ASD symptoms showed that some symptoms could be aggravated by the presence of epilepsy but suggested that the same study should be done on larger population to be more conclusive (75). Our study shows that the subgroups with epilepsy but low ASD-scores, was rated higher on the language and the social interaction symptoms reaching statistical significance (albeit only in language group when including the Bonferroni correction). However, the high cut-off ASD group did not show any statistical significance between the groups with epilepsy and the groups without epilepsy. Thus, an increase of ASD symptomatology caused by the presence of epilepsy was not proven by this study. Furthermore, the slightly higher ASD symptoms on the language and social interaction scales in some of the children with epilepsy could possibly be attributed to the presence of intellectual disability, which is often associated with the combination of epilepsy and ASD (54-56) which was not excluded or examined in this study. A further study that would account for individuals with intellectual disability could provide a better understanding in this matter.

Symptomatic expression of ASD in individuals with epilepsy was different from previous studies (74). In this study, flexibility symptoms were overrepresented in the individuals with only ASD while language and social interaction symptoms were more represented in individuals with only epilepsy and in individuals with both ASD symptoms and epilepsy. This observed difference may suggest that the combination of ASD and epilepsy can be conceptualized as a slightly different phenotype, which may have important implications for diagnostic assessments and follow-up. The predominant symptoms by the time of ASD diagnosis might aid in the prediction of later epilepsy, adding to the better follow up guidelines for the children with ASD diagnosis. Future studies on ASD and epilepsy should take into consideration gender and other neuropsychiatric conditions such as ADHD to elaborate the different presentations of ASD.

Strengths and limitations

The biggest strength of this study is that it is a population-based study covering a big population. In addition, the interviews used in the CATSS 9/12 have been validated through different studies. The limitations in this study are the possibility of cofounders. Although individuals with known neurological and chromosomal disorders were excluded, there is possibility that some of them might have had underlying disorders such as intellectual disability that could affect some of the symptoms. Furthermore, the epilepsy diagnosis was unspecific which can have affected the symptoms. Another symptom pattern could possibly have been presented with a closer specification of the types of epilepsy present in our population.

POPULÄRVETENSKAPLIG SAMMANFATTNING PÅ SVENSKA

Autismspektrumstörning (ASD) karaktäriseras av minskad förmåga till social interaktion och kommunikation, samt av någon form av repetitivt beteende. Även om ASD är en mycket handikappande sjukdom vet man väldigt lite om dess orsaker.

Epilepsi är en grupp av tillstånd som kännetecknas av minst två epileptiska anfall som uppträtt spontant. Dessa beror på störningar i hjärnceller som ger någon form av funktionsstörning i hjärnan. Orsaken till störningen är ofta okänd. Missbildningar, hjärnsjukdomar, skador och genetiska faktorer utgör de viktigaste kända orsak. Kognitiv funktionsnedsättning, neuropsykiatrisk störning och rörelsehinder är vanliga symptom som går hand i hand med epilepsi.

Det finns ett starkt stöd i den vetenskapliga litteraturen om en avsevärd ökning av epilepsi hos individer med en autismspektrumstörning. Tidigare studier har visat att personer med epilepsi löper ökad risk för autismspektrumstörning, särskilt om epilepsi förekommer i barndomen. Man har också märkt att ASD symtom kan vara annorlunda beroende på ASD är associerad med epilepsi eller inte.
Syfte med denna studie var att studera hur mycket epilepsinärvaro bidrar till ASD symptomatologi.

Information hämtades från The Child and Adolescent Twin Study (CATSS) som är en kontinuerlig tvillingstudie som siktar på att innefatta alla tvillingar födda i Sverige från och med den 1 juli 1992. Tvillingföräldrar svarar på en telefonintervju när tvillingar fyller 9 alternativt 12 år. Intervjuerna handlar om tvillingarnas kroppsliga och psykiska hälsa och deras sociala miljö. Intervjun innefattar bland annat 17 frågor om ASD symptom, vilka täcker ut språk, social interaktion och flexibilitet symptom. Dessa frågor användes för denna studien. Data om epilepsi söktes i nationell patient-databas. All data innefattade 27 092 tvillingar. Tvillingarna grupperades beroende på om de hade epilepsi, autismspektrumstörning symtom eller om de hade båda epilepsi och autismspektrumstörnings symtom. Statistiska formler användes för att jämföra medelvärden och variationen av symtomen inom grupperna.

Resultatet visade att ASD var överrepresenterat bland personer med epilepsi och tvärtom, vilket överensstämmer med tidigare studier. Närvaron av epilepsi var associerad något med fler ASD symptom i den generella populationen och i grupper med låg poäng på ASD screenings-formuläret. I grupperna med höga poäng på ASD screeningen visade närvaron av epilepsi något fler ASD symtom inom i språk-domänen men inte på social interaktion och flexibilitets nivå. Hos individer med ASD utan epilepsi kunde man observera att flexibilitet symptom var dominerande medan språk och social interaktion var mest uttalade hos individer med båda konditioner. Att epilepsi kan påverka ASD symptom kunde denna studie inte påvisa eftersom påverkan inte syns hos individer med straka ASD symptom. Ökande ASD symptom hos individer med epilepsi jämfört med individer utan epilepsi beror eventuellt på samsjuklighet med intellektuell funktionsnedsättning som också ofta förekommer hos individer som har epilepsi och ASD samtidigt. Slutligen, flexibilitets-domänen var opåverkad av epilepsi och specifika ASD symptom skiljer sig mellan individer som bara har ASD och individer som har både ASD och epilepsi.

Relationen mellan epilepsi och autismspektrumstörning symtom som visas i denna studie skulle kunna utnyttjas på diagnostik, behandling och även fördjupade forskning inom neuropsykiatri.

ACKNOWLEDGEMENTS

I am very thankful to my supervisors Lars Westberg and Sebastian Lundström for all their support and guidance during all the steps of this thesis.

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APPENDICES

APPENDICE 1. ASD-SCREENING QUESTIONS			
	YES	YES, TO SOME EXTEND	NO
1. Was his/her language development delayed or does s/he not speak at all? If one does not start speaking around age 4-5 one is late. Big problems speaking clearly count.			
2. Does s/he have difficulties sustaining a conversation?			
3. Does s/he like to repeat words and expressions or does s/he use words in a way other people find strange?			
4. Has s/he difficulties with pretend play or does s/he imitate considerably less than other children?			
5. Does s/he talk in too high a pitch or too quietly?			
6. Does s/he have difficulties keeping "on track" when telling other people something?			
7. Does s/he have difficulties expressing emotions and reactions with facial gestures, prosody, or body			

language?			
8. Does s/he exhibit considerable difficulties interacting with peers?			
9. Is s/he uninterested in sharing joy, interests, and activities with others?			
10. Can s/he only be with other people on his/her terms?			
11. Does s/he have difficulties behaving as expected by peers?			
12. Do other people easily influence him/her?			
13. Does s/he get absorbed by his/her interests in such a way as being repetitive or too intense?			
14. Does s/he get absorbed by routines in such a way as to produce problems for himself or for other?			
15. Has s/he ever engaged in strange hand movements or walking high on tiptoe when s/he was happy or upset?			

16. Does s/he get absorbed by details?			
17. Does s/he dislike changes in daily routines?			

From question 1-6: Symptoms related to Language screening; questions 7-12: Symptoms related to Social interaction screening and from 13- 17: Symptoms related to Flexibility screening.