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Original Article

Febrile Seizures and Epilepsy: Association With Autism and Other Neurodevelopmental Disorders in the Child and Adolescent Twin Study in Sweden

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ABSTRACT

BACKGROUND: There is a recently well-documented association between childhood epilepsy and *early symptomatic syndromes eliciting neurodevelopmental clinical examinations* (ESSENCE) including autism spectrum disorder, but the relationship between febrile seizures and ESSENCE is less clear. **METHODS:** The Child and Adolescent Twin Study in Sweden (CATSS) is an ongoing population-based study targeting twins born in Sweden since July 1, 1992. Parents of 27,092 twins were interviewed using a validated DSM-IV-based interview for ESSENCE, in connection with the twins' ninth or twelfth birthday. Diagnoses of febrile seizures (n = 492) and epilepsy (n = 282) were based on data from the Swedish National Patient Register. Prevalence of ESSENCE in individuals with febrile seizures and epilepsy was compared with prevalence in the twin population without seizures. The association between febrile seizures and ESSENCE was considered before and after adjustment for epilepsy. Age of diagnosis of febrile seizures and epilepsy was considered as a possible correlate of ESSENCE in febrile seizures and epilepsy. **RESULTS:** The rate of ESSENCE in febrile seizures and epilepsy was significantly higher than in the total population without seizures (all $P < 0.001$). After adjusting for epilepsy, a significant association between febrile seizures and autism spectrum disorder, developmental coordination disorder, and intellectual disability remained. Earlier age of onset was associated with all ESSENCE except attention-deficit/hyperactivity disorder in epilepsy but not with ESSENCE in febrile seizures. **CONCLUSIONS:** In a nationally representative sample of twins, there was an increased rate of ESSENCE in childhood epilepsy and in febrile seizures. Febrile seizures alone could occur as a marker for a broader ESSENCE phenotype.

Keywords: twin study, autism, attention deficit disorder, epidemiology, intellectual disability, ESSENCE

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Introduction

Seizures are common in childhood and the majority occur in connection with a high body temperature, and are classified as "febrile seizures." In the US and Europe, febrile seizures occur in 2% to 4%[1,2] of the population before age five to six years with peak incidence at 18 months.[3] Febrile seizures are usually defined as an event in infancy or childhood, occurring between age three months and five years, associated with fever but without evidence of

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intracranial infection or defined cause for the seizure.[3] The risk of subsequent epilepsy following febrile seizures is 2% to 4%[4] with an increased risk for those with prolonged or focal febrile seizures. Epilepsy affects at least 1 in 150 children.[5] It is typically defined as two or more unprovoked epileptic seizures occurring more than 24 hours apart.[6]

The term *early symptomatic syndromes eliciting neurodevelopmental clinical examinations* (ESSENCE) has been coined to refer to the reality of children aged less than five years presenting in clinical settings with neurodevelopmental concerns.[7] These children usually have problems across a range of neurodevelopmental domains and need to be assessed across these domains and not just for confirming or refuting the presence or absence of one specifically named disorder. In the present article, ESSENCE refers to autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), developmental coordination disorder (DCD), and learning difficulty (LD). ADHD, ASD, and DCD are defined according to criteria given in the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) (DSM-IV),[8] and LD is defined as all kinds of learning difficulties interfering with academic achievement. A significant association between febrile seizures and ESSENCE has not been found in most population-based studies,[9,10] and this holds for both complex and simple febrile seizures.[9,10] However, some of these population-based studies have specifically excluded children with prior neurological and developmental abnormalities.[9] Furthermore, one population-based study suggested an increased risk for ADHD in those with febrile seizures[11] and prolonged febrile seizures have been associated with impairment in recognition memory and global development.[12,13] There is, however, a lack of population-based studies of febrile seizures which have employed interviews based on DSM/ICD (International Classification of Diseases) criteria to assess ESSENCE.

In contrast to febrile seizures, epilepsy in children has consistently been associated with a high rate of ESSENCE,[14] including ADHD,[14] ASD,[14] intellectual disability (ID),[15] specific cognitive problems,[16] and DCD.[14] These problems are often underdiagnosed in childhood epilepsy[14] despite having a significant impact on health-related quality of life.[17] Earlier age of seizure onset has been associated with an increased risk of ID and ASD[14] but findings have been less consistent with respect to ADHD and there have been limited studies of motor coordination or DCD in epilepsy. Despite the well-documented increased association between epilepsy and ESSENCE, there is a lack of population-based studies employing well-validated psychiatric interviews.

The Child and Adolescent Twin Study in Sweden (CATSS) is based on a Swedish total population twin sample.[18] All parents who take part undergo a telephone interview, which includes the autism-tics, ADHD, and other comorbidities inventory (A-TAC),[19] which is a fully structured interview focusing on neurodevelopmental disorders (including ASD, ADHD, DCD, and LD). The National Patient Register (NPR) in Sweden provides data on all inpatient care and diagnoses assigned according to ICD-10 codes (ICD, Ninth and Tenth revisions, respectively).[20] Since 2001 the NPRs also include information from outpatient consultations with specialists.

The primary aim of this study was to characterize the prevalence and spectrum of ESSENCE in children with febrile seizures and children with epilepsy in a nationally representative sample of twins using a validated DSM-IV[8] interview. A secondary aim was to consider age of diagnosis of seizures as a possible moderator of ESSENCE in both febrile seizures and epilepsy.

Methods

The Child and Adolescent Twin Study in Sweden

Beginning in 2004 the parents of all Swedish twins born since July 1992 were contacted in connection with the twins' ninth or twelfth birthday; twins born from July 1, 1992 to June 30, 1995 were included at age 12 years (n = 6520). After that (those born from July 1, 1995 onward) only nine year olds (n = 20,572) were included. The study has a response rate of 75% and is described in detail elsewhere.[18] In the present study, we included 27,092 twins born in the period from July 1, 1992 to June 30, 2006 whose parents had responded to the A-TAC,[19] a fully structured well-validated interview designed for use by laymen over the telephone. It consists of 96 questions. Seventeen questions correspond to an ASD domain, 18 to ADHD, three to LD, and one to DCD. The ASD and ADHD items correspond to specific DSM-IV symptom criteria. The response categories for each item are "no" (0), "yes, to some extent" (0.5), and "yes" (1). All items are answered with a lifetime perspective and in comparison to similarly aged peers. The A-TAC has been validated in a cross-sectional manner[19,21,22] and longitudinally.[23] The ASD cutoff used here (≥8.5) was established in a community sample and has a sensitivity of 0.61 and a specificity of 0.91.[21] The corresponding figures for ADHD (≥12.5) were 0.56/0.93, LD (≥3) 0.41/0.93,[21] and DCD (≥1) 0.32/0.87.

The telephone interview with parents also includes information on a range of health issues where medical history is systematically addressed via binary disorder–specific questions. Among these, parents are asked if the child has ever experienced a febrile seizure or ever had epilepsy. These questions have not been formally validated but nonetheless have content validity.

National Patient Register

At birth, or on receiving Swedish citizenship, all individuals living in Sweden are assigned a personal identification number, which enables linkage across health and service registers. The Swedish NPR provided data on all inpatient care from 1987 to 2009. Since 2001 the NPR also includes information from outpatient consultations with specialists. For the purposes of this study, children were considered to have a register diagnosis of febrile seizures if they were registered with the ICD-10 codes R56.0 or R56.8 before age six years. There was not a significant difference between the proportion of children born before 2001 or after with a register diagnosis of febrile seizures ($P = 0.422$) based on chi-square analysis. Children were considered as having a register diagnosis of epilepsy if they had a register diagnosis of ICD-10 G40.

Comparison between the register and parent report in the twin study

The validity of the NPR has been examined for other conditions[24,25] and is reported to be excellent. No formal validation study, however, has been conducted for epilepsy or febrile seizures. As the coverage of the NPR may be limited with respect to febrile seizures and epilepsy, all analyses were also conducted on the parental report exposures. On the basis of the parent report, 832 (3.1%) children had febrile seizures (see Supplementary Table 1), whereas 492 children had a register diagnosis of febrile seizures. Of the 492 children with a register diagnosis of febrile seizures, 272 (55%) also had a parent-reported diagnosis of febrile seizures (kappa = 0.399). A total of 209 children (0.8%) had a parent-reported diagnosis of epilepsy (see Supplementary Table 1), whereas 282 children had a register diagnosis of epilepsy (in the comparison, G41

status epilepticus was also included because of wording similarity). Of the 209 children with a parent-reported diagnosis of epilepsy, 153 (73%) also had a register diagnosis of epilepsy (kappa = 0.640). A total of 24 (3.4%) children with parent-reported febrile seizures also had parent-reported epilepsy.

Ethical approval

The data collection in the CATSS and the usage of the NPR has ethical approval from the Karolinska Institute ethical review board (Dnr 02-289 and 2010/507-31/1). No independent approval for any type of epidemiologic study using these data is necessary.

Statistical analysis

The rate of ASD, ADHD, LD, DCD (considered as ESSENCE in this study), and any ESSENCE was calculated for each of five groups: febrile seizures, epilepsy, febrile seizures alone (i.e., febrile seizures without epilepsy), total population, and total population without seizures (i.e., the total population excluding those with febrile seizures or epilepsy). This calculation was done for children with a register diagnosis, a parent-reported diagnosis, both a register diagnosis and parent diagnosis, and either a parent or register diagnosis.

The association between epilepsy or febrile seizures and ESSENCE was calculated using odds ratios (ORs) comparing febrile seizures or epilepsy with the total population of twins who did not have seizures. This calculation was done using register diagnosis and parent-reported diagnosis of epilepsy and febrile seizures. The association between febrile seizures and ESSENCE was calculated before and after adjustment for epilepsy.

Univariable logistic regression analyses were done to identify if age of diagnosis were associated with a register diagnosis of ESSENCE in the epilepsy and febrile seizures. Age of diagnosis was categorized as high and low based on a median split in febrile seizures (0 to 21/22 to 59 months) and epilepsy (0 to 81/82 to 227 months). Gender (male or female) also entered as a possible moderator of ESSENCE in febrile seizures and epilepsy. Epilepsy (present or absent) was entered as a possible moderator of ESSENCE in febrile seizures. Multivariable analysis was carried out by entering all factors (age of diagnosis and gender in the epilepsy groups and age, gender and epilepsy in the febrile seizure group). The α level for univariable and multivariable analyses was set at $P < 0.05$.

All statistical analysis was carried out using SPSS version 22 (IBM SPSS Statistics, IBM Corporation, Armonk, NY).

Results

The distribution of febrile seizures and epilepsy according to age of diagnosis (in years) is in given in Supplementary Table 2. In total 492 (74%) of the 666 children with the ICD-10 R56 codes met the study criteria for registered febrile seizures (febrile seizures diagnosed before age six years). The prevalence of registered epilepsy and registered febrile seizures in the whole data set of the CATSS is shown in Table 1.

The prevalence rates of *register* epilepsy and *register* febrile seizures in the whole sample were 1% and 1.8%, respectively. Sixty-five (0.2%) individuals were registered as having both epilepsy and febrile seizures, and 215 (0.8%) had epilepsy only, 425 (1.6%) had febrile seizures only. The percentage of children with febrile seizures who also had epilepsy was 13.2%, whereas the percentage with epilepsy who had febrile seizures was 23.5%. There was no significant difference between the proportion of males and females in the nonseizure population of twins, compared with epilepsy group ($P = 0.089$) or the febrile seizure group ($P = 0.073$) based on the chi-square analysis. The prevalence of *parent-reported* epilepsy and parent-reported febrile seizures is given in Supplementary Table 2. A total of 209 (0.8%) children had a *parent-reported* diagnosis of epilepsy and 832 (3.1%) had a *parent-reported* diagnosis of febrile seizures.

TABLE 1.
Prevalence of Register Epilepsy and Febrile Seizures in the CATSS

Group	n (M/F)	%
Epilepsy	277 (155/122)	1.0
Febrile seizures	492 (270/222)	1.8
Epilepsy alone	212 (122/90)	0.8
Febrile seizures alone	425 (235/190)	1.6
Both epilepsy and febrile seizures	65 (33/32)	0.2
No epilepsy or febrile seizures	26,390 (13,392/12,998)	97.4
Total population	27,092 (13,782/13,310)	100

Abbreviation:
CATSS = Child and Adolescent Twin Study in Sweden

Prevalence of ESSENCE in febrile seizures and epilepsy

Figures 1-4 show the prevalence of ESSENCE (including ASD, ADHD, DCD, and LD) in those with epilepsy and febrile seizures based on register diagnosis, parent-reported diagnosis, both register and parent-reported diagnosis, and either register or parent-reported diagnosis.

The prevalence rate for all ESSENCE was highest in the epilepsy group followed by the febrile seizures group and then the febrile seizures only group, regardless of the methods for selecting those with epilepsy or febrile seizures.

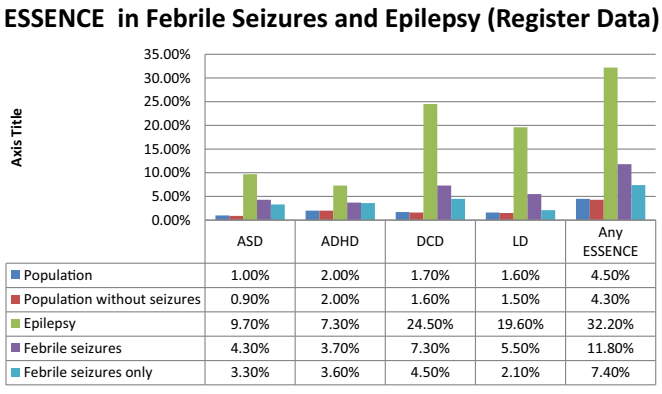
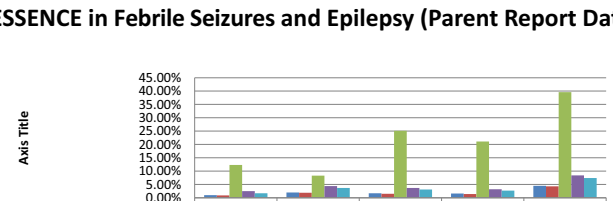


FIGURE 1.
Prevalence of ESSENCE in febrile seizures and epilepsy (register diagnosis). ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; DCD, developmental coordination disorder; ESSENCE, early symptomatic syndromes eliciting neurodevelopmental clinical examinations; LD, learning difficulty. Population without seizures (n = 26,390). (The color version of this figure is available in the online edition.)



	ASD	ADHD	DCD	LD	Any ESSENCE
Population	1.00%	2.00%	1.70%	1.60%	4.50%
Population without seizures	0.90%	1.90%	1.50%	1.40%	4.30%
Epilepsy	12.30%	8.30%	25.10%	21.10%	39.60%
Febrile seizures	2.50%	4.40%	3.70%	3.20%	8.40%
Febrile seizures only	1.70%	3.70%	3.10%	2.70%	7.40%

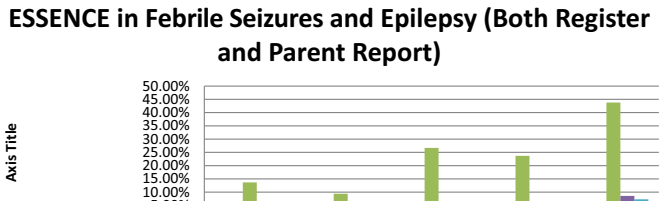
FIGURE 2.
Prevalence of ESSENCE in febrile seizures and epilepsy (parent-reported diagnosis). ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; DCD, developmental coordination disorder; ESSENCE, early symptomatic syndromes eliciting neurodevelopmental clinical examinations; LD, learning difficulty. Population without seizures (n = 25,296). (The color version of this figure is available in the online edition.)

Association between epilepsy or febrile seizure and ESSENCE

ORs for ESSENCE in epilepsy, febrile seizures and febrile seizures after adjusting for epilepsy based on register diagnosis are shown in Table 2.

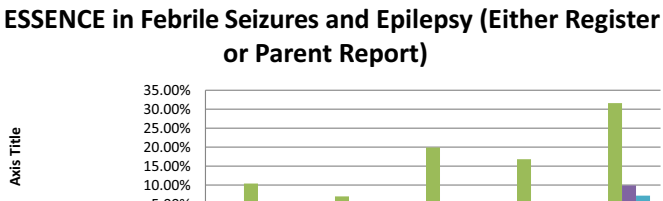
Having either febrile seizures or epilepsy was significantly associated with all ESSENCE. After adjusting for the presence of epilepsy, having febrile seizures was independently associated with ASD, DCD, and LD, but fell short of adjusted significance for ADHD ($P = 0.134$).

The ORs for ESSENCE in parent-reported epilepsy and parent-reported febrile seizures are given in Supplementary Table 3. Having either parent-reported febrile seizures or parent-reported epilepsy was significantly associated with all ESSENCE. After adjusting for parent-reported epilepsy, a significant association remained between parent-reported febrile seizures and all ESSENCE. The associations between parent-reported febrile seizures and ESSENCE remained significant after adjusting for epilepsy.



	ASD	ADHD	DCD	LD	Any ESSENCE
Population	1.00%	2.00%	1.70%	1.60%	4.50%
Population without seizures	1.10%	2.00%	1.80%	1.60%	4.60%
Epilepsy	13.70%	9.40%	26.70%	23.70%	43.80%
Febrile seizures	3.30%	4.10%	5.10%	2.90%	8.60%
Febrile seizures only	2.70%	3.50%	4.60%	2.30%	7.30%

FIGURE 3.
Prevalence of ESSENCE in febrile seizures and epilepsy (both register and parent-reported diagnosis). ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; DCD, developmental coordination disorder; ESSENCE, early symptomatic syndromes eliciting neurodevelopmental clinical examinations; LD, learning difficulty. Population without seizures (n = 27,028). (The color version of this figure is available in the online edition.)



	ASD	ADHD	DCD	LD	Any ESSENCE
Population	1.00%	2.00%	1.70%	1.60%	4.50%
Population without seizures	0.90%	1.90%	1.50%	1.40%	4.20%
Epilepsy	10.40%	7.00%	19.90%	16.80%	31.60%
Febrile seizures	3.20%	4.10%	5.00%	4.40%	9.90%
Febrile seizures only	2.10%	3.70%	3.20%	2.40%	7.20%

FIGURE 4.
Prevalence of ESSENCE in febrile seizures and epilepsy (either register or parent-reported diagnosis). ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; DCD, developmental coordination disorder; ESSENCE, early symptomatic syndromes eliciting neurodevelopmental clinical examinations; LD, learning difficulty. Population without seizures (n = 25,002). (The color version of this figure is available in the online edition.)

Relationship between age of diagnosis and ESSENCE in febrile seizures and epilepsy

Table 3 shows factors significantly ($P < 0.05$) associated with ESSENCE in the epilepsy and febrile seizure group. The complete results of univariable and multivariable analysis are given in Supplementary Table 4.

In the epilepsy group, earlier age of diagnosis was significantly associated with ASD, LD, and DCD, any ESSENCE but not ADHD. Male gender was associated with an increased risk for DCD, ADHD any ESSENCE but not LD or ASD. After adjustment for multiple comparisons (α level of adjustment was $P < 0.01$), earlier age of diagnosis remained significantly associated with LD, DCD any ESSENCE and male gender remained significantly associated with any ESSENCE.

In the febrile seizure group, the presence of epilepsy was associated with an increased risk of all ESSENCE with the exception of ADHD. These significant associations remained after the multivariable analyses.

Discussion

This study provides population-based data from a large sample of twins on the prevalence of ESSENCE using a well-validated parent interview relating to children with a history of epilepsy and children with a history of febrile seizures. There was an increased rate of all ESSENCE disorders in childhood epilepsy confirming previous findings. The finding of an association between febrile seizures and all ESSENCE is novel and possibly of particular importance.

The significant association between a history of febrile seizures and the presence of ESSENCE is at odds with some previous studies, which have suggested that febrile seizures are benign in terms of neurodevelopmental outcome[9,10] and

TABLE 2.
Odds Ratios (OR) for ESSENCE in Register Diagnosis of Febrile Seizures and Epilepsy and for Febrile Seizures After Adjusting for Epilepsy

Group	ASD	ADHD	DCD	LD	Any ESSENCE
Epilepsy	12.2 (95% CI 8.0-18.4), $P < 0.001$	3.9 (95% CI 2.4-6.2), $P < 0.001$	15.0 (95% CI 11.0-20.6), $P < 0.001$	14.1 (95% CI 10.2-19.6), $P < 0.001$	10.4 (95% CI 8.0-13.6), $P < 0.001$
Febrile seizure	4.4 (95% CI 2.8-7.0), $P < 0.001$	1.9 (95% CI 1.2-3.0), $P = 0.014$	4.6 (95% CI 3.3-6.6), $P < 0.001$	3.7 (95% CI 2.5-5.5), $P < 0.001$	2.8 (95% CI 2.1-3.7), $P < 0.001$
Febrile seizures (adjusted for epilepsy)	2.5 (95% CI 1.5-4.1), $P < 0.001$	1.5 (95% CI 0.9-2.4), $P = 0.134$	2.4 (95% CI 1.6-3.6), $P < 0.001$	1.8 (95% CI 1.2-2.9), $P = 0.009$	1.8 (95% CI 1.3-2.4), $P < 0.001$

Abbreviations:
ADHD = Attention-deficit/hyperactivity disorder
ASD = Autism spectrum disorder
CI = Confidence interval
DCD = Developmental coordination disorder
ESSENCE = Early symptomatic syndromes eliciting neurodevelopmental clinical examinations
LD = Learning difficulty

behavior.[26] Differences between our results and those of previous studies may stem from the lack of well-validated interviews or the failure to exclude children with pre-existing brain abnormalities in older studies.[9,10] The significant association between prior febrile seizures and the presence of ASD has not been previously described. The association was found even in those with a history of febrile seizures who did not have epilepsy. The increase in the rate of ADHD in febrile seizures has been noted in a nationwide study in Taiwan,[11] and the presence of febrile seizures had been suggested as a risk factor for minimal brain dysfunction, a "forerunner" of the current category of ADHD.[27] Most population-based studies have not found an increased association between febrile seizures and LD.[26] However, it has been reported that febrile seizures and prolonged febrile seizures are associated with an increased risk for expressive language delay,[26] memory difficulties, and global developmental difficulties.[12,13] The significant association between motor coordination problems and febrile seizures has not been previously noted.

The increased occurrence of ESSENCE in childhood epilepsy has been documented before. With respect to ASD, Reilly et al.[14] reported that 21% of 85 children with current epilepsy met DSM-IV criteria for ASD in a population-based sample, whereas Russ et al.[28] reported that 16% of 977 children with a lifetime diagnosis of epilepsy had ASD based on parental report in a nationally representative sample. The prevalence of ADHD in the present study (7%), although significantly higher than the prevalence in the total population of twins (2%), is lower than the reported prevalence in other studies that have focused on ADHD in epilepsy.[14] One possible reason for this is the choice to use a cutoff with high specificity and lower sensitivity to robustly identify clinical proxies for ADHD. Furthermore, the prevalence of ADHD in the total twin population (2%) is somewhat lower than reported from other

TABLE 3.
Factors Significantly Associated With ESSENCE in Epilepsy and Febrile Seizures

ESSENCE	Factors	Univariable (OR 95% CI), *P* value	Multivariable (OR 95% CI), *P* value
Epilepsy			
ASD	Age of diagnosis	2.6 (1.5-4.4), 0.001	2.6 (1.1-6.0), 0.027
ADHD	Gender	3.3 (1.1-10.2), 0.040	3.3 (1.1-10.3), 0.039
LD	Age of diagnosis	5.1 (2.4-10.7), <0.001	5.1 (2.4-10.8), <0.001
DCD	Gender	2.8 (1.1-4.1), 0.019	2.2 (1.1-4.3), 0.017
	Age of diagnosis	2.8 (1.5-5.2), 0.002	2.8 (1.5-5.4), 0.001
Any ESSENCE	Gender	2.5 (1.4-4.3) 0.001	2.6 (1.5-4.6), 0.001
	Age of diagnosis	2.6 (1.5-4.4), <0.001	2.7 (1.6-4.8), <0.001
Febrile seizures			
ASD	Epilepsy	3.8 (1.5-9.8), 0.006	4.0 (1.5-10.8), 0.005
ADHD	N/A	N/A	N/A
LD	Epilepsy	17.7 (7.5-41.6), <0.001	18.3 (7.6-44.3), <0.001
DCD	Epilepsy	7.6 (3.7-15.5), <0.001	8.0 (3.8-16.9), <0.001
Any ESSENCE	Epilepsy	9.4 (5.0-17.6), <0.001	10.3 (5.3-19), <0.001

Abbreviations:
ADHD = Attention-deficit/hyperactivity disorder
ASD = Autism spectrum disorder
CI = Confidence interval
DCD = Developmental motor coordination
ESSENCE = Early symptomatic syndromes eliciting neurodevelopmental clinical examinations
LD = Learning difficulty
N/A = Not applicable as not significant at $P < 0.05$ level
OR = Odds ratio

epidemiologic studies.[29] The finding of an association between epilepsy and LD is in line with previous studies.[15,16] The relationship between epilepsy and DCD is relatively unexplored although one previous population-based study suggests that children with epilepsy often have problems with motor coordination.[14]

Earlier age of diagnosis was significantly associated with an increased rate of (ESSENCE except for ADHD) in epilepsy but not in febrile seizures. The association between early onset epileptic seizures and cognitive impairment has been well established.[14] In the present study, earlier age of diagnosis was associated with an increase in the prevalence ASD. Although this relationship was not noted in another population-based study,[14] a link between the presence of ID in epilepsy and increase in ASD was noted.[14] This suggests that the presence of ID/LD mediates the relationship between ASD and epilepsy. A previous study suggested that DCD, based on clinical diagnosis, was not associated with early onset seizures but that parent-reported DCD symptoms were associated with early onset seizures[30] suggesting parent and clinical reports may differ. ADHD was not associated with age of onset in epilepsy as has been noted in previous studies.[14,31] Significant relationships between age of diagnosis and ESSENCE were not noted at all in the febrile seizure group suggesting that the age of occurrence of febrile seizure is not a significant factor with regard to the presence of ESSENCE.

Limitations

Data from the Swedish NPR were used in determining the diagnosis of epilepsy and febrile seizures. Validation studies of these diagnoses are needed. It is possible that some diagnoses of febrile seizures were missed as the NPR did not include outpatient data until 2001. However, there was not a significant difference between the proportion of children born before 2001 or after with a febrile seizure register diagnosis. The level of agreement between register diagnosis of epilepsy and parent-reported diagnosis of epilepsy was relatively high. The level of agreement between register diagnosis of febrile seizures and parent-reported diagnosis of febrile seizures was somewhat lower, but 55% of the children with a register diagnosis of febrile seizures also had a parent-reported diagnosis of febrile seizures. Nevertheless, there was an increase in ESSENCE in both those with register febrile seizures and parent-reported febrile seizures. Regarding febrile seizures, we suggest that parents' information may be more valid compared with register data. Not all parents have sought medical care at an acute or emergency department for their child, but very likely they will remember the frightening febrile seizure episode.

The coverage of the constructs of LD and DCD was much more limited than for ADHD and ASD and may thus be considered less valid. ESSENCE diagnoses were based on parent report and not on child observation or assessment (which is rarely feasible in large-scale epidemiologic studies). In addition, it is possible that a part of the association between febrile seizures, epilepsy and ESSENCE might stem from central nervous system malformations. However, given the prevalence of these conditions we believe that, if anything, they would explain only a very small part of the association.

It was beyond the scope of this article to consider a range of clinical factors which may be associated with ESSENCE in epilepsy and febrile seizures, including seizure characteristics (i.e., generalized, focal, duration, frequency), presence of pre-existing brain abnormalities or etiology, and antiepileptic treatment.

Conclusions

In children who have a history of epilepsy or febrile seizures there is a strong association with ESSENCE. This association does not mean that febrile seizures cause ESSENCE, but rather that febrile seizures should be interpreted as a possible coexisting condition in the context of other ESSENCE disorders and problems. Our results suggest that febrile seizures may be one expression of, or a first presenting marker, of ESSENCE. The presence of epilepsy in those with febrile seizures accounts for some, but definitely not all this association. Therefore all children with epilepsy and all children with febrile seizures need to be screened for ESSENCE. This screening could be done by using the short ESSENCE—Questionnaire (ESSENCE—Q), freely available at www.gnc.gu.se, or other screening questionnaires aimed at detecting developmental disorders in children.

In future research there will be a need to explore which children with febrile seizures may be at increased risk for ESSENCE. The role of pre-existing brain abnormalities and the nature of the febrile events need to be considered.

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Appendix

SUPPLEMENTARY TABLE 1.
Prevalence of Parent-Reported Epilepsy and Febrile Seizures in CATSS

Group	n (M/F)	%
Epilepsy	209 (115/94)	0.8
Febrile seizures	832 (479/353)	3.2
Epilepsy alone	181 (95/86)	0.7
Febrile seizures alone	804 (459/345)	3.0
Both epilepsy and febrile seizures	28 (20/8)	0.1
No epilepsy or febrile seizures	25,316 (12,823/12,493)	93.4
Missing*	1537	5.5
Total population	27092 (13,782/13,310)	100

Abbreviation:
CATSS = Child and Adolescent Twin Study in Sweden
* Parents did not respond to indicate whether child had ever had febrile seizures or epilepsy.

SUPPLEMENTARY TABLE 2.
Age Distribution of Diagnosis in (A) Febrile Seizures and (B) Epilepsy on National Patient Register

Age at First Diagnosis (years)	n
(A) Febrile seizures	
0	**72**
1	**191**
2	**107**
3	**65**
4	**32**
5	**25**
6	20
7	23
8	22
9	16
10	10
11	16
12	10
13	7
14	17
15	16
16	6
17	5
18	6
Total	666
(B) Epilepsy	
0	27
1	18
2	18
3	22
4	18
5	23
6	13
7	15
8	26
9	20
10	15
11	19
12	4
13	11
14	8
15	10
16	3
17	3
18	4
Total	277

Only those with a diagnosis of febrile seizures before age 6 years were considered to have febrile seizures (n = 492, 74% of total) in the current study (see bold values in table).

SUPPLEMENTARY TABLE 3.
Odds Ratios for ESSENCE in Febrile Seizures After Adjusting for Epilepsy-Based Parent-Reported Diagnosis

	ASD	ADHD	DCD	LD	Any ESSENCE
Febrile seizures (adjusting for epilepsy)	2.1 (95% CI 1.3-3.3), $P = 0.002$	2·1 (95% CI 1.5-3.0), $P < 0.001$	1.7 (95% CI 1.2-2·0.6), $P = 0.006$	1.6 (95% CI 1.1-2.4), $P = 0.021$	1.7 (95% CI 1.3-2.2), $P < 0.001$

Abbreviations:
ADHD = Attention-deficit/hyperactivity disorder
ASD = Autism spectrum disorder
CI = Confidence interval
DCD = Developmental coordination disorder
ESSENCE = Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations
LD = Learning difficulty

SUPPLEMENTARY TABLE 4.
Univariable and Multivariable Analysis of ESSENCE Disorders in (A) Epilepsy and (B) Febrile Seizures (Register Data)

ESSENCE	Factors	Univariable (OR 95% CI), *P* Value	Multivariable (OR 95% CI), *P* Value
(A) Factors significantly associated with ESSENCE disorders in epilepsy			
ASD	Gender	2.1 (0.9-5.0), 0.089	2.1 (0.9-5.0), 0.085
	Age of onset	2.6 (1.5-4.4), 0.001	2.6 (1.1-6.0), 0.027
ADHD	Gender	3.3 (1.1-10.2), 0.040	3.3 (1.1-10.3), 0.039
	Age of diagnosis	1.3 (0.5-3.2), 0.617	1.3 (0.5-3.6), 0.581
LD	Gender	1.5 (0.8-2.9), 0.188	1.6 (0.8-3.1), 0.168
	Age of diagnosis	5.1 (2.4-10.7), <0.001	5.1 (2.4-10.8), <0.001
DCD	Gender	2.8 (1.1-4.1), 0.019	2.2 (1.1-4.3), 0.017
	Age of diagnosis	2.8 (1.5-5.2), 0.002	2.8 (1.5-5.4), 0.001
Any ESSENCE	Gender	2.5 (1.4-4.3), 0.001	2.6 (1.5-4.6), 0.001
	Age of diagnosis	2.6 (1.5-4.4), <0.001	2.7 (1.6-4.8), <0.001
(B) Factors significantly associated with essence disorders in febrile seizures (register data)			
Autism spectrum disorder	Gender	1.4 (0.6-3.3), 0.501	1.4 (0.6-3.6), 0.435
	Age of diagnosis	1.0 (0.4-2.5), 0.932	1.3 (0.5-3.0), 0.679
	Epilepsy	3.8 (1.5-9.8), 0.006	4.0 (1.5-10.8), 0.005
ADHD	Gender	2.2 (0.8-6.3), 0.138	2.3 (0.8-6.5), 0.123
	Age of diagnosis	1.8 (0.6-4.8), 0.253	2.0 (0.7-5.4), 0.2195
	Epilepsy	1.4 (0.4-5.0), 0.598	1.7 (0.5-6.4), 0.411
LD	Gender	1.0 (0.5-2.3), 0.926	1.1 (0.5-2.8), 0.690
	Age of diagnosis	0.7 (0.3-1.4), 0.336	1.1 (0.5-2.7), 0.780
	Epilepsy	17.7 (7.5-41.6), <0.001	18.3 (7.6-44.3), <0.001
DCD	Gender	1.5 (0.7-3.1), 0.252	1.7 (0.8-3.5), 0.163
	Age of diagnosis	0.7 (3.9-1.5), 0.436	1.1 (0.5-2.2), 0.849
	Epilepsy	7.6 (3.7-15.5), <0.001	8.0 (3.8-16.9), <0.001
Any ESSENCE	Gender	1.4 (0.7-2.4), 0.284	1.6 (0.8-2.8), 0.152
	Age of diagnosis	0.8 (0.5-1.4), 0.501	1.2 (0.6-2.3), 0.486
	Epilepsy	9.4 (5.0-17.6), <0.001	10.3 (5.3-19), <0.001

Abbreviations:
ADHD = Attention-deficit/hyperactivity disorder
ASD = Autism spectrum disorder
CI = Confidence interval
DCD = Developmental coordination disorder
ESSENCE = Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations
LD = Learning difficulty
OR = Odds ratio