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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

Christopher Gillberg MD, PhD [a,b,c], Sebastian Lundström PhD [a,d], Elisabeth Fernell MD, PhD [a,*], Gill Nilsson MD [a], Brian Neville MD [a,b,c]

[a] *Gillberg Neuropsychiatry Centre, University of Gothenburg, Gothenburg, Sweden*
[b] *Research Department, Young Epilepsy, Surrey, UK*
[c] *Institute of Child Health, University College London, London, UK*
[d] *Centre for Ethics, Law and Mental Health, University of Gothenburg, Gothenburg, Sweden*

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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* Communications should be addressed to: Dr. Fernell; Gillberg Neuropsychiatry Centre; University of Gothenburg; Kungsgatan 12; 411 19 Gothenburg, Sweden.
E-mail address: elisabeth.fernell@gnc.gu.se

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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