INTRODUCTION

The prevalence of febrile seizures (FS) varies between 2% and 5% during the first five years of life.1–3 FS are usually categorized into complex and simple FS: complex FS are focal, prolonged (lasting more than 15 min) or recur within 24 h during the same febrile illness. All other FS are simple.1

1 | INTRODUCTION

The behavioral and cognitive outcomes of children with FS have been the subject of many studies, and aspects related to type and duration of FS have been analyzed. Visser et al.4 reported that children with recurrent FS might be at risk for delayed language development. In another study, children with a history of FS had significantly lower results on a non-verbal intelligence test at the age of 6–9 years, compared to healthy controls, and children with prolonged FS had...
Developmental Language Disorder (DLD) and Tourette syndrome—comorbid disorders and includes disorders such as ADHD, ASD, DCD, ID, text, refers to the total group of neurodevelopmental/neuropsychiatric disorders or problems, characterized by major cognitive and/or behavioral problems.

In a Swedish study assessing children, there was an increased risk of developmental coordination disorder (DCD), autism spectrum disorder (ASD) and intellectual disability (ID) at age 9 or 12 in children with a history of FS.7 In a previous study, we found that one-third of children with a history of FS had a neurodevelopmental disorder or developmental problems with for example attention, hyperactivity and behavior at the age of 4–5 years.8

On the other hand, some studies have not demonstrated associations between FS and academic performance, attention problems or behavior in children with recurrent FS.9,10 Ellenberg and Nelson11 studied 431 children who experienced FS, types not specified, and observed no significant difference in their learning compared with sibling controls, except in those children who had neurological abnormalities before their first seizure. In a similar study, 303 children with FS were compared with a control group: children with FS performed as well as the controls in terms of academic progress, intellectual functioning and behavior. However, a greater proportion of children with FS onset in the first year of life was receiving or had been considered for special education at school. There were no differences between children with single vs recurrent or simple vs complex FS.12

The common coexistence and overlap of various neurodevelopmental disorders are now increasingly referred to ESSENCE (Early Symptomatic Syndromes Eliciting Neuropsychiatric/Neurodevelopmental Clinical Examination).13 ESSENCE, in this context, refers to the total group of neurodevelopmental/neuropsychiatric disorders and includes disorders such as ADHD, ASD, DCD, ID, Developmental Language Disorder (DLD) and Tourette syndrome—all characterized by major cognitive and/or behavioral problems.

This study is a follow-up of a large cohort of children with a history of FS who had been assessed clinically with regard to ESSENCE disorders or problems at the age of 4–5 years. The aim was to estimate the rate of developmental disorders or problems, referred to as ESSENCE in the same cohort at age 9–10 years.

## 2 METHODS

### 2.1 Study population

The study population has been described in earlier studies3,8,14 and consisted of all 4-year-old children, born between July 1, 2008, and June 30, 2009, and living in the city of Gothenburg in 2012 and 2013 (N = 6076). A questionnaire screening for any type of seizures, including FS, was distributed to parents at the Child Health Care Centers (CHCs) in Gothenburg when the children were 4 years of age. The response rate was 71%. In all, 161 children had a history of FS, corresponding to a prevalence of 3.7%. Four of these had developed epilepsy by the time they were 4 years and were excluded from further analyses.3

### 2.2 Study participants

Out of the 157 children with a history of FS, 73 (41 boys, 32 girls) participated in a clinical assessment when they were 4–5 years old. The results from this study have been described in earlier papers.8,14 Five years later, the parents of these 73 children were contacted by letter and then by telephone to ask them to participate in a telephone interview.

Parents of 54 children (31 boys, 23 girls) accepted to participate. Mean age of the children at that time was 9.5 years.

The 19 (10 boys, 9 girls) families who chose not to participate had different reasons: parents of two children described child related reasons for not participating; parents of four children were not native Swedish speaking and had problems with the Swedish language. Three did not give a reason, four did not respond at the booked telephone call, and six could not be reached.

With regard to comparison group, please see section on Method.

### 2.3 The autism-tics, ADHD and other comorbidities (A-TAC) outcome measure

A parent interview, the Autism-Tics, ADHD and other comorbidities (A-TAC),15–18 was performed by a market research center. The A-TAC is a fully structured screening interview that has been designed to be used by laymen over the telephone. The interview was conducted with one of the child’s parents. The A-TAC focuses on almost all common child and adolescent psychiatric problems. It has been validated against exhaustive multidisciplinary clinical diagnoses in cross-sectional studies,15,16 and longitudinal studies,17 as well as in
population-based twin samples against National Patient Register diagnoses.\textsuperscript{18} It has been found to be a sensitive tool to screen for autism, ADHD, tics, LD and DCD with good–excellent test–retest values.\textsuperscript{19}

The response categories in the A-TAC interview are: “No” scored as 0, “Yes, to some extent” scored as 0.5 and “Yes” scored as 1. Autism, ADHD, Learning Disorder (LD) and DCD have two cutoffs; “high” which is a proxy for clinical diagnosis with moderate sensitive and high specificity, and “low” which is a broad screening level with high sensitivity but moderate specificity, designed to capture pronounced subthreshold traits that can be taken as a proxy for a subclinical disorder. The different diagnostic domains have different levels for low and high cutoffs. For example, a low cutoff for ADHD corresponds to a score of 6, and a high cutoff to a score of 12.5.\textsuperscript{16,17}

2.4 | Comprehensive outcome measure

The comprehensive outcome variable was based on data from two occasions; we combined neurodevelopmental data from (1) clinical assessment at preschool age and (2) A-TAC interview data at school age. (1) had been performed by a neuropediatrician and a psychologist when the children were 4–5 years old. At that time, the psychologist performed a cognitive test. The neuropediatrician collected medical and neurodevelopmental data, parental interviews, partly through rating scales answered by parents and an examination of the child. The neuropediatrician also carried out a motor test of the child. (2) The A-TAC parental interview was performed when the children were 9-10 years old.

2.5 | Medical records reviewed

In addition to clinical data from the 4–5 years assessment and the A-TAC interview, available child psychiatric and pediatric records were reviewed to find out whether any child had developed epilepsy after the age of 4–5 years.

2.6 | Definition of ESSENCE in the present study

ESSENCE was defined in the following way in the context of the present study: either (1) a diagnosis of ADHD, autism, DCD or LD according to clinical assessment at age 4–5 years, or (2) a diagnosis of any of the four named disorders in the medical records at any age before 10 years, or (3) a subthreshold diagnosis of any of the four disorders at clinical assessment at age 4–5 years, or (4) high- or low-level cutoff scores on A-TAC for any of the four disorders at age 9 years.

2.7 | Comparison data

In order to compare results obtained at A-TAC interviews with parents of children with FS, we used A-TAC results for low- and high cutoff levels for ADHD, autism, DCD and LD obtained in validation studies on clinical and twin samples (n = 25,762) of 9-year-old children.\textsuperscript{18} We are aware that some of the children in those validation studies are likely to have had FS in the past, and so the comparison group is not ideally suited for the purpose of this study but it is the best we could find.

2.8 | Statistical analyses

Statistical analyses were carried out using SPSS version 22 (SPSS). Frequencies, percentages, means and standard deviations were used to summarize demographic characteristics and contrasted against a Swedish comparison group of 25,782 9- and 12-year-olds whose parent completed the A-TAC.\textsuperscript{18} An alpha level of 0.05 was used for all analyses. Mann–Whitney U test for independent samples were used for continuous variables (means) and Chi-square tests for categorical one (prevalences of NDDs), all tests were two-tailed.

2.9 | Ethical approval

The study was approved by the Regional Ethics Committee in Gothenburg. Participating parents have provided written informed consent.

3 | RESULTS

3.1 | A-TAC interview results in the participating group

Of the 54 participating children (31 boys, 23 girls), 13 children (24%) (11 boys, 2 girls) had A-TAC symptom scores corresponding to either a low or a high cutoff level and 41 (76%) (20 boys, 21 girls) reached neither low nor high cutoff levels within the ADHD, autism, DCD or LD domains. In the comparison group, the corresponding rate of children with low or high cutoff scores was 24.4%.\textsuperscript{18}

The mean A-TAC ADHD score in the children with FS was 2.8 (SD 3.2) and in the comparison group,\textsuperscript{18} the mean score was 2.0 (SD 3.1) (p = 0.009).

3.2 | ESSENCE problems at the clinical preschool assessment by A-TAC results in participator and non-participator subgroups

In 15 of the 54 A-TAC participators (28%), there had been a diagnosis or indications of an ESSENCE problem at age 4–6 years. The corresponding rate among A-TAC non-participators was 53% (10/19), (p < .05). Of the 10 non-participants with preschool ESSENCE problems, four had LD combined with at least one additional disorder.
Further, among the A-TAC participators with a preschool ESSENCE problem, 13% (2/15) had had two or more ESSENCE problems at age 4-5 years, while the rate with two or more preschool ESSENCE problems among the A-TAC non-participators was 80% (8/10), ($p < .001$) (Figure 1).

### 3.3 A-TAC results in relation to previous ESSENCE diagnoses at age 4–5 years

Out of the 13 children (11 boys, 2 girls) with A-TAC indications of at least one of the studied ESSENCE domains (ADHD, autism, DCD or...
LD), eight had had preschool indications of ESSENCE. Of the five children with no identified ESSENCE problems at age 4–5 years, two had A-TAC indications of ADHD and one child had a neurologic motor disorder according to review of available child psychiatric and medical records.

3.4 | ESSENCE at 4–5 years and/or 9–10 years in the collapsed groups of A-TAC participators and non-participants in the A-TAC interview

Ten children, not participating in the A-TAC interview, had had ESSENCE disorders or problems at 4–5 years. In addition, 20 children participating in the A-TAC interview at age 9 either had ESSENCE disorders or problems at age 4–5 years but no problems according to the A-TAC interview (n = 7) or had ESSENCE disorders and problems according to the A-TAC interview (n = 13). Thus, 30 of the 73 children (41%) had ESSENCE disorders or problems at any of these assessments from preschool to school age (Table 1).

3.5 | Review of medical records

Of the 73 children in the original clinical study group, no child had developed epilepsy after the age of 4–5 years.

4 | DISCUSSION

In this prospective longitudinal study, 41% of children with FS had had major indications of ESSENCE either in preschool or school age (or both). This is much higher than rates expected in the general population. However, certain methodological problems preclude definite conclusions as to the magnitude of the overrepresentation as compared with the general population of children.

In the preschool part of the study, full clinical assessments were made by an expert pediatrician/child psychiatrist in all participating cases, meaning that parents completed questionnaires and were interviewed in detailed face-to-face interaction, and children were tested and neuropsychiatrically examined in detail. Standardized neuropsychological tests were used throughout. The results from this study in the children’s preschool years must be regarded as reliable and valid, and they reflect the “real” rate of ESSENCE in the group at that age.

In the school age part of the study, the A-TAC telephone interview was used (by a layman, which is “standard procedure”) to screen for “proxy” neurodevelopmental disorders/problems (ESSENCE) in children with a history of FS. This interview has been used in several validation studies and has shown good to excellent validity for a majority of the studied diagnoses. It has been suggested to be a suitable screening tool for a wide range of neurodevelopmental disorders at ages 9 and 12 years. However, the interview has been found to have particularly good validity for children with known diagnoses, possibly related to parents of diagnosed children being better at recognizing the symptoms that were asked about during the telephone interview.

It may be of importance here that the parents of children with FS were not formally clinically diagnosed with ADHD, autism, DCD or LD by the examining research doctor, only recommended to seek further advice or assessment in routine clinical settings, not specifically connected with the research team. According to the medical records review, some of the children with ESSENCE according to the preschool part of the project had not attended specialist clinics at the time of the follow-up study in school age.

In our A-TAC interview follow-up of 9–10-year-old children, with a history of FS, “only” 13/54 (24%) had scores indicating possible diagnoses of ADHD, autism, DCD or LD, which is a rate in line with the frequency reported in a large Swedish twin study that served as control group. Only in respect of ADHD was there a trend toward increased mean A-TAC scores as compared with general population data. However, another 17 children had had indications of ESSENCE at the clinical assessment 5 years earlier, meaning that in all, 30/73 (41%) had symptoms indicating ESSENCE either at age 4–5 or 9 years or both.

The group of children with FS participating in the A-TAC study at school age represented a group with a much lower rate of previously identified ESSENCE problems (28%) compared to the group of children who did not take part in the A-TAC interview study (53%) (p < .001). This finding of much higher ESSENCE/psychiatric problem rates in the non-participants is in accordance with other studies, demonstrating that it is more likely that the families with children with neurodevelopmental diagnoses/problems refrain from participation and thus that the rate of ESSENCE in the group of non-responders is higher.

As noted above, there was a trend in the A-TAC data that the group with FS had a higher mean ADHD score. This accords with previous results, for example from Denmark, where children with FS were found to have increased risk of ADHD. Also in a register study from Taiwan, an association between FS and ADHD was reported. The authors concluded that there may be a common genetic factor between FS and ADHD, a conclusion that may support that also FS may belong to the “ESSENCE family”. With regard to general cognitive abilities, a Danish study examined the association between FS and cognitive function in early adulthood. In general, no association was demonstrated, but a possible relation between cognitive function and FS was found in the youngest age group who had experienced FS before the age of one year. In our previous report, we had similar results, i.e., children with early onset of FS (before 12 months of age)—who often had recurrent FS—had lower full-scale, verbal and processing speed IQ than those who had later onset of FS.

The strengths of the study were the original inclusion of a large community-based cohort with FS, the prospective longitudinal design and well-validated instrument used for targeting neurodevelopmental problems.

An important limitation was the relatively high attrition rate, which included a high rate of possible ESSENCE problem cases.
Another major limitation was that no clinical assessment was combined with the A-TAC interview at 9–10 years. Also, the fact that the population from which comparison data were derived is very likely to have included a non-negligible proportion of individuals with a history of FS, and at least some small part of the failure to clearly separate the FS group A-TAC data from comparison A-TAC- data could be attributable to this.

**TABLE 1** ESSENCE diagnoses at clinical assessment at age 4–5 years and according to A-TAC interview at 9–10 years

| Sex | ESSENCE diagnoses at assessment at 4–5 years | ESSENCE diagnoses according the A-TAC interview at 9–10 years |
|-----|---------------------------------------------|-------------------------------------------------------------|
| 1   | m | ADHD, DCD | ADHD, LD |
| 2   | m | DCD | DCD (high), ADHD, LD, ASD |
| 3   | m | ADHD | DCD |
| 4   | m | ADHD, SLD | LD |
| 5   | m | ADHD | ADHD (high), ASD |
| 6   | m | ADHD, SLD | DCD |
| 7   | f | SLD | LD |
| 8   | f | DCD | DCD, LD |
| 9   | m | 0 | LD |
| 10  | m | 0 | DCD, ADHD |
| 11  | m | 0 | ADHD, LD |
| 12  | m | 0 | ADHD |
| 13  | m | 0 | DCD, ADHD, ASD |
| 14  | m | SLD | 0 |
| 15  | f | SLD | 0 |
| 16  | f | ADHD | 0 |
| 17  | f | SLD | 0 |
| 18  | m | ADHD | 0 |
| 19  | m | ADHD | 0 |
| 20  | m | ADHD | 0 |
| 21  | m | ID, ADHD, DCD | n.p. |
| 22  | m | ID, ADHD, DCD | n.p. |
| 23  | f | ID, ADHD, SLD | n.p. |
| 24  | f | ID, ASD | n.p. |
| 25  | f | ADHD, DCD | n.p. |
| 26  | m | ADHD, DCD | n.p. |
| 27  | m | ADHD, DCD | n.p. |
| 28  | m | ADHD, SLD | n.p. |
| 29  | f | ADHD | n.p. |
| 30  | m | ADHD | n.p. |

Abbreviations: ADHD, Attention-deficit/hyperactivity disorder; ASD, Autism spectrum disorder; DCD, Developmental coordination disorder; ID, Intellectual Disability; LD, Learning disorder; n.p., Not participating; ^4, ADHD Symptoms; SLD, Speech and language disorder.

Combining data from the clinical preschool age assessment and the A-TAC interview at age 9–10 years revealed a much higher than expected rate of ESSENCE problems in children with FS. Based on the group of clinically assessed children at age 4–5 years and on those who participated in the A-TAC interview, a total of 41% had symptoms indicating ESSENCE disorder or problems. This figure should be considered a minimum one given that non-participants in the A-TAC follow-up had had much higher ESSENCE rates at age 4–5 years than those whose parents participated in the follow-up at 9–10 years. Further follow-up studies (including clinical and national register) of this unique FS cohort will be important before definite conclusions can be drawn about the need for prospective neurodevelopmental follow-up of (possibly all) children with FS can be drawn. Nevertheless, already at this time, child health care providers should be made aware of a possible association between FS and neurodevelopmental problems, so that early assessment, diagnosis and psychoeducation/intervention might be implemented without long delays.

**5 | CONCLUSION**

Combining data from the clinical preschool age assessment and the A-TAC interview at age 9–10 years revealed a much higher than expected rate of ESSENCE problems in children with FS. Based on the group of clinically assessed children at age 4–5 years and on those who participated in the A-TAC interview, a total of 41% had symptoms indicating ESSENCE disorder or problems. This figure should be considered a minimum one given that non-participants in the A-TAC follow-up had had much higher ESSENCE rates at age 4–5 years than those whose parents participated in the follow-up at 9–10 years. Further follow-up studies (including clinical and national register) of this unique FS cohort will be important before definite conclusions can be drawn about the need for prospective neurodevelopmental follow-up of (possibly all) children with FS can be drawn. Nevertheless, already at this time, child health care providers should be made aware of a possible association between FS and neurodevelopmental problems, so that early assessment, diagnosis and psychoeducation/intervention might be implemented without long delays.
ACKNOWLEDGEMENTS

The authors are grateful to all children and parents participating in the study.

CONFLICT OF INTEREST

The authors have no conflict of interest.

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REFERENCES

1. Shinnar S, Glauser TA. Febrile seizures. J Child Neurol. 2002;17:44-52.
2. Steering committee on quality improvement and management, subcommittee on febrile seizures American academy of pediatrics. Febrile seizures: clinical practice guideline for the long-term management of the child with simple febrile seizures. Pediatrics. 2008;121:1281-1286.
3. Nilsson G, Fernell E, Arvidsson T, et al. Prevalence of febrile seizures, epilepsy, and other paroxysmal attacks in a swedish cohort of year-old children. Neuropediatrics. 2016;47:368-373.
4. Visser AM, Jaddoe VWV, Ghassabian A, et al. Febrile seizures and behavioural and cognitive outcomes in preschool children: the generation R study. Dev Med Child Neurol. 2012;54:1006-1011.
5. Kölfen W, Pehle K, Konig S. Is the long-term outcome of children following febrile convulsions favorable? Dev Med Child Neurol. 1998;40:667-671.
6. Bertelsen EN, Larsen JT, Petersen L, Christensen J, Dalgaard S. Childhood epilepsy, febrile seizures, and subsequent risk of ADHD. Pediatrics. 2016;138:e20154654.
7. Gillberg C, Lundström S, Fernell E, Nilsson G, Neville B. Febrile seizures and epilepsy: association with autism and other neurodevelopmental disorders in the child and adolescent twin study in Sweden. Pediatr Neurol. 2017;74:80-86.
8. Nilsson G, Westerlund J, Fernell E, et al. Neurodevelopmental problems should be considered in children with febrile seizures. Acta Paediatr. 2019;108:1507-1514.
9. Chang YC, Guo NW, Huang CC, Wang ST, Tsai JJ. Neurocognitive attention and behavior outcome of school-age children with a history of febrile convulsions: a population study. Epilepsia. 2000;41:412-420.
10. Sillanpää M, Suominen S, Rautava P, Aromaa M. Academic and social success in adolescents with previous febrile seizures. Seizure. 2011;20:326-330.
11. Ellenberg JH, Nelson KB. Febrile seizures and later intellectual performance. Arch Neurol. 1978;35:17-21.
12. Verity CM, Greenwood R, Golding J. Long-term intellectual and behavioral outcomes of children with febrile convulsions. New Engl J Med. 1998;338:1723-1728.
13. Gillberg C. The ESSENCE in child psychiatry: early symptomatic syndromes eliciting neurodevelopmental clinical examinations. Res Dev Disabil. 2010;31:1543-1551.
14. Billstedt E, Nilsson G, Leffler L, et al. Cognitive functioning in a representative cohort of preschool children with febrile seizures. Acta Paediatr. 2020;109:989-994.
15. Hansson SL, Svanström Röjvall A, Rastam M, et al. Psychiatric telephone interview with parents for screening of childhood autism-tics, attention-deficit hyperactivity disorder and other comorbidities (A-TAC): preliminary reliability and validity. Br J Psychiatry. 2005;187:62-67.
16. Larson T, Anckarsäter H, Gillberg C, et al. The autism-tics, AD/HD and other comorbidities inventory (A-TAC): further validation of a telephone interview for epidemiological research. BMC Psychiatry. 2010;10:1.
17. Larson T, Lundström S, Nilsson T, et al. Predictive properties of the A-TAC inventory when screening for childhood-onset neurodevelopmental problems in a population-based sample. BMC Psychiatry. 2013;13:233.
18. Mårland C, Lichtenstein P, Degl'Innocenti A, et al. The Autism-Tics, ADHD and other Comorbidities inventory (A-TAC): previous and predictive validity. BMC Psychiatry. 2017;17:403.
19. Larson T, Kerekes N, Selinus EN, et al. Reliability of autism-tics, AD/HD, and other comorbidities (A-TAC) inventory in a test-retest design. Psychol Rep. 2014;114:93-103.
20. Anckarsäter H, Larson T, Hansson SL, et al. Child neurodevelopmental and behavioural problems are intercorrelated and dimensionally distributed in the general population. Open Psychiatr J. 2008;2:5-11.
21. Stormark KM, Heiervang E, Heimann M, Lundervold A, Gillberg C. Predicting nonresponse bias from teacher ratings of mental health problems in primary school children. J Abnorm Child Psychol. 2008;36:411-419.
22. Ku YC, Muo CH, Ku CS, et al. Risk of subsequent attention deficit-hyperactivity disorder in children with febrile seizures. Arch Dis Child. 2014;99:322-326.
23. Nørgaard M, Ehrenstein V, Mahon BE, et al. Febrile seizures and cognitive functioning in young adult life: a prevalence study in Danish conscripts. J Pediatr. 2009;155:404-409.

How to cite this article: Nilsson G, Lundström S, Fernell E, Gillberg C. Neurodevelopmental problems in children with febrile seizures followed to young school age: A prospective longitudinal community-based study in Sweden. Acta Paediatr. 2022;111:586–592. doi:10.1111/apa.16171