Febrile seizures and associated neurodevelopmental disorders

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ABSTRACT

Background: Febrile seizures (FS) are common in young children. There is a lack of knowledge about possible associations between FS and the child's cognitive and behavioural development. **Aim:** Gain further insight into the area of coexisting neurodevelopmental problems in children with FS. **Methods:** Parents of 4,290 of the total population of 6,076 children (71%) born between July 1, 2008 and June 30, 2009 in the city of Gothenburg, Sweden, completed a questionnaire in conjunction with their child´s 4-year health surveillance at the Child Healthcare Centre about any type of seizures that their child might have had. Children with reported FS were invited to a clinical study and parents of 73 children (41 boys, 32 girls) of the total group of 157 children with FS (46%) accepted participation. The methods included a neuropaediatric assessment, the Movement ABC and parental questionnaires; the Five-to-Fifteen (FTF), Strengths and Difficulties Questionnaire (SDQ) and cognitive assessments including the Wechsler Preschool, Primary Scale of Intelligence-III (WPPSI-III). Hospital records were reviewed. Five years after the first clinical study, parents of the 73 children were again contacted and invited to a parental interview, using the Autism-Tics, ADHD and other Comorbidities inventory (A-TAC). Parents of 54 children (32 boys, 22 girls) consented to participating in the interview study. **Results:** Paroxysmal attacks were reported in 248 of the children (5.8%). FS had occurred in 157 children (3.7%), epilepsy in 16 (plus 6 children who were identified through the hospital registers) (0.5%) and other paroxysmal attacks in 75 children (1.7%). Thus, a total of 254 children were found to have any type of paroxysmal attacks (5.9%). When collapsing results from the clinical preschool study and the parental A-TAC interview when the children were 9-10 years, 41% of the children were shown to have or have had at least one neurodevelopmental disorder or definite neurodevelopmental problems, the most common were ADHD or ADHD symptoms. The cognitive assessments showed that children with early onset FS had lower full-scale, verbal and processing speed IQ compared to those with later onset of FS. **Conclusions:** Children with FS were found to have indications of a much increased rate of neuro-developmental disorders/problems compared to the general child population. This does not mean that FS *per se* are the cause of these other disorders but rather that FS, in some cases, may be a marker for possible neurodevelopmental problems. The results suggest that child health care professionals should consider the possibility of associated neurodevelopmental disorders/problems in children with a history of FS, and that this should be kept in mind also at school-age.

Keywords: febrile seizures, preschool children, prevalence, neurodevelopmental disorders, ESSENCE, attention-deficit/hyperactivity disorder, intellectual functioning, A-TAC
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SAMMANFATTNING PÅ SVENSKA

Feberkramper är epileptiska anfall som utlöses av feber hos vissa barn från 6 månaders ålder till 5 års ålder. Förekomsten har beräknats till ca 3-6%. För att anfallet ska kallas feberkramp krävs att det inte föreligger några samtidiga tecken på infektion i hjärna eller hjärnhinnor. Barnet ska heller inte ha haft något tidigare anfall utan feber. Epilepsi innebär upprepade anfall, minst två, som är oprovocerade utan någon uppenbar yttre orsak eller enstaka anfall då risken för ytterligare anfall bedöms vara stor. Epilepsi är inte lika vanligt som feberkramper och uppträder hos cirka 0.5% av alla barn. Feberkramper delas in i två grupper, enkla och komplexa. Enkla feberkramper är vanligast. De är symmetriska, och varar kortare tid än 15 minuter. Komplexa feberkramper är fokala och/eller varar längre än 15 minuter. Feberkramper upplevs ofta skrämmande för föräldrar.

Syftet med denna avhandling var att undersöka olika typer av svårigheter/problem inom områdena generell begåvning och andra kognitiva funktioner, social förmåga, språk, motorik, koncentration/uppmärksamhet och beteende i form av aktivitetsreglering samt impulskontroll i en populationsbaserad grupp av förskolebarn som haft feberkramper och att följa denna grupp från förskoleåldern till skolåldern. Barn födda 1 juli 2008 till och med 30 juni 2009, rekryterades till studien i samband med deras 4-årskontroll på Barnavårdscentraler i Göteborg, där deras föräldrar ombads besvara ett formulär med frågor om barnet haft någon form av anfall, inklusive feberkramp.

Föräldrar till 4,290 av totalt 6,076 barn (71%) besvarade frågeformuläret. För 248 barn (5.8%) rapporterades någon form av anfall. Feberkramper rapporterades hos 161 barn. Fyra av dessa utvecklade epilepsi före 5 års ålder, varför feberkrampen tolkades som ett feberutlöst anfall och därmed en tidig manifestation av epilepsi. Antalet barn med feberkramper blev då 157 barn (3.7%). Förutom de fyra barnen med epilepsi som också haft feberutlösta anfall, rapporterades epilepsi hos 12 barn och hos ytterligare 6 barn i sjukhusregister. Totalt var det alltså 22 barn som hade epilepsi (0.5%). Andra paroxysmala attacker (bland annat affektanfall) rapporterades hos 75 barn (1.7%). Detta innebär en total prevalens av paroxysmala attacker på nästan 6%, där den största gruppen var feberkramper.

Föräldrar till samtliga 157 barn med feberkramper inbjöds att delta i den kliniska studien som innefattade bedömningar av barnneurolog, frågeformulär till föräldrar avseende barnets emotionella, beteendemässiga och kognitiva profil

med: Fem Till Femton (FTF) och Strengths and Difficulties Questionnaire (SDQ) och en bedömning av psykolog med de kognitiva testen (WIPPSI-III), Leiter International Performance Scale och NEPSY. Av 157 barn deltog 73 barn (41 pojkar, 32 flickor) (46%) och deras föräldrar.

Fem år efter den kliniska studien kontaktades föräldrarna till de 73 barnen, som deltagit i ursprungsstudien, med förfrågan om att delta i en uppföljande telefonintervju, "The Autism - Tics, ADHD and other comorbidities" (A-TAC). Barnen var då 9-10 år gamla. I intervjun ställdes frågor om barnet har symtom/svårigheter inom områden social förmåga, koncentration/ uppmärksamhet, motorik, inlärning och beteende. Föräldrar till 54 (32 pojkar, 22 flickor) av de 73 barnen deltog i intervjustudien.

En tredjedel av barnen, som deltog i den kliniska studien i förskoleåldern hade minst en utvecklingsneurologisk funktionsnedsättning enligt DSM-5, eller tydliga problem inom minst ett av områdena uppmärksamhet, aktivitetsreglering, beteende, tal och språk, allmän kognition eller motorisk funktion. Det framkom inga skillnader mellan barn som haft enkla, komplexa eller återkommande feberkramper. Barn med feberkramper under första levnadsåret och särskilt de med återkommande feberkramper hade lägre resultat avseende verbal IQ och kognitiv processhastighet, jämfört med de barn som haft en senare debut av feberkramp.

Vid den uppföljande telefonintervjun med föräldrar, då barnen var i skolåldern, skilde sig inte resultaten i deltagargruppen från en jämförelsegrupp. Det fanns dock en trend att ADHD-symtom var vanligare i gruppen med feberkramper. Vid undersökning i förskoleåldern hade barnen i bortfallsgruppen, dvs. de skolbarn vars föräldrar inte deltog i A-TAC intervjun, haft en mycket högre förekomst av utvecklingsneurologiska problem jämfört med de barn vars föräldrar deltog i intervjun. När resultat från både studien i förskoleålder och i skolålder slogs samman framkom att 41% uppfyllde kriterier för en utvecklingsneurologisk diagnos eller hade tydliga sådana symtom, vilket är en mycket högre andel än förväntat.

Frågan om samband mellan feberkramper hos barn och kognitiva/beteendemässiga svårigheter har hittills varit bristfälligt belyst. Resultaten från studierna i avhandlingen talar för att det kan föreligga ett samband, om än inte ett orsakssamband. Feberkramper kan vara en markör för samtidig förekomst av utvecklingsneurologiska funktionsnedsättningar eller

funktionsproblem, nu ofta sammanfattade med termen ESSENCE (Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations). Det talar för att det behövs riktlinjer för uppföljning av barn som har haft feberkramper inom barnhälsovård och barnsjukvård, för att kunna erbjuda tidiga insatser.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Nilsson, G., Fernell, E., Arvidsson, T., Neville, B., Olsson, I. & Gillberg, C. 2016. Prevalence of Febrile Seizures, Epilepsy, and Other Paroxysmal Attacks in a Swedish Cohort of 4-Year-Old Children. *Neuropediatrics,* 47, 368-73.

II. Nilsson, G., Westerlund, J., Fernell, E., Billstedt, E., Miniscalco, C., Arvidsson, T., Olsson, I. & Gillberg, C. 2019. Neurodevelopmental problems should be considered in children with febrile seizures. *Acta Paediatrica,* 108, 1507-14.

III. Billstedt, E., Nilsson, G., Leffler, L., Carlsson, L., Olsson, I., Fernell, E. & Gillberg C. 2019. Cognitive functioning in a representative cohort of preschool children with febrile seizures. *Acta Paediatrica* [Epub ahead of print].

IV. Nilsson, G., Lundström, S., Olsson, I., Fernell, E. & Gillberg, C. Febrile seizures from preschool to school; a prospective longitudinal community-based study. In manuscript

CONTENT

ABBREVIATIONS

AD/HD	Attention-Deficit/Hyperactivity Disorder
APA	American Psychiatric Association
ASD	Autism Spectrum Disorder
A-TAC	The Autism-Tics, ADHD and other comorbidities interview
BIF	Borderline Intellectual Functioning
CHC	Child Healthcare Centre
CNS	Central Nervous System
DCD	Developmental Coordination Disorder
DLD	Developmental Language Disorder
ESSENCE	Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations
FSE	Febrile Status Epilepticus
DSM	Diagnostic and Statistical Manual of Mental Disorders
FS	Febrile Seizures
FTF	Five to Fifteen Questionnaire
ID	Intellectual Disability
IQ	Intelligence Quotient
LD	Learning Disorder
NEPSY	NEuro PSYchological assessment
SDQ	Strengths and Difficulties Questionnaire
WPPSI-III	Wechsler Preschool and Primary Scale of Intelligence, 3rd Edition

1 INTRODUCTION

Febrile seizures (FS) or febrile convulsions are epileptic seizures with generalized tonic-clonic presentation. FS are usually benign and self-limiting, and antiepileptic treatment is not recommended (Steering Committee on Quality Improvement and Management, Subcommittee on Febrile Seizures 2008). The seizures are age dependent and are trigged by fever, usually >38.5°C in a child aged between 6 months and 5 years, with a peak incidence between 12 and 18 months (Hauser 1994, Camfield et al 2015). The maximum temperature rather than the speed of the temperature rise has been shown to be the most significant risk for a first FS (Scharawat et al 2016, Canpolat et al 2018). FS are slightly more common in boys than in girls (Forsgren et al 1990, Hwang et al 2015) and have a strong genetic predisposition (Veisani et al 2013). By definition, FS are not due to an intracranial infection or other definable causes and are not preceded by afebrile epileptic seizures (Shinnar et al 2002). Usually, FS resolve spontaneously but are often perceived as extremely dramatic and frightening for the parents (Kanemura et al 2013, Westin et al 2018).

1.1 FEBRILE SEIZURES SOME HISTORICAL NOTES

FS have been scientifically studied and mentioned in the literature since the 19th century (described in Livingstone 1947). In the 1930s, animal studies of the role of fever in FS focused on the age of the animal at the febrile episode and the rapidity with which the body temperature rose. It became evident that FS only existed in young but not in adult animals (Wegman 1939).

The distinction between FS and epilepsy has been discussed in the literature. It was formerly thought that FS was "epilepsy unmasked by fever" and thus an indication of epilepsy (Livingston 1947). Peterman stated that "a febrile seizure does not occur in a normal child" (Peterman 1952).

Over the past several decades there has been an evolution as to the meaning of the term. Some series, especially prior to the 1980s, did not exclude seizures with fever that may have been associated with an underlying neurologic disease such as meningitis, encephalitis or toxic encephalopathy (Van der Berg and Yerushalmy 1969). The prognosis of FS in the early literature was fairly pessimistic, due to the inclusion of symptomatic seizures (Wallace 1980). The modern viewpoint has been that the vast majority of FS, using a more strict definition, have a benign

outcome (Steering Committee on Quality Improvement and Management, Subcommittee on Febrile Seizures 2008, Leaffer et al 2013).

The definition of epilepsy as unprovoked, recurrent seizures excludes FS which are always provoked by fever (Berg and Shinnar 1994).

1.2 PREVALENCE

FS are the most common form of childhood seizures and the prevalence (or accumulated incidence) of FS varies in different parts of the world. The prevalence has been found to be stable over the years, occurring in 2-6% of children in Western Europe and North America (Verity et al 1985, Forsgren et al 1990, Sillanpää et al 2008, Vestergaard et al 2009). In certain populations (e.g. Japan, Guam) FS are even more common (8-14%). The reason for this geographical discrepancy remains unexplained, but may be related to genetic predisposition, environmental factors or both. Most studies report that boys are more likely to have FS. The risk of recurrence, once a child has had FS is not dependent on the sex of the child (Berg et al 1997, Hwang et al 2015).

1.3 TYPES OF FEBRILE SEIZURES

FS are usually classified into simple or complex. Complex FS are focal, prolonged (lasting more than 15 minutes), or recur within 24 hours during the same febrile illness. All other FS are classified as simple (Shinnar and Glauser 2002). The definitions of simple and complex FS are outlined in the International League Against Epilepsy (ILAE) classification of febrile seizures (FS; Steering Committee 2008) (Table 1). Simple FS are more common and account for about two thirds of all FS (Berg and Shinnar 1996). More recent studies have shown that simple FS account for about 80–85% of all FS (Leung et al 2018, Canpolat et al 2018).

Children with complex FS are often younger at their first seizure and are more likely to have associated developmental disorders (Hessdorffer et al 2011).

About one third of children with a first febrile seizure will experience at least one recurrence (Berg et al 1995, Pavlidou et al 2008, Graves et al 2012) and about 10% will have three or more FS (Fetvait 2008, Camfield and Camfield 2015). The main predictors for recurrence of FS are occurrence before one year of age, a positive family history of FS and a low degree of fever (Berg et al 1997, Shinnar and Glauser 2002).

Febrile status epilepticus (FSE) means continuous seizures or intermittent seizures, without the regain of consciousness, lasting for 30 minutes or longer (Shinnar et al 2008, Epstein et al 2012).

Table 1. International League Against Epilepsy (ILAE) classification of FS

	Simple FS (~75%)	Complex FS* (~25%)
Clinical presentation	Generalized, usually tonic-clonic seizures (clonic seizures are also possible) Symmetrical No other apparent neurologic disorders	Focal onset Pronounced on one side of the body Transient hemiparesis and speech impairment **FS are considered complex if at least one of the three criteria regarding clinical presentation are met**
Duration and frequency	< 15 min Maximum of one seizure within 24 h	> 15 min > one seizure within 24 h
Age	6 months to 5 years	More commonly outside the typical range of 6 months to 5 years
Postictal phase	Typically a quick return to normal. Confusion and drowsiness may be present for a short period of time. Prolonged drowsiness or deviated eyes may be a sign of other etiologies (e.g. meningitis or of ongoing seizure activity (see status epilepticus)	

1.4 FEBRILE SEIZURES AND EPILEPSY

Some children experience FS as their first manifestation of what will emerge as epilepsy, but it is not possible to predict with certainty which child will develop afebrile seizures (Berg and Shinnar 1994).

A new definition of epilepsy was published in 2014 (Fisher et al 2014). However, most epidemiological studies have been based on the old definition (Two or more epileptic seizures, unprovoked by an immediate identifiable cause).

Table 2. Definition of epilepsy (Fisher et al 2014)

Epilepsy is a disease of the brain defined by any of the following conditions
1. At least two unprovoked (or reflex) seizures occurring >24 h apart 2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60 %) 3. Diagnosis of an epilepsy syndrome
Epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no pharmacological therapy for epilepsy for the last 5 years.

Children with FS have an increased risk of later developing epilepsy. A risk of 7% up to the age of 25 years was reported by Annegers et al (1987), with a range from 2.4% among children with simple FS to 6 - 8% among children with complex FS. These figures can be compared with the prevalence of epilepsy in the general population (0.5%).

Previous neurodevelopmental abnormalities have been found to be risk factors that are associated both with FS and with the development of epilepsy after a first FS (Verity et al 1991).

Knowledge about comorbidity, i.e., coexisting developmental/ neuropsychiatric disorders, in children with epilepsy has increased and several studies have shown that epilepsy is very often combined with Attention-Deficit/Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD) and/or Intellectual Disability (ID) (Davis et al 2010, Reilly et al 2014, 2017, Åndell et al 2015). Comorbidities, such as ADHD, have been reported especially in early onset epilepsy (Davis et al 2010).

ADHD is more common in people with epilepsy than in the general population. It has been estimated that 12–39% of children with epilepsy also have ADHD (Verotti et al 2018).

A large register- and population-based study in Denmark found a strong association between epilepsy in childhood and FS and the subsequent development of ADHD, even after adjusting for socioeconomic and perinatal risk factors, and for a family history of epilepsy, FS, or psychiatric disorders (Berthelsen et al 2016).

Abnormal neurological development before the FS, the occurrences of FS among relatives and FSE represent important risk factors for the development of epilepsy after FS (Seinfeld et al 2016).

1.5 RISK FACTORS FOR FEBRILE SEIZURES

FS are age related, i.e. due to a susceptibility of the developing brain to the effects of fever (Sharawat et al 2016, Leung et al 2018). Besides age, the most common risk factors are high fever, viral infections and a family history of FS (Veisani et al 2013, Yousefichaijan et al 2014). The detailed mechanism of this increased susceptibility remains unclear. Earlier, the key factor was thought to be the rapidity of the rise of the fever (Livingstone et al 1947) but later data suggest that the most important factor is the child´s peak temperature (Berg et al 1995, Canpolat et al 2018).

Prenatal risk factors for FS include maternal smoking (Nelson et al 1990, Berg et al 1995) and a first-degree family history of FS (Forsgren et al 1991, Verity et al 1991, Bethune et al 1993, Berg et al 1995, Huang et al 1999). It might be of interest in this context that maternal smoking is also an indicator of maternal ADHD (Fuller-Thomson et al 2016). A genetic predisposition for FS has been recognized for a long time. Among first-degree relatives of children with FS, 10-20% will have or have had FS (Seinfeld et al 2016).

Perinatal risk factors such as low birth weight and preterm birth have also been found to be risk factors for a first FS (Verity et al 1991, Forsgren et al 1991, Bethune et al 1993).

Moreover, increased number of febrile illnesses (Huang et al 1999), day-care attendance (Bethune et al 1993) and temperature higher than 39.4º C (Berg et al 1995) are also reported to be risk factors of FS. Viral infections are commonly identified in association with FS, whereas bacterial infections are uncommon (Shah et al 2002).

Hippocampal abnormalities have been identified in children and families with FS and may be a link to genetic factors and to the development of future temporal lobe epilepsy (Fernandez et al 1998). In a study by Martinos et al (2012) children

with prolonged FS were found to have recognition memory impairment that was linked to a smaller hippocampal size.

1.6 CLINICAL ASPECTS OF FEBRILE SEIZURES

The initial assessment of children with FS must include a detailed history as regards the cause of fever, such as a central nervous system infection, and psychomotor development. A thorough physical examination should be carried out to find the underlying cause of the fever (Leung and Robson, 1991).

The condition may cause severe anxiety and even panic in parents who may be under the impression that their child might die during the seizure and/or develop brain damage if surviving (Kanemura et al 2013, Westin et al 2018).

Mostly, FS are benign and self-limiting, and, in general, antiepileptic treatment is not recommended. Previously oral diazepam was used at the onset of a febrile illness to prevent FS, but that is not a general recommendation today. Although antipyretics may improve the comfort of the child, they will not prevent the FS (Steering Committee on Quality Improvement and Management, Subcommittee on Febrile Seizures 2008).

An electroencephalogram (EEG) is not indicated after a febrile seizure but epileptiform discharges have been described to be a predictive risk factor for epilepsy (Wo et al 2013).

There is, to our knowledge, no regular recommendation regarding follow-up of children after a first FS. However, Gillberg and colleagues (2017) suggested that children with FS should be screened with a questionnaire, such as ESSENCE-Q (freely available at www.gnc.gu.se) or another screening questionnaire in order to identify potential developmental disorders.

1.7 COGNITIVE AND DEVELOPMENTAL OUTCOME IN CHILDREN WITH FEBRILE SEIZURES

The neurodevelopmental prognosis after FS has been reported to be good (Ellenberg and Nelson 1978, Verity et al 1985, Chang et al 2000

A population-based study by Chang et al (2000) reported that early childhood FS did not have adverse effects on behaviour, scholastic performance, and neurocognitive attention.

Ellenberg and Nelson (1978) compared children who had experienced FS with their siblings and found no differences with regard to full scale IQ, assessed with the Wechsler Intelligence Scales for children (WISC), or academic performance between the groups.

Verity et al (1985) compared children with simple or complex FS at age five years with their peers who had not had FS and found no differences between the groups regarding performance in simple intellectual tests – except in those children who had neurologic abnormalities before their first seizure.

Simple FS were also considered to have an excellent prognosis by the Steering Committee on Quality Improvement and Management, Subcommittee on Febrile Seizures (2008).

However, onset of FS before one year of age was a risk factor for deficits in memory function (Chang et al 2001).

A study of children with FS from low socioeconomic status communities (Leaffer et al 2013) concluded that FS do not imply an increased risk for poor developmental or behavioural outcome in the year after the first febrile seizure.

An increased risks of Developmental Coordination Disorder (DCD), autism, and Learning disorder (LD) at age 9 or 12 years were found in children with a history of FS (Gillberg et al 2017) in a Swedish population-based study of twins, using a well-validated parent interview relating to children with a history of epilepsy and children with a history of FS.

Several studies have reported a relation between complex FS and cognitive outcome. In one study, children with prolonged FS (n=80) had significantly lower nonverbal intelligence compared to children with simple FS and controls (Kölfen et al 1998). Moreover, children with multiple recurrences of FS performed poorer in all tests when compared to children with only one FS or with controls. Also, a population-based study from the Netherlands showed that recurrent FS were associated with an increased risk of delayed language development (Visser et al 2012). A review of some clinical follow-up studies of children with FS is presented in Table 3.

Table 3. Review of clinical follow-up studies of children with febrile seizure

Article	Study design	Study population	Methods	Results
Nelson & Ellenberg (1978)	Approximately 54,000 pregnant women participating in the National Institute of Neurological and Communicative Disorders and the Stroke Collaborative Perinatal Project (NCPP), between 1959 and 1966, received prenatal care and were delivered of their babies at one of 12 cooperating urban teaching hospitals	Medical histories which included questions about the occurrence of seizures were recorded to the age of seven years. Records from the physician or medical facility were reviewed for each medically attended seizure reported. There were 1,821 children who met the stated criteria for FS. Of these, 1,706 or 94% were followed up to the age of 7 years and formed the study sample.	The measure of intelligence was the full-scale IQ, Wechsler Intelligence Scales for Children, at 7 years of age.	There was no significant difference in their learning compared with sibling controls, except in those children who had neurological abnormalities before their first seizure.
Rasmussen and Gillberg (1983)	A representative sample of seven-year-old children with perceptual, motor and attentional deficits in Gothenburg.	A screening questionnaire with 34 questions about motor control, speech/language, perception, conceptualization and attention/behaviour was distributed to all preschool teachers in Gothenburg in 1977. 72% completed the questionnaire.	A total of 141 children from the questionnaire study were selected for assessment.	Children with with perceptual, motor and attentional deficits had experienced simple febrile convulsions significantly more often than controls.
Verity et al (1995)	A national birth cohort of 13,135 British children followed up from birth to the age of 5 years.	303 children with FS were compared with control children.	The children's intellectual ability was assessed at 5 years using relatively simple tests that could be administered by a health visitor at the child's home: e.g. the copying designs test, the draw a man test, the English picture vocabulary test.	The children did not differ at age 5 years from their peers without FS. No differences were found between children with single vs recurrent or simple vs complex FS.
Verity et al (1998)	In a national population-based study in the United Kingdom, 14,676 children were enrolled in the Child Health and Education Study.	398 children with FS born in one week in April 1970 were identified and 381 were included in the study.	Children with FS were compared with the rest of the cohort using measures of academic progress, intelligence, and behaviour that included questionnaires, standardized tests, and formal tests.	Children with FS performed as well as other children in terms of their academic progress, intellect and behaviour at 10 years of age. There were no difference in children with simple, complex or recurrent seizures. Special schooling was required for more children who had FS in the first year of life.
Kölfen et al (1998)	Children who had been treated for FS at the University Children's Hospital in Mannheim, Germany for a period of two years (1989 to 1990) were selected.	80 children assessed at ages 6-9 years with a history of FS were compared with healthy controls.	A neurological examination, an interview to assess psychiatric anomalies, and a series of neuropsychological tests were performed.	Children with prolonged FS, in comparison with children with simple FS, had significantly lower results on a non-verbal intelligence test. Children with multiple recurrences of FS performed poorer in all tests when compared with children with only one FS or with the controls

Article	Study design	Study population	Methods	Results
Chang et al (2000)	A prospective population-based case control study.	From a population survey of 4,340 live-birth new-borns in Tainan City, Taiwan, 103 children with confirmed febrile convulsions (FC) by age 3 years were followed up until they were at least 6 years old.	An achievement test, behavioural ratings, and a computerized neurocognitive battery, assessing various subcomponents of attention were given to 87 FC children and 87 randomly selected population-matched controls.	FS in early childhood does not have adverse effects on behaviour, scholastic performance, and neurocognitive attention.
Chang et al (2001)	A prospective, population-based, case-control study.	From a population survey of 4,340 live-birth new-borns in Tainan City, Taiwan, 103 children with confirmed febrile convulsions (FC) by age 3 years were followed-up until they were at least 6 years old.	Three analogous searching tasks dissociating the mnemonic and executive aspects of performances were administered to 87 of these school-aged children and to 87 randomly selected age-matched control subjects to assess the learning, spatial, and sequential working memory.	School-aged children with FC had significantly better mnemonic capacity, more flexible mental processing, and higher impulsivity than their age-matched control subjects. Onset of FC before age one year was a risk factor for deficits in memory function.
Sillanpää et al (2010)	A birth cohort sample was collected from a Finnish southwestern province in 1986 (total population 713,000), using a stratified, randomized cluster sampling procedure. A random birth cohort (n = 900) was prospectively followed from early pregnancy and examined at ages 12 and 18 years to study the relationships between FS and school achievement.	The total sample comprised 1,294 children with an IQ > 70, 1003 were assessed at the age of 5 years. At the age of 12 years, 900 (70%) and at 18 years, 787 (61%) of the 1294 children participated in the follow-up assessment.	School achievement was assessed, and behaviour and social competence (Achenbach Childhood Behaviour Checklist, Youth Self-Report), life management (Antonovsky Sense of Coherence Scale) and social participation.	No significant differences could be found between children with vs. without FS or between boys vs. girls in academic achievement, behaviour, social competence, life management, or social participation, neither at age 12 nor at 18 years,
Visser et al (2012)	A population-based cohort study in Rotterdam from early fetal life and onwards. Participant recruitment started in April 2002 and baseline data collection was completed January 2006.	In total, 7,295 participants were enrolled for the postnatal phase of the study. Questionnaires about the occurrence of FS distributed at age 1,2 and 3 years. 3,157 participants were eligible for the study.	Behavior and emotion assessed by the Child Behaviour Checklist. Information on expressive language development by the Language Development Survey and about Executive functioning by the Behaviour Rating Inventory of Executive Function - Preschool Version.	FS were not associated with problem in behaviour or executive functioning problems in preschool children, but children with recurrent FS might be at risk for delayed language development.
Martinos et al (2012)	A prospectively recruited cohort of children from the North London epilepsy research network. Included were those who had experienced at least one episode of prolonged febrile seizure between December 2006 and March 2010.	26 children assessed soon after a prolonged febrile seizure (median: 37.5 days) and one year later, comparing their results to those of 37 normally developing children.	The children were assessed with magnetic resonance imaging (MRI) and neuropsychological tests to test memory, including the visual paired comparison task.	Recognition memory impairment that was linked to the hippocampal size, was found in children with prolonged FS

Article	Study design	Study population	Methods	Results
Leaffer et al (2013)	A prospective cohort study of children from a low socioeconomic status community, with a first FS from March 1999 to April 2004 in the Morgan Stanley Paediatric Emergency Department at New York Presbyterian Hospital,	159 children (aged 6 months to 5 years) with FS were compared to 142 controls on measures of cognition, motor ability, and adaptive behaviour. Children were evaluated within one month of the emergency department visit and one year later, and difference in performance over one year was examined.	Children aged 1 month to 3 years were assessed with The Bayley Scales of Infant Development (Bayley-II). In children older than 3 years the Developmental Indicators for the Assessment of Learning (DIAL-3). Vineland Adaptive Behaviour Scales to all parents.	A first FS does not pose developmental or adaptive behavioural consequences in a low socioeconomic environment in the year after the first FS.
Ku et al (2013)	A nationwide cohort database study in Taiwan.	1081 children with FS as the case cohort matched with healthy controls.	Medical records from the Longitudinal Health Insurance Database 2000 (LHID2000) was collected and maintained. The LHID2000 contains 1 million randomly selected insurants from the NHI programme in 2000 and includes all medical records from 1996 to 2010.	FS may increase the risk of subsequent ADHD occurrence in children. Children who visited physicians for FS more than twice had a significantly higher cumulative incidence of ADHD.
Tsai et al (2015)	320 medical records of children with a clinical diagnosis of FS and aged between 6 and 15 years were reviewed from the Departments of Pediatrics at Cathay General Hospital and Cheng-Hsin General Hospital in Taipei, Taiwan.	147 children and age-matched healthy controls were enrolled.	Patients were evaluated with Wechsler Intelligence Scale for Children (WISC; Chinese WISC-IV), behaviour test scores (Chinese version of Conners' continuous performance test and behaviour rating scales).	Children with complex FS had significantly lower FSIQ, perceptual reasoning index, and working memory index scores than did the control group.
Bertelsen et al (2016)	Prospective population-based cohort study of children born in Denmark between January 1, 1990 and December 31, 2007.	In a cohort of 906 379 children, 33 947 (3,8 %) were diagnosed with FS.	Information on FS diagnoses was obtained from the Danish National hospital register and data on ADHD diagnoses was obtained from the Danish Psychiatric Central register.	Children with FS had a 20-35% increased risk of ADHD compared to children without FS.
Gillberg et al (2017)	The Child and Adolescent Twin Study in Sweden (CATSS), 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 FS (n= 492) were based on data from the Swedish National Patient Register.	The rate of ESSENCE in FS was significantly higher than in the total population without seizures.

1.8 FEBRILE SEIZURES AND ESSENCE

Developmental disorders comprise a group of conditions that are present from early life, affecting a single area of development or several, e.g. general cognitive ability, motor performance, attention, speech and language, social and communicative abilities. The common coexistence of neurodevelopmental disorder is now increasingly presented as ESSENCE (Gillberg 2010).

The acronym, ESSENCE (Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations), refers to the total group of neurodevelopmental/neuropsychiatric disorders and includes e.g. autism, ADHD, DCD and ID.

The ESSENCE concept emphasizes the very common co-occurrence of these disorders and the importance of considering different diagnostic entities in the evaluation of children referred for one major symptom (Gillberg 2010).

An increased rate of ESSENCE in FS was found in a population-based twin study including 492 children with FS. The rate of ESSENCE in FS was significantly higher than in the total population without FS, even after adjusting for epilepsy (Gillberg et al 2017).

In a register study from Taiwan, an association between FS and ADHD was reported (Ku e al 2014). 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".

In a Swedish population-based study, 17% of seven-year-old children with the combination of ADHD and DCD were found to have a history of FS (Rasmussen et al 1983).

It has been suggested that if psychomotor deficits, learning difficulties and behavioural problems are found in children with FS, these are not related to the seizures but probably reflect the overall developmental status of the child (Wallace 1984).

2 AIMS

Based on the hypothesis that FS may be associated with other neurodevelopmental abnormalities (ESSENCE), the overall aim of this thesis was to gain further insight into the area of coexisting developmental disorders (ESSENCE) in children with FS.

More specifically, the aims were to:

1. Study the prevalence of all types of paroxysmal attacks of children under the age of five years, including FS and epilepsy, in a one-year birth cohort in Gothenburg, Sweden.
2. Investigate the occurrence of coexisting neurodevelopmental disorders (ESSENCE) in the community-based cohort of children with FS.
3. Assess cognitive functions through neuropsychological tests in the cohort of children with FS.
4. Combine clinical neurodevelopmental data from the assessments at child preschool age with results from school age parent interview and estimate the overall prevalence of ESSENCE in children with FS.

3 PARTICIPANTS AND METHODS

3.1 PARTICIPANTS

The thesis is based on the results from one and the same population-based cohort of children, with a history of FS, in the city of Gothenburg born between July 1, 2008 and June 30, 2009.

- Study I included the 4.290 children of the total child population of 6,076 (71%), whose parents completed a questionnaire about the occurrence of paroxysmal attacks in their child at the child´s four-year-health check-up at CHC in Gothenburg The study included 157 children with FS, 22 with epilepsy (16 identified from CHC and 6 from hospital records) and 75 children with other paroxysmal attacks (Figure 1).

- Study II included 73 (41 boys, 32 girls) of the 157 children with FS (46%), whose parents gave consent to participate in a study pertaining to clinical neurodevelopmental assessments of children with FS at ages 4-5 years (a few at 6 years).

- Study III assessed different types of cognitive functions in the 71/73 children with FS participating in the clinical study (see study II).

- Study IV included the total group of the clinically assessed 73 children and a subgroup consisting of the 54 children (74%), whose parents participated in an interview when the children were 9-10 years old.

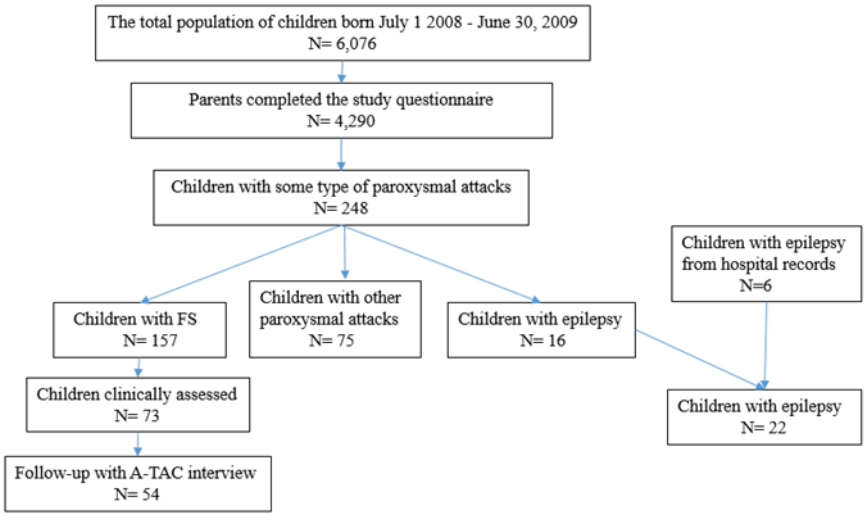

Figure 1. Flowchart demonstrating the total child population and children included in the different studies

3.2 METHODS

3.2.1 Study I The prevalence study

Before the study was launched, the author visited the CHCs in Gothenburg and gave lectures about FS and epilepsy in children and provided information about the upcoming study.

Child Healthcare Centres (CHC) are an important part of child healthcare in Sweden. During the first six years of life, 95-99% of all children attend the routine health care program in Gothenburg (Arvidsson et al 2012). In addition to parental support and advice and providing the immunization program, the CHC has an important role in developmental surveillance, performed by nurses and physicians during infancy and preschool ages.

In Sweden, a language screening has been conducted at most CHCs since the early 1990s at the age of 2.5-3 years (Miniscalco Mattsson et al 2001) and in Gothenburg an autism screening at the age of 2.5 years has been implemented since 2008 (Nygren et al 2012). Currently there is no screening or routine check-up whether the child has experienced FS or other paroxysmal attacks.

A parent questionnaire (Figure 2) about any type of seizures (FS, epilepsy) and other paroxysmal attacks that their child might have experienced was distributed to parents in conjunction with their child´s 4-year health surveillance at the CHC. Parents who reported any kind of seizures or other attacks in their child were contacted by telephone by the author or one of the two investigating psychologists. If a history of FS could be confirmed, the children and their parents were invited to take part in a full clinical assessment.

In addition, hospital registers and individual medical records of the same age group were checked as regards diagnoses for ICD-10 codes of epilepsy or FS (G 40.0-40.9, R 56.0 and R 56.8).

This prevalence study was performed as a background to the ensuing studies regarding developmental aspects and occurrence of coexisting developmental disorders in children with FS or epilepsy – with a special focus on the group with FS.

Questions to parents at the 4-year surveillance at the Child Healthcare Centre

With this questionnaire, we want to find out how common febrile seizures, epilepsy and unconsciousness for other reasons are among children in Gothenburg

	Yes	No
1. Has your child at any time had		
a) febrile seizures?	☐	☐
b) other convulsions?	☐	☐
c) absence seizures or similar episodes?	☐	☐
2. Is your child being treated for epilepsy?	☐	☐
3. Has your child been unconscious at any time?	☐	☐

Figure 2. Questions to parents at the 4-year surveillance at the Child Healthcare Centre

3.2.2 Study II Neurodevelopmental disorders and problems at preschool age

Parents of the 157 children with FS were invited to come for a clinical assessment of their child. Parents of 73 children (46%) (41 boys, 32 girls) accepted participation. The age of the children at the clinical assessment was between 4 and 5 years.

The assessments included a neuropaediatric examination, with a detailed parental interview regarding the child´s seizure type/s, developmental history, heredity factors and the child´s general health. Each child had a structured motor test (Movement ABC) (Hendersom and Sugden 1992, Schultz et al 2011), performed by the neuropaediatrician (GN) and cognitive assessments, performed by one of four psychologists in the research team. The parental interview was supplemented with data from structured questionnaires; the Five – to – Fifteen questionnaire (FTF) (Kadesjö et al. 2004, Trillingsgaard et al 2004) and the Strengths and Difficulties Questionnaire (SDQ) (Goodman 2001). Data from the child´s speech and language screening at the CHC were collected. Hospital and CHC records were reviewed, when applicable. All available data were compiled and merged to establish if the child met criteria according to DSM-5 (APA 2013) for a neurodevelopmental diagnosis or had definite neurodevelopmental problems. This procedure included the so called LEAD standard (Longitudinal, Expert and All Data) (Spitzer 1983).

The Movement ABC, a test of motor performance, is a norm-referenced test and most frequently used for diagnostic purposes in DCD. The revised version is subdivided into three age bands. The age band from 3 years to 6 years and 11 months was used. The test scores motor performance on three main components: manual dexterity (MD), aiming & catching (AC) and balance (BA) (Henderson and Sugden 1992, Schultz et al 2011).

The FTF questionnaire was used to cover the range of issues that pertain to neurodevelopmental/neuropsychiatric disorders or problems. The questionnaire consists of 181 statements divided into eight domains (motor skills, executive functions/ADHD, perception, memory, language, learning, social skills/autism and emotional/behavioural problems). The learning domain was not considered in this study. The items are rated on a 3-level Likert scale; an item is scored as 0 when the statement "does not apply", 1 when it "applies sometimes or to some extent" or 2 when it "definitely applies". Questions regarding impairments are included in the newest version. The norms are based on ratings from parents. The

questionnaire has been used in a stratified sample of 854 Swedish children from the general population, subdivided into three age groups and medians, means, 75th, 90th and 98th percentiles for domain scores have been published for boys and girls in Nordic norm groups (Kadesjö et al 2004, Trillingsgaard et al 2004). A score above the 90th percentile, in any of the eight domains, corresponds to a definite problem.

The SDQ is a parent (and teacher) screening questionnaire of the adjustment and psychopathology of 3-16-year olds. It has been widely used and has good psychometric properties (Goodman 2001). There are 25 statements concerning emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems and prosocial behaviour. There are three response alternatives and parents are asked to disagree (0), agree to some extent (1) or agree (2). The sum score of 20 items, i.e. except prosocial behaviour, generates a total difficulties score with a range of 0 to 40. The prosocial domain measures the child's ability to behave in a prosocial manner, and on this domain, higher scores indicate better performance. On the other scales, a high score indicates problems. The FS group was compared with a Swedish 4-year-old norm group.

Overall clinical diagnostic evaluation All available data were compiled and jointly scrutinized by four of the authors (GN, IO, EF and CG) to establish if the child met criteria according to the DSM-5 (APA 2013) for a neurodevelopmental diagnosis or had definite developmental problems, i.e. corresponding to a "subthreshold level" with regard to DSM-5 diagnostic criteria. DCD was diagnosed based on the result from the Movement ABC and/or when an impairing gross and/or fine motor problem was observed at the clinical examination and described by parents. Borderline Intellectual Functioning (BIF) was defined as an IQ level between 70 and 84 and intellectual disability (ID) as an IQ below 70 (75) with a corresponding adaptive level (DSM-5). A diagnosis of ADHD (DSM-5) or ADHD symptoms (when criteria for ADHD were not fully met) or of ASD (DSM-5) or ASD symptoms (when criteria were not fully met) was based on results from the FTF, SDQ, clinical observations of the child in the test/assessment situations, information given by parents and if applicable, from information in hospital records.

Wechsler Preschool and Primary Scale of Intelligence-III (WPPSI III), NEPSY and Leiter International Performance Scale, see Study III

Language ability All children had been screened for language delay and for autism, when they were 2.5 years old (Miniscalco Mattsson et al 2001, Nygren et al 2012). Children who failed the screening had been referred to the Department of Paediatric Speech and Language Pathology at the Paediatric Hospital, prior to the present study. Therefore, the hospital registers were scrutinised to identify children from the study group diagnosed with an ICD-10 language disorder (The ICD-10 classification 1992).

3.2.3 Study III The study of cognitive functions

In this study cognitive profiles, according to test data, of the 4- to 5-year old children with FS from the population based cohort, were assessed. This assessment was carried out in conjunction with the other clinical developmental assessments (see Study II). The study group consisted of 71 children, since two with ID had been tested prior to the study.

Wechsler Preschool and Primary Scale of Intelligence-III (WPPSI III)

The child´s cognitive level was evaluated with the Wechsler Preschool and Primary Scale of Intelligence-III (WPPSI-III) (Wechsler 2005). Each child was examined in a single session, approximately 90 min long. The scale provides a full scale IQ (FSIQ), verbal IQ (VIQ), and performance IQ (PIQ) and also generates a Processing Speed Quotient (PSQ) and a General Language Composite (GLC). Executive functioning was measured with the **NEPSY** (Korkman et al 1998) subtests; Statue test, the Narrative memory, the Sentence Repetition and the Visual Attention test. Visual memory were measured with the **Leiter International Performance Scale** (Roid and Miller 1997) using the subtests Immediate recognition and Delayed recognition from the Memory battery. Cognitive test results were separately analysed for the groups with simple and complex FS and with single and recurrent FS. The psychologist also used a structured form to rate behaviour, activity and endurance.

A comparison group (n=20 children, 11 boys and 9 girls) with no history of FS was selected matched for sex and age (+/-3 month) and collected from the same CHC:s. The comparison group was recruited from the same 4-year-health check-up and parents were contacted by one of the psychologists in the research team and gave consent.

3.2.4 Study IV Neurodevelopmental disorders and problems from preschool to school

The parents were contacted by a letter of information and by telephone regarding participation in a telephone interview, using the Autism-Tics, ADHD and other comorbidities questionnaire (A-TAC) (Hansson et al 2005). The interview was performed by an experienced layperson from a market research centre.

The interview has been shown to have excellent psychometric properties and has been used in many clinical research studies. (Halleröd et al 2010, Pettersson et al 2015, Barnevik Olsson et al 2016). The A-TAC is a screening interview focusing on child and adolescent psychiatric problems and designed to be used by an experienced layperson from a market research centre. Criteria for a clinical and subclinical proxy of ASD, ADHD, LD or DCD will be provided by the interview. For ASD, ADHD, LD/ID and DCD two cut-offs exist (1) "high" which is a proxy for a clinical diagnosis and (2) "low" which is a broad screening level to capture pronounced subthreshold traits that can be taken as a proxy for a subclinical disorder (Larson et al. 2010, 2013).

The results were compared with A-TAC results from previously published clinical and (twin) population studies (Mårland et al 2017). Results were also compared with the results from the assessments at age 4-5 years and from medical records that were scrutinized when applicable.

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 the 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 cut-off scores on A-TAC for any of the four disorders at age 9-10 years.

Statistics

In study I descriptive statistics were used.

In study II Chi-square goodness-of-fit was used to analyse if the number of children with FS who had a definite problem in the different domains of the FTF deviated significantly from that expected by chance. Mean total scores as well as mean scores on the five subscales on the SDQ for boys and girls, respectively, in the present sample were compared to mean scores in the Nordic comparison group (Kadesjö et al 2004, Trillingsgaard et al 2004) using one-sample t-tests. The chi-square test of independence was used to compare the proportion of children with neurodevelopmental disorders or symptoms in the groups with single FS or

recurrent FS, and simple or complex FS, respectively. An alpha level of .05 was used for all analyses.

In study III statistical analyses were carried out using SPSS version 22 (SPSS, Chicago, IL, USA). The significance threshold was set at .05. Frequencies, percentages, means, and standard deviations were used to summarize demographic characteristics.

Chi-square tests with Yates corrections for continuity were used for group comparisons regarding categorical variables, and Mann-Whitney U Test were used for continuous variables. One-sample Wilcoxon Signed Rank Test was used to compare the study group scores with the norms.

In study IV Statistical analyses were carried out using SPSS version 22 (SPSS, Chicago, IL, USA). Frequencies, percentages, means, and standard deviations were used to summarize demographic characteristics and contrasted against a Swedish comparison group of 25,782 children aged 9 and 12 years (Mårland et al 2017) whose parent completed the A-TAC. An alpha level of .05 was used for all analyses. T-test for independent samples were used for continuous variables (means) and Chi-square tests for categorical one; (prevalences of NDDs), all tests were 2-tailed.

Ethics

The studies were approved by the Regional Ethics Committee in Gothenburg, Sweden (case number 980-17/971-11). Written informed consent was obtained from all parents participating in the studies.

4 RESULTS

4.1 STUDY I THE PREVALENCE STUDY

Parents of 4,290 of the total population of 6,076 children (71%) completed the questionnaire pertaining to different types of seizures. For 248 children (5.8%), any type of paroxysmal attack was reported: FS in 157 children (3.7%), epilepsy in 16 (four of these had developed epilepsy but were initially reported to have FS, and another six children were identified through the hospital registers). Thus 22 children had epilepsy (0.5%), and 75 children had other paroxysmal attacks, e.g. syncope and breath-holding spells (1.7%). A total of 254 children had any type of paroxysmal attacks, including FS and epilepsy (5.9%).

4.2 STUDY II NEURODEVELOPMENTAL DISORDERS AND PROBLEMS AT PRESCHOOL AGE

About one third (25/73) of children with FS met criteria for at least one neurodevelopmental diagnosis or had clear neurodevelopmental problems at preschool age. No differences were found between children with single vs recurrent or simple vs complex FS. Types of FS and numbers of FS are presented in Table 4.

Table 4. Type and numbers of febrile seizures in the study group

Type of Febrile Seizures	N (m/f)	%
Single Simple FS	36 (18/18)	50 %
Recurrent Simple FS	16 (14/2)	22 %
Single complex FS	6 (3/3)	8 %
Recurrent Complex FS	14 (7/7)	19 %
Unclassified	1 (0/1)	1 %
Total	73 (42/31)	100 %

FS=Febrile seizures

Familial factors

A family history (in a first-degree relative) was obtained from 71/73 children Twenty-six (37%) had a family history of either FS and/or epilepsy and/or neurodevelopmental problems.

Movement ABC

Of the 73 children, 69 participated in the Movement ABC. Two could not take part due to severe motor impairment combined with ID, and two due to reasons that were not related to the child. Four children (6%) had motor problems compared to the norms of Movement ABC-2.

FTF

Seventy of the 73 parents completed the FTF (two did not due to language difficulties, and one parent had a child with moderate intellectual disability). Significantly more children with FS had definite memory problems according to the FTF, compared to the Swedish reference group (Kadesjö et al 2004) (Table 4).

Table 5. Numbers and percentages with 95% confidence intervals of the 70 children scoring above the 90th percentiles (indicating a definite problem) on the FTF

Domain	No. above the 90th percentile	Percentages above the 90th percentile (expected 10%)	95% CI for percentages		Chi-square (*df* = 1)	*p*
Motor	6	8.6	4.0	17.5	0.159	.690
Executive	11	15.7	9.0	26.0	2.540	.111
Perception	10	14.3	8.0	24.3	1.429	.232
Memory	12	17.1	10.1	28.4	3.968	.046
Language	10	14.3	8.0	24.3	1.429	.232
Social	9	12.9	6.9	22.7	0.635	.426
Emotional	8	11.4	5.9	21.8	0.159	.690

SDQ

Parents of 72 of the 73 children completed the SDQ (one did not due to language difficulties). Of the 72 children, 56 (36 boys, 20 girls) were four years of age. These children were compared with a Swedish four year-old norm group. Both boys and girls with FS had a significantly lower score on the subscale conduct disorder and girls had higher scores on the subscales emotional problems and the prosocial subscale.

Intellectual level

Seventy-one children participated in the cognitive assessment. Two girls with ID, one with mild and one with moderate ID had been assessed prior to the study. Two boys, tested within the study had an FSIQ below 70 indicating ID. Thus, in total four children (5.4%) had ID. Nine children (6 boys, 3 girls) had FSIQ between 71 and 84, indicating BIF.

Clinical diagnostic evaluation

According to all available information, 25/73 children (34%) had clear indications of at least one neurodevelopmental disorder according to the DSM-5 or marked neurodevelopmental problems within areas of attention, activity regulation, behaviour, speech and language, general cognition or motor functioning. The co-existence of disorders were common (Table 6).

Table 6. Developmental disorders in the clinically assessed children with FS

	Sex f=0 m=1	ID	BIF	ADHD or ADHD symptoms	ASD	DLD	DCD/motor problems
1	1	X		X[s]			X
2	1	X		X			X
3	0	X		X		X	
4	0	X			X		
5	0		X	X			X
6	1		X	X			X
7	1		X			X	
8	1						X
9	1		X	X			X
10	1			X			
11	0					X	
12	0			X			
13	1			X			X
14	1			X[s]		X	
15	0					X	
16	1			X		X	
17	0			X			
18	1			X			
19	1		X	X		X	
20	0					X	
21	0						X
22	1			X[s]			
23	1			X[s]			
24	1			X[s]			
25	1			X[s]			

ID = Intellectual Disability; BIF = Borderline Intellectual Function;
ADHD = Attention-Deficit/Hyperactivity Disorder; X[s] = ADHD symptoms;
ASD = Autism Spectrum Disorder; DLD = Developmental Language Disorder;
DCD = Developmental Coordination Disorder.

4.3 STUDY III THE STUDY OF COGNITIVE FUNCTIONS

Intellectual level

Two of the 73 children had a previously diagnosed intellectual disability (ID) (one mild, one moderate) and were not retested within the study. Another two were diagnosed with mild ID within the study. Thus 5,4% in this group of preschool children with FS has ID. No differences were found regarding FSIQ, VIQ, or PSQ between the study group (n=71) and norms or between the study group and the comparison group.

Executive functions

There was no difference regarding Delayed recognition using the Leiter test between the study group and the compared norms. However, the median score for Immediate recognition was significantly higher in the study group. NEPSY subtests showed that a majority of the FS group performed above average on these tests. There was no significant difference between the FS group and the comparison group.

Intellectual level and executive functions in relation to age at first febrile seizure

Children who had their first febrile seizure before the age of 12 months (12/73) and particularly those with recurrent FS (9/12) had significantly lower VIQ and PSQ, contributing to a lower FSIQ. No differences were found between the early and late FS group on visual memory measured by the Leiter subtests. Nor were there any differences between the early and late FS onset group, according to the NEPSY Statue test, the Narrative memory and the Visual Attention test. The early onset group performed significantly worse on Sentence Repetition test, measuring verbal short-term memory, compared to the late FS onset group.

4.4 STUDY IV NEURODEVELOPMENTAL DISORDERS AND PROBLEMS FROM PRESCHOOL TO SCHOOL

A-TAC interview

Of the 54 children, 13 (24%) had symptom levels corresponding to either low or high cut-off level of ADHD, autism, DCD or LD domains (figure 3) which is a rate in line with the frequency reported in a large Swedish twin study that served as control group. The mean score for ADHD in children with FS was 2.8 and in the comprising group 2.0 (Mårland et al 2017) (p=0.067).

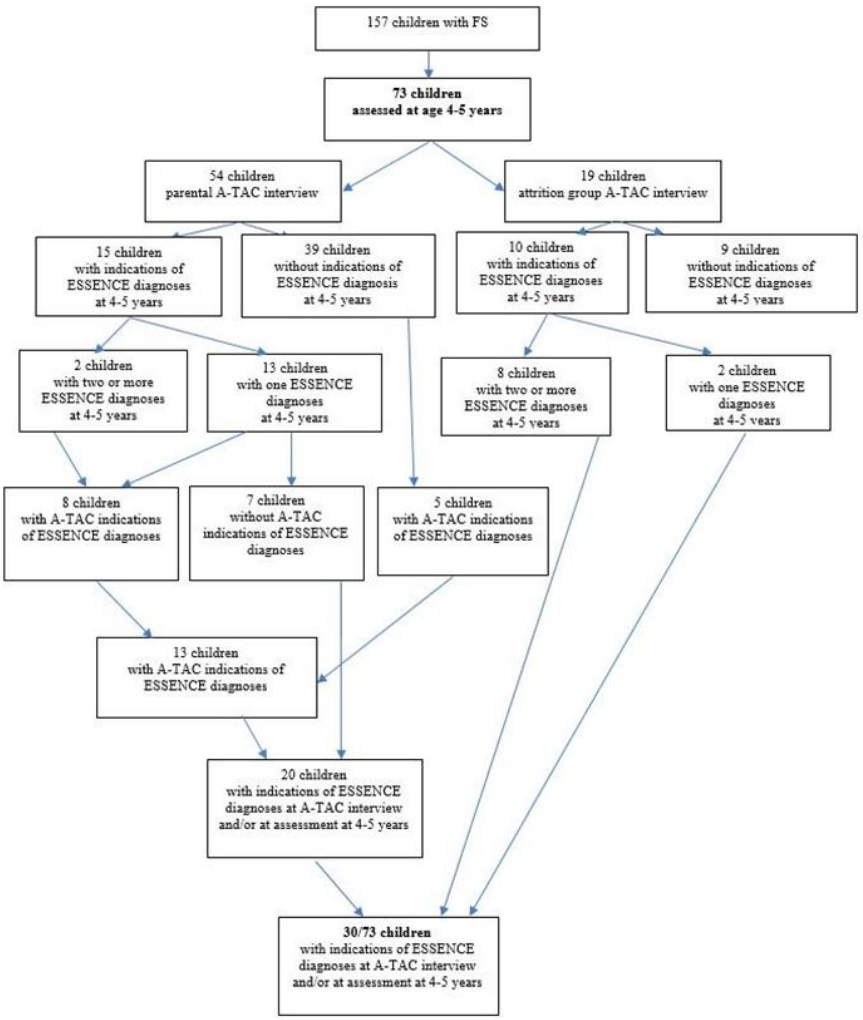

Figure 3. Flow chart demonstrating the inclusion procedure in the A-TAC interview and the clinical assessment at 4-5 years

A-TAC results combined with results from the assessment at 4-5 years

Of the 54 children participating in the A-TAC interview, 15 (28%) had indications of an ESSENCE disorder or neurodevelopmental problems at the clinical assessment at 4-5 years of age. The corresponding rate, with indications of an ESSENCE disorder or definite neurodevelopmental problems at the clinical preschool assessment among the non-participating children was 53% (10/19), ($p=0<.05$). In addition, 8/10 children (80%) in the non-participating group had two or more ESSENCE disorders at the earlier clinical assessment, compared with 2/15 (13%) in the participating group ($p=<0.001$). Four of the eight with two or more diagnoses in the non-participating group had ID in combination with at least one additional disorder.

Overall findings

When summing up results from the clinical study when the children were 4-5 years and from the parental A-TAC interview study when the children were 9-10 years, 30 of the 73 children (41%) had at least one neurodevelopmental disorder or definite neurodevelopmental problems on either occasion or both (Table 7).

Table 7. ESSENCE diagnoses at clinical assessment at age 4-5 years and according to A-TAC interview at 9-10 years

	Sex m/f	ESSENCE diagnoses at assessment at 4-6 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^{s}, 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^{s}	0
19	m	ADHD^{s}	0
20	m	ADHD^{s}	0
21	m	ID, ADHD^{s}, 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^{s}	n.p.

ID=Intellectual Disability, ADHD=Attention-Deficit/Hyperactivity Disorder, ASD=Autism Spectrum Disorder, SLD=Speech and Language Disorder, DCD=Developmental Coordination Disorder, ^{s}=ADHD symptoms, n.p. = not participating

5 DISCUSSION

5.1 GENERAL FINDINGS

The thesis reports data on the prevalence of FS in a one-year birth cohort of children born in 2008-2009 in Gothenburg, Sweden, and includes follow-up neurodevelopmental data in the children with FS at ages 4-5 years and 9-10 years. The prevalence found (3.7%) was in accordance with that found in many other prevalence studies of FS (Verity et al 1985, Forsgren et al 1990 Sillanpää et al 2008, Vestergaard et al 2009). The combined data from the two follow-up assessments of the children – at preschool and at school age – revealed that about 40% of the children had at least one neurodevelopmental disorder or a definite neurodevelopmental problem, such as ID, ADHD, speech and language disorder and DCD. This rate is considerably higher than expected in these age groups. The occurrence of these accompanying neurodevelopmental disorders and problems does not mean that FS per se is the cause of these disorders but rather that FS may be a marker for possible neurodevelopmental problems (Wallace 1984, Gillberg et al 2017).

5.2 STUDY I THE PREVALENCE STUDY

The prevalence study included, in addition to FS, also data about epilepsy and other paroxysmal attacks. The total rate for any seizure disorder/ paroxysmal attack was found to be nearly 6%, and FS constituted the largest group. The rate of 6% is similar to the estimated, collapsed rate for all kinds of neurodevelopmental/neuropsychiatric disorders in preschool children (Gillberg 2010). Paroxysmal attacks in children are usually associated with marked fear and anxiety in the parents (Kanemura et al 2013, Westin et al 2018).

Prevalence rates of FS will vary depending on methods of case ascertainment and the geographical area under study. The present study was based on parental reports at the child´s 4-year-check-up at CHC, where all parents in the study area were asked to fill in a questionnaire about any type of paroxysmal attacks that might have occurred in their child. The questionnaire was specifically designed for this study.

There have been very few studies in which questionnaires to parents have been used for case ascertainment. In an earlier Swedish study different professionals who might have come in contact with children with FS (district nurses and physicians/paediatricians) were asked to report or refer cases. In that study EEG

files from the neurophysiological laboratories were also used for further identification of cases (Forsgren et al 1990). However, it is not routine to refer for an EEG after FS. In that study a cumulative incidence of 4.1% up to the age of five years was found. In the present population-based study using parent questionnaires a recall bias is a possibility, but it is unlikely that underreporting occurred, given that the occurrence of FS is usually a frightening experience which parents are not likely to forget. The study by Forsgren et al (1990) included children up to the age of five years, but very few children have their first FS between ages four and five years. In the present study, all the parents who had answered that their child had some sort of paroxysmal event were contacted by phone, and cases were excluded if the history was not that of FS (e.g. cases of febrile shivering or syncope). In accordance with other studies (Forsgren et al 1990, Hwang et al 2015) there were more boys than girls with FS, 1.72:1 in the study by Forsgren et al. (1990) and 1.45:1 in the present one.

The prevalence of epilepsy in the cohort was 3.6 to 5.1/1000 (22/6,076-22/4290). This is in accordance with a previous Swedish study, reporting a prevalence of 3.4/1000 in children between the age of 1 month and 16 years (Larsson et al 2006). The incidence of epilepsy is highest during the first year of life; an incidence of 81 /100 000 was reported in Rochester, Minnesota (Hauser et al 1993), 118/100 000 in Nova Scotia (Camfield et al 1996) and 130/100 000 in Iceland (Olafsson et al 2005). The incidence decreases thereafter, being 48/100 000 between the age of one and five years (Camfield et al 2015). It was obvious that all children with epilepsy did not attend the regular check-ups at the CHC, which might imply that these families do not get access to the general CHC programme. Six out of 22 (27%) were not picked up through questionnaire to parents at the CHC but only through hospital records. There is a theoretical possibility that children with epilepsy may have been seen by a paediatrician in an outpatient clinic. However, this seems unlikely, since in another Swedish study only 5 of 105 children were followed in outpatient clinics and the younger the children, the more likely that they were followed by neuropediatricians at the hospital (Larsson et al 2006).

In the present study 2% reported other types of paroxysmal events such as anoxic spells and temper tantrums. It is important for CHC professionals to be aware also of these attacks as differential diagnoses of epilepsy, and these parents may also need counselling.

Limitations and strengths

The most important limitation is that only 71% of the parents of children in the cohort completed the questionnaire about paroxysmal attacks at the CHC, even though there is no indication that responders would have children with higher problem rates. The strengths of the study were its population-based design, and the fact that all parents who had reported any kind of paroxysmal event in their child had been contacted by telephone so that diagnoses could be confirmed or disproved.

5.3 STUDY II AND IV NEURODEVELOPMENTAL DISORDERS AND PROBLEMS FROM PRESCHOOL TO SCHOOL

The question as to whether or not later diagnosed neurodevelopmental disorders, particularly ADHD, in children with a history of FS, are associated with pre-existing brain abnormalities and/or a genetic predisposition, has been raised in epidemiological and experimental studies (Ku et al 2013, Bertelsen et al 2016, Gillberg et al 2017). These studies support the notion that neurodevelopmental disorders occur at a higher rate in children with FS than in children without FS. Such disorders (ESSENCE) occur in about 5% of preschool children and in about 10% of school age children (Gillberg 2010), in the general population.

The concept of ESSENCE was introduced with a view to emphasize the considerable co-occurrence of neurodevelopmental disorders/problems with early onset, both with regard to genetics, pre-and perinatal risk factors, clinical presentation and outcome. The "ESSENCE family" includes disorders such as ID, other learning disorders, autism, ADHD, DCD, Tourette syndrome epilepsy, cerebral palsy and eating disorders. Their risk of leading to academic failure, if appropriate support measures and adaptations are not implemented early on, are highlighted under the ESSENCE concept.

Of the clinically assessed children with FS, about one third (25/73) had additional neurodevelopmental disorders or problems at the age of 4-5 years, most commonly ADHD or marked ADHD symptoms, often combined with other disorders/problems. Excluding the four children with ADHD symptoms only, the total rate of neurodevelopmental disorders was 29% (21/73), still a much higher rate than expected.

ADHD with underlying executive function deficits, was the most common disorder recorded in the clinically assessed group at 4-5 years. Both ADHD and

epilepsy share common neuropsychological impairments leading to inattentive behaviour. Mediators, connecting central nervous system (CNS) dysfunctions to inattentive behaviour in childhood epilepsy, have been discussed (Noeker and Haverkamp 2003). The present results may indicate that such a relationship is also conceivable for FS.

In the present study significantly more children with FS had memory problems at ages 4-6 years according to the FTF compared with the Swedish reference group. The finding may indicate an increased rate of attention end executive problems in children with FS.

The significantly lower score on the SDQ subscale conduct disorder in both boys and girls with FS is difficult to explain. The finding may however relate to the findings of higher scores in girls on the subscale emotional problems, indicating that these girls may present more internalizing or sensitive behaviour, combined with their more prosocial behaviour according the SDQ.

The study was comprehensive, including both neurodevelopmental and cognitive assessments and parental questionnaires in a community- representative group. In contrast to the present findings, a Dutch population based study (Visser et al 2012) did not show an increased occurrence of behavioural problems in children with a history of FS. However, their study was based exclusively on questionnaires to parents and included younger children.

Based on clinical assessments at preschool age (4-5 years) and at school age (9-10 years) the rate of neurodevelopmental disorders or definitive neurodevelopmental problems was found to be 41%, which is considerably higher than expected in the general child population. ADHD was the single most prevalent disorder 12/73 (16%), diagnosed in the group of children with FS.

The A-TAC interview has been found to have particularly good validity for children with known diagnoses, possibly related to the fact that parents of diagnosed children are better at recognizing the symptoms that are asked about during the telephone interview (Anckarsäter et al 2008, Mårland et al 2017).

Limitations and strengths

One limitation was that only about half the group, in the preschool study, could be clinically assessed, mainly because parents did not have the time to participate. On the one hand it cannot be excluded that more parents of children with developmental concerns accepted to participate in the preschool study, contributing to the high rate of ESSENCE problems in the study group.

However, the opposite may actually be more likely, i.e. that families with children with neurodevelopmental/neuropsychiatric problems refrain from participation and that the rate of ESSENCE problems may be a minimum figure (Stormark et al 2008).

No clinical neurodevelopmental assessment was carried out in conjunction with the A-TAC interview at school age and this of course is a limitation. Another limitation was the lack of a comparison group.

The fact that only 74% of those participating in study II (and about one third of the whole cohort with FS) accepted to participate in the A-TAC study is also a limitation. However, this attrition rate was largely due to parents of children with neurodevelopmental disorders/problems declining participation, meaning that if anything reported results would be conservative rather than overestimations.

Strengths included the population-based design of the study and the thorough assessment of each child in the clinical preschool study, taking different developmental aspects into consideration and using well validated and comprehensive tests and questionnaires.

5.4 STUDY III THE STUDY OF COGNITIVE FUNCTIONS

This study focused on cognitive data, i.e. general cognitive ability, verbal and non-verbal capacity, visual memory and attention, collected at the neuropsychological assessments that were carried out in conjunction with the first clinical assessment when the children were 4-5 years of age.

Five per cent of the children with FS had ID which is a higher rate than in the child population in general, in which a rate of about 2% would be expected.

The evidence for the possible importance of the age of onset of a first FS as a marker for cognitive deficits is limited. In the present study, FS occurring before one year of age was associated with significantly lower VIQ and PSQ, contributing to a lower FSIQ and significantly lower results on Sentence Repetition tests (measuring verbal short term memory) compared to the later onset FS group. Processing speed reflects the child's capacity to work independently and requires graph motor speed, accuracy, mental flexibility and set shifting capacity in order to sustain attention to task. A low PSQ might indicate a later appearance of executive dysfunctions. A similar finding was reported by Chang et al (2001) and Verity et al (1998), who found that special schooling was required for more children who had FS in the first year of life than for those with later FS onset.

Limitations

A limitation in this study was the small size of the comparison group, albeit it had been drawn from the same original population-based group of children as the group with FS. Nerveless, all tests used had appropriate norm groups.

6 CONCLUSION AND IMPLICATIONS FOR CLINICAL PRACTICE AND RESARCH

According to the results presented here, there appears to be an important association between FS and other neurodevelopmental disorders/problems (ESSENCE) at preschool and school ages. In the current routines at CHCs, there is no routine question about FS at the developmental surveillance at four years of age. I suggest that a question about FS be added at this age. When a history of FS is reported, more detailed information about the child's development and functioning should be collected. It is important to identify early symptoms of developmental problems in children with FS, so that proper assessments and interventions can be initiated, thereby reducing the likelihood of negative long-term consequences. It is also possible that all children presenting with FS should be screened for the occurrence of ESSENCE at the time of the FS or shortly thereafter.

Future research should aim at replicating these findings and explore predisposing factors, including genetic predisposition for FS as well as the occurrence of ESSENCE in the family (Gillberg et al 2017). It might also be worthwhile to study other paroxysmal attacks from the same point of view.

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APPENDIX

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