Childhood-onset seizures: A long-term cohort study of use of antiepileptic drugs, and drugs for neuropsychiatric conditions

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Objective: We conducted a long-term follow-up of a cohort of children with newly diagnosed unprovoked seizures to assess treatment with antiepileptic drugs (AEDs), neuroleptics, antidepressants and medication for attention deficit hyperactivity disorder (ADHD) with special attention to the impact of comorbidities on the use of such medication.

Methods: Our study cohort comprised 769 children (28 days-18 years), living in Stockholm Sweden, with a first unprovoked seizure identified between 2001 and 2006. Information on neurodevelopmental comorbidities and Cerebral Palsy (CP) at seizure onset was collected from medical records. Information on treatment with AEDs, neuroleptics, antidepressants and ADHD medication was retrieved by linkage to the Swedish National Prescription Registry between 2005 and 2014. The association between comorbidities and drug treatments was assessed by odds ratios (OR) with 95 % confidence intervals (CI), adjusted for age and sex.

Results: Eight years after the index seizure, 31 % of the children were on AEDs, and this was more common among children with any of the comorbidities studied (OR: 4.0 95 % CI 2.9–5.6) compared to those without such comorbidities, and within this group of comorbidities particularly for those with CP (OR; 5.2 95 % CI: 2.9–9.3). Children with neurodevelopmental comorbidity or CP at baseline were more likely to receive neuroleptics (ORs 8 years after the index seizure; 6.9, 95 % CI: 2.4–19.8), antidepressants (OR; 2.3, 95 % CI: 1.0–5.5) and ADHD medication (OR; 3.6, 95 % CI: 1.8–7.2) than children without the studied comorbidities.

Conclusion: Children with seizures in combination with neurodevelopmental comorbidities or CP, especially CP, have a more frequent use of AEDs, neuroleptics, antidepressants, and ADHD medication up to 13 years following the initial seizure than children without comorbidity. Our data highlight the treatment burden in children with epilepsy and comorbidities.

1. Introduction

The conceptual definition of epilepsy proposed by the International League Against Epilepsy (ILAE) emphasizes that epilepsy is more than the enduring predisposition to generate unprovoked seizures, it also encompasses the neurobiological, cognitive, psychological and social consequences/aspects of the disorder (Fisher et al., 2005). The more recently adopted ILAE classification of the epilepsies reinforces this broader view of epilepsy not least by highlighting that comorbidities need to be considered at all stages of the epilepsy classification scheme (Scheffer et al., 2017).

Comorbidities are common in childhood-onset epilepsy overall, particularly with regard to neuropsychiatric conditions. Furthermore, seizures are common in children with neurodevelopmental comorbidities and related health problems (Scheffer et al., 2017; Stein et al., 2018).

Abbreviations: AEDs, antiepileptic drugs; ADHD, attention deficit hyperactivity disorder; CP, Cerebral Palsy; OR, odds ratio; CI, confidence intervals; ILAE, International League Against Epilepsy; SPDR, Swedish Prescribed Drug Register; SIRE, Stockholm Incidence Registry of Epilepsy; ASD, autism spectrum disorder; HR, hazard ratio; SES, socioeconomic status; ATC, The Anatomical Therapeutic Chemical Classification System; ICD, International Statistical Classification of Diseases and Related Health Problems.

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affecting the majority of children with seizures (Aaberg et al., 2016), who have several-fold increased risks for both mental and psychiatric disorders (Jennum et al., 2017). Comorbidities are important, not just because they add to the burden of the disease, but also since their presence may have an impact on the overall prognosis of the seizure disorder. In support hereof, we found that children with neurodevelopmental comorbidities or CP diagnosed at the time of a first unprovoked seizure were less likely to be seizure free within two years of the first seizure (Andell et al., 2018). Furthermore, two Nordic studies with 45–50 years follow-up of childhood-onset epilepsy found higher terminal seizure remission rates among children without other neurological abnormalities or intellectual disabilities (Bronson et al., 2019; Sillanpaa et al., 2014) than among those with comorbidities. Other studies from different parts of the world, and with variable duration of follow-up, have also reported that comorbidities have a detrimental impact on the prognosis of childhood-onset epilepsy (Berg et al., 2011; Bronson et al., 2011; Pereira et al., 2014; Tsubouchi et al., 2019). Limitations of these studies include a small number of patients (Bronson et al., 2019; Sillanpaa et al., 2014), selected cohorts (Pereira et al., 2014; Tsubouchi et al., 2019) and potential loss to follow-up (Berg et al., 2011).

This study aimed to investigate the prognosis of children with newly diagnosed, unprovoked seizures in terms of treatment with antiepileptic drugs (AEDs), neuroleptics, antidepressants and medication for attention deficit hyperactivity disorder (ADHD). We specifically sought to assess the association between future drug use and neurodevelopmental comorbidities and CP diagnosed at the time of seizure onset. We hypothesised that children with seizures and neurodevelopmental comorbidities or CP use AEDs for a longer period of time than children with seizures and no comorbidities, and that children with seizures use more of the studied drugs than children in the general population.

2. Method

Analyses were based on a large population-based cohort of children with incident seizures followed up to 13 years through a national drug register with complete coverage. The Stockholm Incidence Registry of Epilepsy (SIRE) includes all children (29 days–18 years) who sought medical advice, for the first time, for what was concluded to be an unprovoked seizure (hereafter; the index seizure) between September 1st, 2001 and December 31st, 2006 in a defined area of Northern Stockholm (primarily urban and suburban). The registry has been described in detail in previous publications (Adelow et al., 2009; Andell et al., 2015). In short, recruitment to SIRE was made from reviewing the requests for EEG to the neurophysiological department reading all EEG requests from the defined region, screening of medical records at the neuropediatric ward, and-, the neuropediatric outpatient clinic, and lastly, after reviewing paediatric emergency care unit records of emergency visits at the referral hospital of the area, the Karolinska University Hospital. Additionally, there was a network of healthcare providers in the area instructed to alert (and regularly approached by) the SIRE research team about any child potentially meeting the SIRE criteria that they came across in their clinics. At the time, there was no other Neuropediatric facilities than the one at Karolinska University Hospital in the defined area and very few private paediatric clinics. Decisions regarding inclusion in SIRE, and definition of the seizures was then made by the research team of SIRE, at the time consisting of; a registered nurse (Hellebro, E), a neurologist (Tomson, T), a neuropediatrician (Amark, P), a resident in neurology (Adelow, C) and a resident in neuropediatrics (Andell, E). Exclusion criteria were: diagnosed unprovoked seizures (or treatment for seizures) within 5 years before the index seizure, living outside the catchment area or if the date of the index seizure was outside the study period.

Medical records from before the index seizure, and up until six months after the index seizure, were collected and reviewed by at least two members of the research team for baseline information. Patients for whom the medical records confirmed unprovoked seizures (hereafter: seizures) before the index seizure (for which the patient had not sought medical advice) or additional seizures within six months of the index seizure, were classified as having recurrent seizures at baseline. The seven a priori defined comorbidities (developmental delay, speech/language and learning difficulties, intellectual disability, CP, autism spectrum disorder (ASD), ADHD, and an unspecified psychiatric disorder) were considered as certain if a diagnosis with a corresponding ICD-10 code (International Statistical Classification of Diseases and Related Health Problems -10) was in the medical records. Comorbidity was classified as suspected if a clear description of the child’s symptoms or problems was present in the medical records but without a corresponding ICD-10 code. For the purpose of analyses, these two groups (certain and suspected) were combined into one. “Any comorbidity” refers to one or more certain or suspected comorbidities out of the seven mentioned above.

SIRE was linked to The Swedish Prescribed Drug Register (SPDR) (Wettermark et al., 2007) for the period July 2005 to December 2014 using the unique personal identity number assigned to every Swedish resident. All children in SIRE were found in SPDR. The SPDR records all dispensed drugs, through a nationwide prescription software, from July 1st, 2005, classified according to The Anatomical Therapeutic Chemical (ATC) Classification System. In this study, we used ATC codes; N03A (antiepileptic drugs; AEDs), N05A (neuroleptics), N06A (antidepressants) and N06BA 01, 02, 03, 04, 09, 12 (medications licensed for the treatment of ADHD; hereafter ADHD medication).

2.1. Statistics

Among children with incident unprovoked seizures followed for up to 13 years, we wanted to address the following questions: a) What proportion of children are treated with AEDs, neuroleptics, antidepressants and ADHD medication (outcome) at different time points since their first seizure and does the proportion differ in relation to baseline characteristics (exposures), i.e. sex, age at seizure debut, single vs recurrent seizures, comorbidity?; and b) What proportion of children on AEDs discontinue treatment over a 13-year-period and does the proportion differ by baseline characteristics (as above), after adjustment for potential confounders (age, sex, single/recurrent seizures, index date, comorbidity)?

The association between baseline characteristics (sex, age at seizure debut, single vs recurrent seizures, comorbidity) and treatment with AEDs, neuroleptics, antidepressants and ADHD medication, respectively at 4 and 8 years after the index seizure was reported as odds ratios (OR) and 95% confidence intervals (CI). ORs were both assessed in relation to individual comorbidities (in the same model to adjust for overlap between them) and any vs. no comorbidity. The ORs were estimated by logistic regression and adjusted for age at index and sex. We also investigated discontinuation with AEDs in relation to baseline characteristics in children who were on AEDs between July 1st, 2005 and December 31st, 2014. In these analyses, children were followed from the time of the first drug dispensing prescription (2005 onwards) until stop of medication or end of follow-up (Dec 31st, 2014), which ever came first. We defined the date of discontinuing medication as the date of the last dispensing followed by at least one year without additional dispensing of the drug. These results are presented as Kaplan-Meier curves that shows the probability of discontinuing treatment across groups and hazard ratios (HR) estimated by Cox proportional hazard regression (Fisher and Lin, 1999). The HRs were adjusted for age at index (age-groups; <1, 1–5, 6–8, 9–12, 13–18) and sex (model 1) and additionally for single/multiple seizures, any vs. no comorbidity, and date of index seizure (as a continuous variable) in order to adjust for treatment strategies potentially changing over time and if some children had come off and on AEDs more than once (model 2). As above, analyses of individual comorbidities included all comorbidities in the same model. Additional analyses regarding seizure types (defined according
to prevailing guidelines from ILAE at the time (Commission, 1989, 1993, 1997), and in consistency with previous reports from SIRE (Andell et al., 2015, 2018) and a sensitivity analyses regarding recurrent seizures (starting before the index seizure/ with the index seizure as the first) are presented as supplements (Table S1-S3 and Fig. S2-S3). All analyses were made in SPSS version 22. Data was analysed in Sörmland, Sweden.

The study was approved by the Regional ethical review board in Stockholm Sweden (No 2005/979–31/4, 2008/507–31/2 and 2009/ 2046–31/2).

3. Results

3.1. Characteristics

The study cohort included 769 children, 56 % were boys and median age at baseline was 6.8 years (range: 29 days-18 years). Out of those, 514 (67 %) had recurrent seizures at baseline, 192 already before the index seizure and 322 within six months of the index seizure. The children were followed for a median of 10.3 years after the index seizure at baseline, were more likely to use AEDs up until 13 years after the index seizure at baseline compared to those with a single seizure compared to those with recurrent seizures at baseline, more were likely to use AEDs up until 13 years after the index seizure. There was a significant difference in AED treatment between children with and without comorbidity at baseline, and this remained over the entire follow-up period (Table 1).

3.2. Treatment with antiepileptic drugs

Four years after the index seizure 46 % (350/769) of the children used AEDs, and 31 % (240/769) used AEDs after eight years (Table 1). Treatment with AEDs was more common in children with recurrent seizures at baseline than in those with single seizures. The children with a neurodevelopmental comorbidity or CP at baseline were four times more likely to receive AEDs 4 and 8 years after the index seizure than those without comorbidity. The highest proportion of AED use was seen in children with CP or ADHD (Table 1). A younger age at baseline was associated with lower prevalence of AED use during follow-up. As shown in Fig. 1, the proportion of children on treatment with AEDs was highest the first year after the index seizure, when 79 % (217) of the 275 children who had their index seizure during, or within a year from when data from SPDR was available, received treatment, whereas for those with a 12-year-follow-up, only 18 % (36/197) were on AEDs. The proportion on treatment with AEDs was similar in boys and girls. Children who had recurrent seizures at baseline compared to those with a single seizure at baseline, were more likely to use AEDs up until 13 years after the index seizure. There was a significant difference in AED treatment between children with and without comorbidity at baseline, and this remained over the entire follow-up period (Table 1).

3.3. Factors associated with discontinuing treatment with AEDs

The children in SIRE who dispensed AEDs between the start of SPDR (July 1st, 2005) and Dec 31st, 2014 (n = 473) were analysed regarding discontinuation of their treatment. As shown in Fig. 2 a–b the probability of discontinuing AEDs up to 13 years following the index seizure were similar in boys and girls as well as in children initially diagnosed with a single seizure compared to those with recurrent seizures at baseline. Comparing children with vs. without co-morbidity at baseline indicated that children with comorbidity were much less likely to discontinue AEDs than those without (HR 0.4, 95 % CI 0.3–0.5). Adjustment for age, sex, single/recurrent seizures, comorbidity yes/no and date of the index seizure had a minor influence on this association (Table 2). Children younger than 13 years of age at the time of the index seizure had a higher chance of discontinuing AEDs than children who were 13–18 years at the time of the index seizure (Table 2). Children with symptomatic seizures were found to discontinue AED after a longer time than those with cryptogenic seizures (OR after 8 years; 4.3, 95 % CI: 2.9–6.2), and children with idiopathic seizures were on AED treatment more often than those with cryptogenic seizures (OR after 4 years; 2.4, 95 % CI: 1.6–3.5) but were able to discontinue treatment more often (HR; 1.4, 95 % CI: 1.0–1.8) (Suppl. Fig. S2 and table S2).

3.4. Treatment with neuroleptics, antidepressants and ADHD medication

Overall, 4% of the children in the cohort received ADHD treatment four years after the index seizure, and 5% after eight years. The proportion was higher in children with recurrent seizures compared to those with a single seizure at baseline (Table 3). Among children with a certain or probable ADHD at the time of the index seizure, 24 % were treated with ADHD medication 8 years later and OR compared to children without any comorbidity at baseline was estimated at 8.8, 95 % CI; 3.7–20.8 (Table 3).

This study identified few children treated with antidepressants during follow-up, only 2% after 4 years, and 3% after 8 years. Children with comorbidity at baseline were twice as likely to be treated with antidepressants as those without (OR after 8 years; 2.3, 95 % CI; 1.0–5.5). A higher age at the index seizure was also associated with dispensing of antidepressants (Table 3).

Only 1 % (at 4 years) to 2 % (at 8 years) of the children were treated with neuroleptics. Children with comorbidities were more likely to receive neuroleptics than those without comorbidities (OR after 8 years:

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**Table 1** Odds Ratio (OR) for antiepileptic drugs 4 and 8 years following a first unprovoked seizure.

| Age at INDEX seizure | 4 years | 8 years |
|----------------------|---------|---------|
| 13–18 years          | 146     | 162     |
| 9–12 years           | 134     | 149     |
| 6–8 years            | 139     | 162     |
| 1–5 years            | 236     | 262     |
| <1                   | 114     | 133     |

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**Table 2**

| Number of seizures at baseline | 4 years | 8 years |
|-------------------------------|---------|---------|
| Total N (%) OR CI          | 4 years | 8 years |
| One seizure                  | 255     | 34/8.8  |
| Recurrent seizures           | 514     | 5.0/7.9 |

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**Table 3**

| Comorbidity AT BASELINE | 4 years | 8 years |
|-------------------------|---------|---------|
| without comorbidity     | 519     | 114     |
| With any comorbidity    | 250     | 126     |
| Intellectual disability | 119     | 63      |
| Cerebral Palsy          | 68      | 44      |
| Autism Spectrum         | 50      | 29      |
| Disorder                | 49      | 24      |
| ADHD                    | (74)    | (49)    |

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**Table S1-S3 and Fig. S2-S3**

a ORs are adjusted for age-groups at the time of the index seizure and sex.

b Information abstracted from medical records covering six months’ post index seizure, and pertaining to pre-index seizure, index seizure, and any subsequent seizures within six months from the index seizure, and information on comorbidities.
6.9, 95% CI: 2.4–19.8), this was especially true for those with ASD (OR after 8 years: 9.1, 95% CI: 2.2–37.4) (Table 3).

4. Discussion

This long-term follow-up of a large, population-based, cohort of children with incident unprovoked seizures shows that less than 1/3 of the children are under treatment with AEDs eight years after seizure diagnosis, that the proportion still treated with AEDs is higher for those with neurodevelopmental comorbidities and CP at baseline, and that such comorbidities are associated with a decreased probability of discontinuation of AED treatment. Furthermore, children with comorbidities are more likely to receive treatment with neuroleptics, antidepressants and ADHD medication.

4.1. Treatment with antiepileptic drugs

Four years after the index seizure, 46% of the children in our cohort where on AEDs but only 31% where on AED treatment after eight years. These findings are in line with those reported in a Portuguese study in which 72% of the children received AEDs two years after the index seizure, and 23% where still treated after 15 years (Pereira et al., 2014). A Canadian study found 80% of the included children without AED 100 months after a first unprovoked seizure, with estimates of intelligence (normal/intellectual disability), age (younger/older than 12 years) and preceding neonatal seizures (no/yes) being predictors regarding long term seizure outcome (Camfield et al., 1993). A British community-based study, found the number of seizures during the first six months after an index seizure to be the dominant predicting feature for remission (i.e. seizure freedom with or without AEDs) (MacDonald et al., 2000). We also found that children with recurrent as compared with single seizures at baseline more often were treated with AEDs 4 and 8 years after the index seizure. This shows that not having any seizures the first six months after the index seizure is a good long term prognostic factor, why treatment with AEDs in these cases rarely is needed. However, when we followed children who were on AEDs from 2005 (start of the SPDR) onwards, there was no difference in AED discontinuation between children with single vs. recurrent seizures. This is to be expected since the children with only one seizure at baseline, who were on AEDs during follow-up, most likely got the AEDs in response to subsequent seizures after the initial 6 months. Older children have a lower chance of discontinuation of AEDs. At this age, both patient and treating physicians might be less inclined to tamper with the treatment due to the approach of transition to adult care and driver’s license.

Children with comorbidities were more often treated with AEDs and were less likely to discontinue their AED treatment. We have previously
shown that children with neurodevelopmental comorbidities and CP are less likely to be seizure free within 2 years of diagnosis (Andell et al., 2018) and we could now extend these findings by showing that they have poorer prognosis in terms of being on AEDs up to 13 years following diagnosis. The Portuguese study, earlier referred to, found a remission rate of 59 % after 5 years, and 80 % after 15 years, in an unselected group of 200 children with a first unprovoked seizure at a mixed municipal and tertiary hospital (Pereira et al., 2014). In another study comprising children who all had CP and epilepsy, only 47 % (n = 34/72) were in seizure remission after a median follow-up time from seizure start of 11 years (Tsubouchi et al., 2019), also indicating that CP makes remission of seizures less likely. Another study showed that children with intellectual disability and neurologic abnormalities were less likely to become seizure free (Brorson et al., 2019). Our findings support the hypothesis that the seizures and the neurodevelopmental comorbidities might be symptoms of a more complex common cause which enhances the need for long term treatment.

Children with idiopathic seizures started AED treatment more often than those with cryptogenic seizures, but discontinued treatment after some time, which fits well with the age-dependent nature of many of the idiopathic epilepsies.

4.2. Treatment with neuroleptics, antidepressants and ADHD medication

We specifically evaluated if neuropsychiatric or psychiatric medications were used, since such comorbidities are prevalent among children with seizures and because there is widespread fear that some of the drugs for these comorbidities might lower the threshold for seizures (Hedges et al., 2003; Jerrell and McIntyre, 2008; Kanner, 2016) thereby excluding children with epilepsy from effective treatment of comorbidities. In a study where more than 100 children with epilepsy were evaluated for psychiatric disorders, 2/3 had a psychiatric diagnosis, but only 1/3 received any mental service (Ott et al., 2003). We found that 7% of the children with seizures used neuroleptics, antidepressants or drugs against ADHD after 4 years and 10 % after 8 years. At follow-up of 159 Portuguese children 15 years after incident seizures, 13 % used “psychiatric drugs” (including methylphenidate) (Pereira et al., 2014). The longer follow-up and possibly more kinds of drugs included in

Fig. 2. Survival functions for discontinuing AED medication.

[Graphs showing survival functions for discontinuing AED medication. The graphs depict the proportion of children remaining on AED treatment over time, with different lines representing various categories such as sex, presence of comorbidity, etc.]

1Analysis of all children in Stockholm Incidence Registry of Epilepsy (SIRE) (index dates between Sept 1 st, 2001 till Dec 31 st, 2006) who received AED any time after the index date and after the start of Swedish Prescribed Drug Register (SPDR) (July 1 st, 2005) up until Dec 31 2014.
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In Sweden, 65 for ADHD in 0.4 % of all children in Stockholm County in 2006 (the first during follow-up. Data from SPDR show an overall use of drug treatment of 6.4 % of the children had a suspected or certain ADHD at baseline, and ADHD than those with a single seizure at baseline. In the present study, years after the index seizure) to 31 % (4 years after the index seizure) of Board of Health and Welfare in Sweden, 2014). In contrast, 24 % (8 years after the index seizure) to 31 % (4 years after the index seizure) of children starting AED treatment for valuable treatment in the same way as children without seizures. The

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Table 2

| Number of seizures AT BASELINE | Model 1 \(N = 473\) | Model 2 \(N = 473\) |
|--------------------------------|---------------------|---------------------|
| One seizure                    | ref                 | ref                 |
| Recurrent seizures             | 217/2755            | 0.9 (0.6–1.3)       | 1.0 (0.7–1.4) |
| Comorbidity AT BASELINE        |                     |                     |
| without comorbidity            | 180/1705            | 0.5 (0.3–0.7)       | –               |
| with any comorbidity           | 80/1561             | 0.4 (0.3–0.5)       | 0.4 (0.3–0.5) |
| Intellectual Disability        | 30/793              | 0.5 (0.3–0.7)       | –               |
| CP                             | 19/480              | 0.5 (0.3–0.8)       | –               |
| Autism Spectrum Disorder       | 13/362              | 0.7 (0.4–1.2)       | –               |
| ADHD                           | 16/328              | 0.6 (0.4–1.0)       | –               |

Age at INDEX seizure

| 13–18 years | 34/737 | ref | ref |
| 9–12 years  | 45/621 | 1.6 (1.0–2.5) | 2.0 (1.2–3.1) |
| 6–8 years   | 71/615 | 2.5 (1.7–3.8) | 2.9 (1.9–4.4) |
| 1–5 years   | 77/873 | 1.9 (1.3–2.8) | 2.3 (1.5–3.5) |
| <1 year     | 33/420 | 1.8 (1.1–2.8) | 2.6 (1.6–4.2) |

a Analysis of all children in Stockholm Incidence Registry of Epilepsy (SIRE) (index dates between 1/9 2001 till 31/12 2006) who received AED any time after the index date and after the start of Swedish Prescribed Drug Register (SPDR) (1/7 2005–31/12 2014). N = 473.

b Model 1 is adjusted for age and sex.

comorbidity yes/no (comorbidity excluded in analyses of seizures with/ without comorbidity).

4 Information abstracted from medical records covering six months’ post index seizure, and pertaining to pre-index seizure, index seizure, and any subsequent seizures within six months from the index seizure, and information on comorbidities.

“psychiatric drugs”, might explain the higher proportion of “psychiatric drugs” compared to our findings.

Children with seizures have been found to have ADHD 2–7 times more often than children in the general population, with reported prevalence’s of 12–38 % (Aaberg et al., 2016; Bertelsen et al., 2016; Brikell et al., 2018; Dunn et al., 2003; Reilly et al., 2014). We found that children with recurrent seizures are more likely to receive treatment for ADHD than those with a single seizure at baseline. In the present study, 6.4 % of the children had a suspected or certain ADHD at baseline, and 4–5 % of all the children in our cohort received treatment for ADHD during follow-up. Data from SPDR show an overall use of drug treatment for ADHD in 0.4 % of all children in Stockholm County in 2006 (the first full calendar year included in SPDR) and 2.1 % in 2014 (our last year of follow-up) (Welfare, 190704). In Sweden, 65–75 % of all children with a new diagnosis of ADHD 2011–2012 tried medical treatment and of the 5–9 year olds, 55–60 % continued treatment for five years (The National Board of Health and Welfare in Sweden, 2014). In contrast, 24 % (8 years after the index seizure) to 31 % (4 years after the index seizure) of the children in our cohort with ADHD at baseline received these medications. One reason behind the lower prescription rates could be that many guidelines, including expert recommendations from the Swedish Medical Products Agency (Låkemedelsverket, 2016), recommend caution with treatment of ADHD with methylphenidate in children with seizures, even though several studies (Brikell et al., 2018; Gucuyener et al., 2003; Parisi et al., 2010) and a Task Force Report from ILAE (Besag et al., 2016a) have concluded that there is no evidence that drug treatment of ADHD in children with epilepsy causes seizures. It is important to secure that children with seizures are taken into account for valuable treatment in the same way as children without seizures. The use of ADHD medication does not seem to increase with time in our cohort as in the general population, this may in part be explained by the fact that the cohort is getting older and these medications have mostly been used in schoolchildren during the initial, larger, part of our study period.

We can confirm previous findings indicating that depression and anxiety are more common among children with epilepsy than in the general paediatric population (Aaberg et al., 2016; Hesdorffer et al., 2006; Reilly et al., 2014; Russ et al., 2012). In SIRE, 2–3 % the children received antidepressants 4 and 8 years following seizure onset, compared to 0.5 % of all 0–18 years old in Stockholm County in 2006 and 1% in 2014 (Welfare, 190704). In addition, we could show that children with a comorbidity at baseline were more likely to be treated with antidepressants than children without. Intellectual disability, ASD, CP, ADHD and epilepsy are all independently related to poor Quality of Life, psychosocial problems (Arias et al., 2018; Laurens et al., 2019; Lee et al., 2016; Moreira et al., 2013; Pinquart and Teubert, 2012) and to depression (Cianchetti et al., 2018; Daviss, 2008; Kwong et al., 2016; Pezzimenti et al., 2015; Tung et al., 2016; Whitney et al., 2019a, b) which could explain the higher use of antidepressants among children with seizures and in particular those with additional comorbidities.

Studies based on population-based registries in Denmark and Finland have shown 2–5 times higher rates of psychosis in adults with epilepsy than in the general population (Clarke et al., 2012; Qin et al., 2005). A study of children with epilepsy and psychosis found that these children are more likely to have other comorbid neurodevelopmental diagnoses like autism and intellectual disability than children with only psychosis (Lax Pericall and Taylor, 2010). We can confirm that children with seizures are more likely to receive neuroleptics, e.g., 2.5 % of the children in SIRE were dispensed such drugs after 8 years of follow-up compared to 0.2 % of the general population of Swedish children 0–18 years old in 2014 (Welfare). We also find that children with comorbidity at baseline, especially ASD and ADHD were dispensed neuroleptics more often. On the other hand, some studies have shown that children with epilepsy and psychosis more often have other comorbid neurodevelopmental diagnosis like ASD and intellectual disability than children with psychosis only. This could support the hypothesis of a common cause of the different disorders.

4.3. Strengths and limitations

This is a large population based study with good coverage in particular of children (Adelow et al., 2009) and virtually no loss-to-follow up since information was retrieved from medical records and registries. The SPDR covers all drugs dispensed at Swedish pharmacies (Wallertstedt et al., 2016; Wettermark et al., 2007) and is more likely to reflect drugs actually taken by the patient than information on prescriptions. Hence, our study provides reliable data on long-term dispensing of AEDs, neuroleptics, antidepressants, and ADHD medica-

dedication in children with unprovoked seizures. Discontinuation of AED treatment may indicate remission of seizures, but it could also reflect non-adherence to treatment or care. ADHD has been shown to be negatively associated with adherence to AED treatment which could lead to an underestimation of the number of children with ADHD who would benefit from AED treatment (Jacob et al., 2017). Unfortunately, we did not have information on seizure remission from medical records during follow-up. It should also be noted that drugs may be used for more than one disease, many AEDs are licensed for more indications than epilepsy, e.g. psychiatric disorders (Karlsson Lind et al., 2018), so we cannot readily use drugs dispensed as an indicator of the conditions of interest. Furthermore, children with epilepsy probably have more frequent contact with health care which may make them more likely to be prescribed medications in general. This could contribute to the higher prescription patterns in this group. Similarly, children with epilepsy together with neurodevelopmental comorbidities or CP may have more frequent health care contacts than children with only epilepsy. This would also result in an overestimation of the potentially detrimental impact of comorbidity on long term health assessed through prescription patterns.

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38 % (Aaberg et al., 2016; Bertelsen et al., 2016; Brikell et al., 2018; Gucuyener et al., 2003; Parisi et al., 2010) and a Task Force Report from ILAE (Besag et al., 2016a) have concluded that there is no evidence that drug treatment of ADHD in children with epilepsy causes seizures. It is important to secure that children with seizures are taken into account for valuable treatment in the same way as children without seizures. The use of ADHD medication does not seem to increase with time in our cohort as in the general population, this may in part be explained by the
On the other hand, the seizures and comorbidities might disguise and take precedence over the need of treatment for other diagnoses.

Another limitation is that baseline information about comorbidities was retrieved from medical records, which did not always include a fully worked-up diagnosis. On the other hand, these records do reflect the actual clinical setting in which treatment decisions regarding AEDs are based. SPDR shows all dispensed drugs since July 1st, 2005 but it does not include information of the indication for the drug, which means that some dispensed drugs might be used for other indications than those we presume. We also lack information about earlier dispensed drugs for children with index seizure before the start of SPDR. This means that more children in SIRE might have tried the different medications with insufficient effects, or adverse effects, that made them discontinue treatment before the start of SPDR. This probably leads to an underestimation of drugs used in the SIRE cohort. In addition to this, we lack complete information on family history of epilepsy or other neuro-developmental problems, why this has not been included in the analyses. Knowledge of a family history of epilepsy or any of the co-morbidities under study might have led to earlier diagnosis in the child and a higher probability of pharmacological treatment.

Socioeconomic factors might influence the use of health care as well as the use of prescription drugs, both regarding adherence to treatment in the follow-up and also subsequent increased risk of recurrent seizures at baseline. Moreover, there is in general a higher use of prescription drugs in groups with lower socioeconomic status (SES) (Weitsof et al., 2008). Unfortunately, access to information regarding SES and parents’ education was incomplete in the younger age groups, why we were unable to adjust for this. However, there was no association between the risk of unprovoked seizures and SES or education in previous studies based on SIRE (Adelow et al., 2011, 2012; Mahler et al., 2018).

With regard to generalisability, this was a population-based study and the results should be generalizable to settings with similar seizure aetiology, health care services, and treatment traditions regarding neuropsychiatric disorders.

5. Conclusion

This study provides data to facilitate individualized counselling. The question of prognosis in terms of long-term medication after a first seizure is often one of the caregiver’s or patient’s main concerns. We confirm that neurodevelopmental comorbidities and particularly CP on epilepsy are associated with poorer epilepsy prognosis in terms of continued AED treatment, and also find that these conditions are associated with more frequent use of neuroleptics, antidepressants and drugs against ADHD. This highlights the need to carefully consider these diagnoses when managing children with seizures, and if possible to take into account the possible future drug-drug interactions if need for co-morbidity drug treatment, when making AED choices.

Table 3
Odds Ratio (OR) of children treated with drugs against ADHD, with antidepressants or neuroleptics 4 and 8 years following a first unprovoked seizure in children.

| Comorbidity at baseline | Intellectual disability | CP | Autism Spectrum Disorder | ADHD |
|-------------------------|-------------------------|----|--------------------------|------|
| Without comorbidity     | N=119                   | 4 (3) | 61 (1) | 10 (4) |
| With any comorbidity    | N=250                   | 9 (4) | 22.2 | 6.9 |
|                         | (2.8–178.2)             | (2.4–19.8) |
| Odors (OR* (95% CI)     | 2.4 (0.5–11.2)          | 1.3 | 1.8 | 6.3 |
|                         | 2.0 (0.5–7.3)           | (0.1–14.6) | (0.3–11.5) | (1.2–33.5) |
|                         | 2 (0.1–3.9)             | 1 (0.4–8) | 7 (2.2–37.4) | (0.0–3.9) |
|                         | 3 (0.3–5.53)            | (1) | 91 | 1 (2) |
|                         | 0.5 (0.5–14.3)          | 1.2 | 1.1 | 4 (6) |
|                         | 2 (0.5–9.7)             | 2.6 | 2 | 2.7 |
|                         | 3 (0.8–9.7)             | 2.6 | 2 | 2.6 |
|                         | 5 (0.2–2.2)             | 2.6 | 2 | 2.7 |
|                         | 0.5 (0.1–1.6)           | 2.6 | 2 | 2.6 |
|                         | 4 (0.6–6.2)             | 2.6 | 2 | 2.6 |
|                         | 1.9 (0.0–1.8)           | 2.6 | 2 | 2.6 |
|                         | 0.2 (0.0–1.8)           | 2.6 | 2 | 2.6 |
|                         | 0.2 (0.0–1.8)           | 2.6 | 2 | 2.6 |
|                         | 0.2 (0.0–1.8)           | 2.6 | 2 | 2.6 |
|                         | 0.2 (0.0–1.8)           | 2.6 | 2 | 2.6 |
|                         | 0.2 (0.0–1.8)           | 2.6 | 2 | 2.6 |
|                         | 0.2 (0.0–1.8)           | 2.6 | 2 | 2.6 |
|                         | 0.2 (0.0–1.8)           | 2.6 | 2 | 2.6 |
|                         | 0.2 (0.0–1.8)           | 2.6 | 2 | 2.6 |
|                         | 0.2 (0.0–1.8)           | 2.6 | 2 | 2.6 |
|                         | 0.2 (0.0–1.8)           | 2.6 | 2 | 2.6 |
|                         | 0.2 (0.0–1.8)           | 2.6 | 2 | 2.6 |
|                         | 0.2 (0.0–1.8)           | 2.6 | 2 | 2.6 |
|                         | 0.2 (0.0–1.8)           | 2.6 | 2 | 2.6 |
|                         | 0.2 (0.0–1.8)           | 2.6 | 2 | 2.6 |
|                         | 0.2 (0.0–1.8)           | 2.6 | 2 | 2.6 |
|                         | 0.2 (0.0–1.8)           | 2.6 | 2 | 2.6 |
|                         | 0.2 (0.0–1.8)           | 2.6 | 2 | 2.6 |
|                         | 0.2 (0.0–1.8)           | 2.6 | 2 | 2.6 |
|                         | 0.2 (0.0–1.8)           | 2.6 | 2 | 2.6 |
|                         | 0.2 (0.0–1.8)           | 2.6 | 2 | 2.6 |
|                         | 0.2 (0.0–1.8)           | 2.6 | 2 | 2.6 |
|                         | 0.2 (0.0–1.8)           | 2.6 | 2 | 2.6 |
|                         | 0.2 (0.0–1.8)           | 2.6 | 2 | 2.6 |
|                         | 0.2 (0.0–1.8)           | 2.6 | 2 | 2.6 |

* Odds Ratios (ORs) adjusted for age groups and sex.

† Information abstracted from medical records covering six months’ post index seizure, and pertaining to pre-index seizure, index seizure, and any subsequent seizures within six months from the index seizure, and information on comorbidities. †Reference value equals 0.
Declaration of Competing Interest

The authors report no declarations of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eplepsyres.2020.10.649.

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