Epilepsy Research 143 (2018) 33–40

Contents lists available at ScienceDirect

Epilepsy Research

journal homepage: www.elsevier.com/locate/epilepsyres

Neurodevelopmental comorbidities and seizure control 24 months after a first unprovoked seizure in children

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ARTICLE INFO

Keywords:
Epilepsy
Children
Neurodevelopmental
Comorbidity
Seizure control
Follow-up

ABSTRACT

Purpose: To follow children with newly diagnosed unprovoked seizures to determine (1) whether the prevalence of neurodevelopmental comorbidities and cerebral palsy (CP) changed after the initial seizure, and (2) the association between studied comorbidities and seizures 13–24 months after seizure onset or initiation of treatment.

Methods: Analyses were based on 750 children (28 days–18 years) with a first unprovoked seizure (index) included in a population-based Incidence Registry in Stockholm between 2001 and 2006. The children were followed for two years and their medical records were examined for a priori defined neurodevelopmental/psychiatric comorbidities and CP and seizure frequency. Baseline information was collected from medical records from before, and up to six months after, the index seizure. Odds ratios (OR) of repeated seizures 13–24 months after the first seizure or after initiation of anti-epileptic drug treatment was calculated by logistic regression and adjusted for age and sex.

Results: At baseline, 32% of the children had neurodevelopmental/psychiatric comorbidities or CP compared to 35%, 24 months later. Children with such comorbidities more often experienced seizures 13–24 months after the index seizure (OR 2.87, CI 2.07–3.99) with the highest OR in those with CP or attention deficit hyperactivity disorder (ADHD). Children diagnosed at age < 1 year exhibited the highest prevalence of comorbidities as well as OR for repeated seizures. A combination of young age and comorbidity was associated with an OR for repeated seizures of 5.12 (CI 3.03–8.65). Among the children without comorbidities 76% were seizure free 13–24 months after the index seizure or after initiation of AED treatment compared to 53% of children with comorbidities.

Conclusions: This study indicates that neurodevelopmental comorbidities and CP in children with epilepsy tend to be present already at seizure onset and that such comorbidities are strong indicators of poor outcome regarding seizure control with or without treatment.

1. Introduction

Accumulating evidence indicates that neurodevelopmental comorbidities (for example; developmental delay, speech/language and learning difficulties, ADHD, intellectual disability, autism spectrum disorders) are common already at the time of or even prior to epilepsy onset (Andell et al., 2015; Austin et al., 2011; Berg et al., 2005; Hermann et al., 2012; Hesdorffer et al., 2006; Hesdorffer et al., 2004; Oostrom et al., 2003; Pohlmann-Eden et al., 2015). Cerebral palsy and psychiatric disorders are also known comorbidities in epilepsy (Graham et al., 2016; Josephson and Jette, 2017). Moreover, the presence of such comorbidities exerts an impact on the prognosis, predicting more frequent recurrence of seizures following a single unprovoked seizure (Berg, 2008), lower probability of remission (Hosking et al., 1990; Oskoui et al., 2005) and greater need for antiepileptic drug (AED) polytherapy (Aksu, 1990). In addition, cognitive impairment and repeated seizures are associated with negative psychosocial outcomes (Chin et al., 2011; Geerts et al., 2011). Nonetheless, comorbidities associated

Abbreviations: CP, cerebral palsy; ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorders; SIRE, Stockholm Incidence Registry of Epilepsy; ESSENCE, Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations; AED, antiepileptic drugs; OR, odds ratio

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https://doi.org/10.1016/j.eplepsyres.2018.03.015
Received 14 December 2017; Received in revised form 1 March 2018; Accepted 20 March 2018
Available online 20 March 2018
0920-1211/

with childhood epilepsy are often not recognized (Hermann et al., 2008) and may be particularly difficult to diagnose at the onset of seizures. Earlier investigations in this area have involved smaller cohorts that were not population-based (e.g., specific epilepsy syndromes, selected ages or patients from tertiary referral hospitals) and focused on only certain comorbidities (Austin et al., 2001; Hesdorffer et al., 2004; Oostrom et al., 2003; Oskoui et al., 2005).

Our previous population-based study of incident cases of unprovoked seizures in children, revealed that neurodevelopmental comorbidity and CP are common already at the time of seizure onset (Andell et al., 2015). In the present study, we have followed-up this large cohort in order to (1) determine whether the prevalence and type of neurodevelopmental/psychiatric comorbidities and CP have changed two years after the first unprovoked seizure, (2) examine the probability of being free from seizures two years after onset or the initiation of treatment and (3) to assess the association between these comorbidities identified already at the onset of seizure and lack of seizure control at a later stage. We also highlight non-specific neurodevelopmental comorbidities in younger children (both separately and grouped as in ESSENCE (Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations)) with seizures in a manner not previously reported.

2. Methods

For the period of September 1, 2001–December 31, 2006, the population-based Stockholm Incidence Registry of Epilepsy (SIRE) (Adelow et al., 2009; Andell et al., 2015), covers 750 children with newly diagnosed unprovoked seizures from the northern Stockholm area (an urban area in which approximately 230,000 less than 19 years of age lived at that time) (StatisticsSweden).

In brief, we identified all children who lived in the area during the designated time period who sought medical care for anything suspected by the clinician of being a seizure and if this event was classified as an unprovoked seizure by our expert panel, it was designated as *the index seizure* and the patient included in the registry. Exclusion criteria for this study were; neonatal seizures, acute symptomatic seizures (e.g. febrile seizures), or non-epileptic seizures, previously documented epileptic seizures within five years of the index seizure or patient being 19 years old, or older, at the time of the index seizure.

Data was abstracted at two time points. Baseline data encompassed information abstracted from medical records pertaining to pre-index seizure, index seizure, and six months post index seizure. Seizure diagnosis, classification and information about comorbidities was also collected for 6–24 months following the index seizure or initiation of AED, and in combination with the information from the baseline data, this is referred to as *2 year data*. Sometimes the additional information (e.g. results of MRI) made the diagnosis more precise, sometimes it revised the baseline diagnosis, and sometimes the original diagnosis was still valid. Cases were defined as *recurrent seizures within six months* if the child had experienced additional seizures either before or within six months after the initial index seizure. Lack of remission was defined as seizures during the last 12 months of follow-up (13–24 *months after the index seizure or initiation of AED treatment*). The follow-up of the children who received AED treatment within 24 months from index was prolonged to 24 months after AED initiation. This to allow adequate assessment of the effect of the treatment. Information concerning seizure control and treatment was obtained from the patient/parental report in the medical records (for a more detailed description of our method, please see (Andell et al., 2015; Adelow et al., 2009)).

Seizure definition and classification (symptomatic, cryptogenic, idiopathic or of unknown origin) was done in accordance with the guidelines for epidemiological studies of epilepsy issued by the International League Against Epilepsy (ILAE) at the time of inclusion of the children in SIRE (Commission, 1989, 1993, 1997). All patient records were evaluated independently by at least two persons in our panel which at that time consisted of a neuropediatrician (PÅ), a resident in neuropediatrics (EÅ), and the study coordinator, a trained nurse (EH).

The medical records were examined for the comorbidities at two time-points (baseline and 2 year data) as described earlier (Andell et al., 2015). The comorbidities were defined a priori as (1) developmental delay, (2) speech/language and learning difficulties, (3) intellectual disability, (4) cerebral palsy (CP) (5), autism spectrum disorder (ASD), (6) Attention-deficit/hyperactivity disorder (ADHD) and (7) unspecified psychiatric disorder. Groups 3, 4, 5 and 6 were classified according to the ICD-10 (International Classification of Diseases) and *developmental delay* defined as unspecific psychomotor delay, present primarily in younger children. *Speech/language and learning difficulties* encompassed a wide variety of problems, including dyslexia, as well as difficulties at school that required extensive extra help and/or repetition of a grade. Finally, *unspecified psychiatric disorders* included children with a description in the medical records of a wide range of problems such as tics, depression and anxiety, for which the child/caregiver reported that the child had received any kind of professional help *before the two time-points (baseline or two year data)*. Our panel classified the comorbidity as *certain* when a specific diagnosis was registered in the records or as *suspected* in the absence of a diagnosis according to ICD 10, but a clear clinical description of the problem. For analytical purpose these certain and suspected groups were often combined. These various comorbidities were not mutually exclusive.

We focused in particular on the ESSENCE group, an acronym (Fernell and Gillberg, 2010; Gillberg, 2010) proposed to reflect our less precise understanding (and thus less reliable diagnoses) of cognitive problems at an early age. In the present study children less than 6 years of age at the time of their index seizure and who exhibited confirmed or suspected comorbidity in the cognitive domains (developmental delay, speech/language and learning difficulties, intellectual disability, ASD and ADHD) at the time of the six-month follow-up belonged both to an ESSENCE group and a more specific group based on the nature of their comorbidity.

This study was approved by the Regional Ethical Review Board at Karolinska Institutet, Stockholm, Sweden (No. 2005/4:8 and 2008/2:4).

2.1. Statistical analyses

Characteristics are displayed as means (SD) and medians (interquartile range IQR). Odds ratios (OR) and 95% confidence intervals (CI) were calculated by logistic regression. The OR for seizures during months 13–24 was estimated in relationship to sex, age at onset, aetiology, presence of comorbidity and the type of comorbidity. All seven individual comorbidities were examined simultaneously in the same model. ORs were adjusted for age (< 1 year, 1–5, 6–8, 9–12 and 13–18 years of age) and sex. All analyses were performed with the SAS 9.4 software.

3. Results

The total number of children eligible for the present follow-up was 750 (56% boys, median age: 7 years, range 28 days-18 years) (Table 1). Sixteen children were lost before the two years follow-up, 5 of these died. At baseline 67% (n = 503) had experienced more than one seizure compared to 74% (n = 553) at 24 months. At both times more children with a comorbidity had more than one seizure than those without comorbidity (Table 1).

The prevalence and type of the seven comorbidities 2 years after the index seizure was similar to that at baseline, at which time-points, suspected or confirmed neurodevelopmental or psychiatric comorbidity or CP was present in 32% and 35% of the children, respectively (Fig. 1). The comorbidities were distributed equally among the different age groups at both time-points, although the specific comorbid diagnosis for certain individuals had changed. At two years, neurodevelopmental or psychiatric comorbidities or CP were found in 8% (n = 39) children not