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RESEARCH ARTICLE

Outcome at age 7 of epilepsy presenting in the first 2 years of life. A population-based study

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Abstract

Objective: Existing data suggest that epilepsy presenting in the first few years of life carries a worse prognosis than later onset. However, studies are few and methods differ, making interpretations of data uncertain. This study analyzes outcome at age 7 and potential prognostic factors in a well-characterized population-based cohort with epilepsy onset during the first 2 years of life.

Methods: An incidence cohort of 116 prospectively identified cases of epilepsy with seizure onset before age 2 years was described in Stödberg et al. (2020). Cases were originally retrieved from the Stockholm Incidence Registry of Epilepsy (SIRE), which registered all cases with a first unprovoked epileptic seizure from September 1, 2001, in Northern Stockholm. Data on treatment and outcome at age 7 years were collected from electronic medical records and through interviews with parents. Outcome and potential prognostic factors were analyzed with descriptive statistics and multivariable log binomial regression analysis.

Results: Eleven children (9.5%) died before age 7. Polytherapy was common. Epilepsy surgery was performed in two children. At age 7 years, 61 of 116 children (53%) had been seizure-free for the last 2 years or longer. Intellectual disability was diagnosed in 57 of 116 children (49%), autism spectrum disorder in 13 (11%), and cerebral palsy in 28 (24%). West syndrome had a similar seizure remission rate but a worse cognitive outcome. There was no difference in outcome between first and second year onset. Six predictors, including etiology, remained associated with two or more outcome variables after regression analysis.

Significance: About half of children with infantile-onset epilepsy will become seizure-free and half of them will have intellectual disability. Etiology was confirmed as a major independent predictor of outcome. Our study contributes to a more firm knowledge base when counseling parents of infants diagnosed with epilepsy.

KEYWORDS
comorbidities, etiology, infantile epilepsy, outcome, seizure remission

1 | INTRODUCTION

Counseling the parents of an infant diagnosed with epilepsy can be challenging. Cases with seemingly similar presentations may have dramatically different futures. Potential etiologies are many and diverse and the prognosis varies—from benign in self-limited epilepsy syndromes to very serious and sometimes early death in progressive neurodegenerative etiologies and developmental and epileptic encephalopathies.

The clinical course and outcomes of a disease are best studied in population-based incidence settings. For pediatric epilepsy in general, two thirds of patients will attain long-term seizure freedom, about one fourth of cases will be drug resistant and as many have intellectual disability.[1–6] For infantile-onset epilepsy presenting during the first or second year of life, a worse outcome could be expected. Developmental and epileptic encephalopathy syndromes present early in life, as do often other severe epilepsies caused by brain disorders like cerebral malformations, neurometabolic diseases, and perinatal hypoxic–ischemic encephalopathy.[7] However, outcome studies on infantile-onset epilepsy are scarce and methods differ, making comparisons and interpretations of data uncertain. A few population-based studies, with varying inclusion criteria, follow-up time, and outcome variables, include data after seizure onset during the first few years of life.[1,4,8–12] In addition, hospital-based reports of outcomes in infantile-onset epilepsy often show worse outcomes in terms of seizure freedom and cognition due to selection bias.[13–16] Recurrently reported prognostic factors include seizure-onset age, developmental delay at onset, and etiology.[1,4,8–12] Etiology appears to be the main independent prognostic factor but it is often unknown.[1,9,10]

We recently described epilepsy syndromes and etiologies in a population-based prospective incidence cohort of 116 children presenting with epilepsy during the first 2 years of life.[7] An epilepsy syndrome classified by the International League Against Epilepsy (ILAE) criteria could be diagnosed in 54% of the children. A cause was revealed in 65% of cases and 29% (34/116) had a confirmed molecular genetic diagnosis. Here we describe treatment and outcome at age 7 in the same cohort. Factors that are potentially prognostic for outcome in terms of mortality, seizures, neurodevelopmental comorbidities, and type of school attended are analyzed.

Key Points

- Half of children with infantile-onset epilepsy will be in seizure remission at age 7 years.
- Half of the children will be diagnosed with intellectual disability.
- A substantial proportion of the children will attend mainstream school.
- Etiology is the main independent predictor of outcome in infantile-onset epilepsy.
- Improved dissection of etiologies will further improve prognostics and enable the development of precision treatments.

2 | METHODS

2.1 | Study cohort

The study cohort was defined as all children living in the study area who had their first unprovoked epileptic seizure before 2 years of age between September 1, 2001, and December 31, 2006, and met epilepsy criteria before age 7 years. The personal identification numbers of potential cases were retrieved from the prospective Stockholm Incidence Registry of Epilepsy (SIRE). This registry has been described previously in detail.[7,17] Briefly, SIRE aimed to register all cases in Northern Stockholm of a first unprovoked epileptic seizure leading to medical attention, referred to as the index seizure. Northern Stockholm is an urban area with about 1 million inhabitants during the study period. Approximately 13 000 children were born each year. Seizures during the first 4 weeks of life, typical febrile seizures, and seizures during the first week after acute brain injury/disease such as stroke, head trauma, or encephalitis were considered provoked.[18] Pediatric cases were identified from multiple sources including review of electronic medical records with an International Classification of Diseases, 10th revision (ICD-10) code of G40, G41, or R56.8d and scanning of all electroencephalography (EEG) referrals. The Karolinska University Hospital has the only inpatient pediatric wards, neuropediatric outpatient clinic, and EEG laboratory in the study area. All children with epilepsy in Northern Stockholm are expected to be treated at the Karolinska University Hospital. Cases in SIRE with the index seizure during the study period and before 2 years of age were reassessed by review of medical records and in some cases by a structured telephone interview with parents. Considering all available data, cases fulfilling the latest ILAE epilepsy diagnostic criteria[19] before age 7 years were selected for the study cohort.

2.2 | Data collection

Structured information about each case was compiled from the hospital electronic medical records.[7] In cases

with incomplete medical records, the families were contacted by letter, followed up by a structured telephone interview, and asked for permission to obtain copies of medical records from other relevant health care providers. Data were gathered from available sources up to age 7 years. The workup and treatment of each case had been determined by the doctors caring for the patient. In all cases the epilepsy diagnosis and the classification were evaluated by two of the authors (TS, PÅ) and discussed until consensus was reached. The results in terms of background characteristics, workup, seizures, epilepsy syndromes, and etiology were analyzed and have been reported recently.[7]

In addition, data on treatment, clinical course, and outcome were compiled (Table S1). Recorded treatments encompass pharmacological treatment with antiseizure medications (ASMs), epilepsy surgery, vagus nerve stimulation (VNS), and ketogenic diet. Seizure variables include daily seizures for more than 4 weeks at any time (as opposed to never having had daily seizures for 4 weeks in a row) and occurrence of status epilepticus. Daily seizures for more than 4 weeks was chosen as a measure of maximum seizure frequency and a potential predictor of outcome based on the authors' clinical impression that daily seizures for several weeks in a row often is associated with abnormal development and drug resistance. Outcome at age 7 was described from several perspectives: mortality, ongoing treatment, seizure freedom, and neurodevelopmental comorbidities as diagnosed and described in the medical records and type of school attended (mainstream or special education). The comorbidities considered were intellectual disability, autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD)/attention deficit disorder (ADD), other learning difficulties, cerebral palsy, and other motor impairments. The ASD diagnosis was based on neuropsychiatric evaluation. Intellectual disability, defined as an intellectual quotient (IQ) <70, was diagnosed based on formal neuropsychological evaluation, except in cases where formal testing was not possible due to severe cognitive disability.

2.3 | Statistics

Descriptive statistics were applied to analyze the proportions in percentage, of the whole study cohort and of subgroups, with different outcomes. Assessed potential predictors of outcome included sex, epilepsy in first-degree relative, febrile seizures in first-degree relative, prematurity, birth weight, neonatal disease, first seizure febrile, developmental delay at epilepsy onset, age at epilepsy onset, seizure type at onset, daily seizures for more than 4 weeks, status epilepticus, West syndrome, etiology (three categories: known, structural/metabolic/infectious, confirmed genetic), any early EEG abnormality (within 6 months of onset) and magnetic resonance imaging (MRI) abnormality. Differences in outcome between groups were univariably analyzed as relative risk (RR) using likelihood-ratio test and 95% confidence intervals (CI). A multivariable log binomial regression analysis[20,21] was performed using R free software to assess the independent effects of factors showing significance in the univariable analysis. The multivariable model was reduced by stepwise backward selection dropping non-significant factors (p-value > .05).

3 | RESULTS

3.1 | Study cohort

As previously described, 163 cases were retrieved from SIRE.[7] After reassessment of all available data up to age 7, a total of 116 cases were classified as epilepsy and constitute the study cohort. The remaining cases from SIRE were excluded due to nonepileptic events only ($n = 7$), provoked seizures only ($n = 17$), or a single unprovoked seizure only, and no other factor motivating epilepsy diagnosis after a first seizure ($n = 24$). Of the children with epilepsy, 24 of 116 (21%) had previous neonatal seizures of various causes (acute symptomatic 17, cerebral malformations 3, unknown 4). Some of the characteristics of the cohort, described in detail in the previous publication, are summarized in Table 1. Epilepsy onset occurred at a mean age of 7.4 months (median 6, span 1–23). Eleven children (9.5%) died before 7 years of age, including 2 with West syndrome. The causes of death were progressive neurodegenerative disease in nine cases, influenza in a child with lissencephaly, and probable sudden unexpected death in epilepsy (SUDEP) in one case.

3.2 | Treatment

Most children (106/116, 91%) were treated with at least one ASM before age 7 years. Medication was first started at a mean age of 7 months (median 5, span 0–28). The mean number of ASMs tried was 3.8 (median 3, span 1–14); 59 children (51%) tried more than two ASMs and 47 (41%) were at some point on polytherapy with 3 to 6 drugs. At age 7 years, 51/105 living children (49%) were still taking ASMs. Five children were treated with ketogenic diet from a mean age of 5 years. Two children had a vagus nerve stimulator implanted at ages 6.5 and 7 years, respectively. One child with hemimegaloencephaly had a hemispherotomy performed at 27 months and a child with

TABLE 1 Characteristics in 116 cases of epilepsy with onset before age 2 years

	All cases, *n* (%)	West syndrome, *n* (%)
All	116 (100)	33 (100)
Male sex	59 (51)	17 (52)
Epilepsy first-degree relative	19/115 (17)	4 (12)
Febrile seizure first-degree relative	7/106 (7)	0/30 (0)
Gestation: <37 weeks	9 (8)	3 (9)
Birth weight: <2.5 kg	9/107 (8)	3 (9)
Neonatal disease[a]	38 (33)	14 (42)
First febrile seizure	23 (20)	1 (3)
Developmental delay at onset	46 (40)	17 (52)
Age at onset		
<4 months	33 (28)	12 (36)
<12 months	88 (76)	31 (94)
Type of seizure onset		
Focal	53 (46)	4 (12)
Spasm	24 (21)	24 (73)
Generalized	7 (6)	2 (6)
Daily seizures for >4 weeks	74/115 (64)	28/32 (88)
Status epilepticus	16 (14)	3 (9)
Any epilepsy syndrome	63 (54)	33 (100)
West syndrome	33 (28)	33 (100)
MRI abnormality	37/57 (65)	14/21 (67)
Early EEG abnormality[b]	83 (72)	33 (100)
Type of etiology		
Known[c]	69 (59)	24 (73)
Structural/Met/Inf[d]	52 (45)	18 (55)
Confirmed genetic	34 (29)	11 (33)

Note: Onset refers to the first unprovoked seizure.

Abbreviation: *n (%)*, number of cases (% of all cases). EEG, electroencephalogram; MRI, magnetic resonance imaging.

[a]Neonatal disease includes any disease with potential central nervous system (CNS) affection like hypoxic-ischemic encephalopathy (HIE), stroke, sepsis, meningitis, epileptic seizure, hypoglycemia.

[b]Any abnormality on EEG within 6 months of onset.

[c]Includes also presumed genetic etiology (= cases of tuberous sclerosis (3), metabolic disease (3) and familial epilepsy syndromes (6) without confirmed mutations).

[d]Includes structural (39), metabolic (10) and infectious (3) cases.

widespread cortical dysplasia had a frontal resection at 27 months followed by hemispherotomy at 7 years of age.

3.3 | Seizure outcome

At age 7 years 61 of 116 children (53%) had been seizure-free for the last 2 years or longer, and the majority (42% of all children) for more than 5 years. Seven children (6%) had been seizure-free between 6 months and 2 years, 37 (32%) for less than 6 months, and the remaining children were deceased before age 7. Of the whole cohort, 54 children (47%) were alive and off ASMs at age 7, and they all had been seizure-free for the last 2 years or more. Seizure outcome was similar in the subgroup of West syndrome cases, with 19 of 33 (58%) being seizure-free for at least 2 years, 15 (45%) for more than 5 years, and 11 (33%) for less than 6 months. Fifteen children (45%) with West syndrome were alive and off ASMs at age 7, of which all had been seizure-free for more than 5 years. Of etiological subcategories, perinatal asphyxia had the worst seizure outcome, with only 10% of cases being seizure-free for more than 2 years, and the unknown etiology group had the best with 77% being seizure-free. The corresponding

values for other etiologies and etiology groups are shown in Table 2.

3.4 | Comorbidities

At death or age 7 years, 57 of 116 children (49%) had a diagnosis of intellectual disability, 13 (11%) had been diagnosed with ASD, and 28 (24%) had cerebral palsy. These conditions occurred in isolation in 29 cases (25%) or in any combination in 34 (29%). A combination of severe motor symptoms and intellectual disability was seen in 10 cases of metabolic disease. An additional 11 children (9%) had other neurodevelopmental problems (ADHD, learning difficulties, other motor impairments), and 42 (36%) had no documented neurodevelopmental issues. For West syndrome cases, outcomes in terms of comorbidities were worse: 23 of 33 (70%) intellectual disability, 6 (18%) ASD, 10 (30%) cerebral palsy, 3 (9%) learning difficulties, and 5 (15%) without neurodevelopmental issues. Comorbidities for etiological subcategories are displayed in Table 2. Altogether 40 of 116 children (34%) had a normal outcome in the sense that they had no neurodevelopmental problems and were seizure-free for 2 years or more at age 7. In the West syndrome cohort, 5 of 33 children (15%) had a normal outcome, whereas for etiological subcategories values ranged from 0% to 64%.

3.5 | Educational support needs

At 7 years of age, 43 of 116 children (37%) attended special education school. Sixty-two children (53%) went to mainstream school with (19 cases) or without (43 cases) extra support. The remaining children did not reach school age. For West syndrome, the values were 19 of 33 (58%) special education and 12 (36%) mainstream school with (7 cases) or without (5 cases) extra support.

3.6 | Predictors of outcome

Eighteen potential prognostic factors (predictors) were analyzed in relation to eight outcome variables. All variables and case numbers are shown in Table S2. The results of univariable analysis (RR using likelihood-ratio test and 95% CI) are displayed in Table 3. *Developmental delay at epilepsy onset*, *Daily seizures for more than 4 weeks*, *Status epilepticus*, *Early EEG abnormality*, *Structural/metabolic/*

TABLE 2 Outcome at age 7 years by etiology

	Intellectual disability	ASD	Cerebral palsy plus[a]	No NDV	Seizure-free > 2 years[b]	Seizure- free and no NDV
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Cerebral malformation, *n* = 16	13 (81)	2 (12)	11 (69)	1 (6)	3 (19)	2 (12)
Perinatal asphyxia, *n* = 10	8 (80)	0(0)	9(90)	0(0)	1(10)	0(0)
Metabolic disease, *n* = 10	10 (100)	0(0)	10(100)	0(0)	2(20)	0(0)
Tuberous sclerosis, *n* = 5	3 (60)	3(60)	0(0)	0(0)	1(20)	0(0)
Stroke, *n* = 5	3 (60)	0(0)	3(60)	2(40)	3(60)	2(40)
Struct/Met/Inf etiology, *n* = 52	40 (77)	5(10)	36(69)	6(12)	13(25)	6(12)
Genetic etiol, no s/m[c], *n* = 17	12 (71)	2(12)	2(12)	4(24)	12(71)	4(24)
Unknown etiology, *n* = 47	5(11)	6(13)	0(0)	32(68)	36(77)	30(64)

Abbreviations: ASD, autism spectrum disorder. NDV = neurodevelopmental problem, includes intellectual disability, autism spectrum disorder, cerebral palsy, attention-deficit/hyperactivity disorder, other learning difficulties, other motor impairments. Struct/Met/Inf etiology, includes structural, metabolic and infectious etiology.

[a]"Cerebral palsy plus" includes 28 cases of cerebral palsy and 10 cases of similar motor symptoms in progressive metabolic disease.

[b]Seizure-free for 2 years or longer at age 7.

[c]Molecularly confirmed genetic etiology without structural or metabolic abnormality.

Infectious etiology, and *Known etiology* (also including confirmed and presumed genetic etiology) showed statistical significance ($p \leq .05$) for the highest number (six to seven of eight) of outcome variables. Specific individual etiologies were not included as predictors because of the small case numbers. Onset age showed limited predictive value with *Onset <4 months* only being significant for cerebral palsy plus (includes cerebral palsy and similar motor symptoms in metabolic disease). Onset <6 months and <12 months did not show higher significance (results not displayed). For ASD, *Male sex* was the only significant predictor. Premature birth (*Gestation <37 weeks*) and *Birth weight <2.5 kg* did not show significance for any outcome variable.

Nine of the predictors and six outcome variables were selected for multivariable log binomial regression analysis for reasons explained together with results in Table 4. *Developmental delay at epilepsy onset* and *Daily seizures for >4 weeks* showed independent significance for five of the outcomes, *Structural/metabolic/infectious etiology* for four outcomes, *Status epilepticus* for three outcomes, and *First seizure febrile* and *Early EEG abnormality* both for two outcomes. *Neonatal disease*, *Onset <4 months* and *West syndrome* did not show independent significance for any of the six outcomes.

4 | DISCUSSION

In this population-based cohort, 9.5% of patients had died by age 7, mainly due to neurodegenerative disease and one case of SUDEP. Two-year seizure remission rates were in the range of 53% to 60% for the cohort as a whole as well as for West syndrome and epilepsy caused by stroke. For perinatal asphyxia, cerebral malformations, tuberous sclerosis complex (TSC), and metabolic disease remission rates were lower at 10%–20%, whereas genetic etiology without structural or metabolic abnormality and unknown etiology had remission rates at 71% and 76%, respectively. Half of the cohort had intellectual disability and two thirds any neurodevelopmental impairment, with the West syndrome subgroup having a worse prognosis with the corresponding fractions 70% and 85%, respectively. No children with perinatal asphyxia, TSC, or metabolic disease had normal outcome. Still, at age 7, half of all children and one third of children with West syndrome attended mainstream school. The strongest independent predictors against seizure remission and/or for neurodevelopmental impairments were *Developmental delay at epilepsy onset, Daily seizures for >4 weeks, Structural/metabolic/infectious etiology*, and *Status epilepticus*. There were no significant differences in outcome between first and second year onset.

4.1 | Strengths and weaknesses

Our study cohort was identified prospectively for an incidence registry and gives a full population-based picture of outcome; this is a strength. Conditions in the study area and methods applied, as described in this and a previous report,[7] favor a high ascertainment rate, a standardized management of pediatric epilepsy, and readily available complete clinical information through electronic medical records. The fact that clinical information was retrospectively compiled and not prospectively documented in a study protocol is a weakness. This is in part compensated for through all children being managed at the same neuropediatric unit in accordance with written guidelines for workup and treatment. The size of the study cohort is comparable to the few previous incidence cohorts of infantile epilepsy. The follow-up time at age 7 years is sufficient to detect major comorbidities and evaluate seizure remission.

To our knowledge, only one previous population-based study focused on outcome of epilepsy, defined and classified according to present recommendations in terms of epilepsy, epilepsy syndromes, and etiologies, with onset in the first year of life; however, with a short follow-up at age 2 years and limited genetic workup.[9] One older report included cases already after a single unprovoked seizure but excluded cases with previous neonatal seizures.[8] Another study reports outcome after seizure onset during the first 2 years of life and for the first-year onset subgroup.[10] Two studies included children with seizure onset up to age 7 and 13 years, respectively, but also reported some outcome data on their first-year onset subgroups.[1,4] In addition, one report described outcome after seizure onset up to age 3 years, with no onset age subgroup data[11] and a recent study from the same group focused on outcome of focal epilepsy with onset before age 2.[12]

Mortality at 9.5% in our study is in line with previous data, as is the observation that mortality is related mainly to severe underlying etiology and impairments, with pneumonia being a common fatal complication.[10–12] Cases of aspiration due to seizures[10,11] and SUDEP[9,12] add to mortality. Mortality after first-year seizure onset is somewhat lower in previous studies than the 11% in our cohort, possibly due to their shorter follow-up time[9] and inclusion of milder cases.[8]

4.2 | Treatment

Polytherapy is common in drug-resistant epilepsy (DRE).[22] DRE according to the ILAE definition[23] is not addressed directly in our study, but one third of children had been seizure-free for less than 6 months at age 7 and

TABLE 3 Results of univariable analysis

Outcome → Predictors↓	Deceased*		ID		ASD*		CP plus
	RR (CI)	*p*	RR (CI)	*p*	RR (CI)	*p*	RR (CI)
Male sex*	0.81 (0.24–2.53)	.71	1.07 (0.74–1.57)	.71	11.59 (2.40–207.70)	<.001	0.87 (0.51–1.47)
Epilepsy in FDR*	6.06 (2.03–19.24)	.002	0.95 (0.51–1.48)	.83	0.46 (0.03–2.16)	.38	1.35 (0.67–2.32)
Febrile seizure in FDR*	0.00 (NA-2.63)	.23	0.00 (NA-0.48)	.002	0.00 (NA-2.36)	.21	0.00 (NA-0.74)
Gestation < 37 weeks*	1.19 (0.07–5.27)	.87	1.40 (0.71–2.08)	.27	0.00 (NA-1.70)	.14	1.40 (0.51–2.61)
Birth weight < 2.5 kg*	1.09 (0.06–4.82)	.93	1.56 (0.89–2.16)	.10	0.91 (0.05–3.88)	.92	1.28 (0.46–2.39)
Neonatal disease[a]	2.46 (0.79–8.08)	.12	1.72 (1.21–2.46)	.003	0.17 (0.01–0.82)	.02	2.82 (1.71–4.87)
First febrile seizure	0.40 (0.02–1.96)	.31	0.97 (0.56–1.47)	.89	1.21 (0.29–3.61)	.76	0.48 (0.15–1.05)
DD at epilepsy onset	15.22 (3.07–274.48)	<.001	3.30 (2.25–5.22)	<.001	1.78 (0.63–5.20)	.27	6.74 (3.51–15.54)
Epilepsy onset < age 4 months	2.10 (0.64–6.52)	.21	1.16 (0.76–1.68)	.46	0.46 (0.07–1.59)	.24	1.83 (1.08–3.02)
Daily seizure > 4 weeks	>999 (4.46-NA)	<.001	4.40 (2.56–8.84)	<.001	1.32 (0.47–4.15)	.60	5.45 (2.55–15.05)
Status epilepticus	0.63 (0.04–2.95)	.62	2.03 (1.45–2.71)	<.001	1.88 (0.46–5.41)	.33	1.94 (1.05–3.15)
West syndrome	0.56 (0.09–2.03)	.41	1.70 (1.19–2.40)	.005	2.16 (0.74–6.04)	.15	1.31 (0.73–2.19)
Known etiology[b]	>999 (2.96-NA)	.001	5.69 (2.78–5.37)	<.001	0.64 (0.23–1.86)	.39	>999 (10.93-NA)
Struct/Met/Inf etiology	>999 (6.66-NA)	<.001	2.90 (1.94–4.67)	<.001	0.77 (0.24–2.17)	.62	22.15 (7.27–32.41)
Conf mol gen etiology	6.43 (2.00–28.07)	.002	2.17 (1.56–3.08)	<.001	0.72 (0.17–2.20)	.59	1.95 (1.17–3.23)
Early EEG any abnormality[c]	1.79 (0.49–11.33)	.41	2.84 (1.57–6.29)	<.001	2.19 (0.63–3.64)	.24	3.38 (1.49–10.67)
MRI abnormal*	>999 (0.93-NA)	.06	1.74 (1.12–3.22)	.01	0.81 (0.26–2.86)	.72	6.22 (2.14–36.29)
First seizure type spasm vs focal*	0.00 (NA-3.43)	.22	1.51 (0.94–2.36)	.09	3.31 (1.04–1.99)	.04	1.03 (0.44–2.11)

Abbreviations: ASD, autism spectrum disorder; ASM, antiseizure medication; 95% CI, 95% confidence interval; CP plus, cerebral palsy and similar motor symptoms in metabolic disease; DD, developmental delay; EEG, electroencephalogram; FDR, first-degree relative; ID, intellectual disability; MRI, magnetic resonance imaging; NDV, any neurodevelopmental problem (includes ID, ASD, CP plus, attention-deficit/hyperactivity disorder, other learning difficulties, other motor impairments); RR, relative risk.

Relative risk (RR) using likelihood-ratio test and 95% CIs.

[a]Neonatal disease includes any disease with potential CNS affection like HIE, stroke, sepsis, meningitis, epileptic seizure, hypoglycemia.

[b]Known etiology includes also presumed genetic etiology.

[c]Early EEG = within 6 months from onset. Green color = significant with $p \leq .05$ and 95% CI.

*Excluded from the following multivariable regression analysis due to small numbers or lack of univariable significance, see Table 4 and supplementary data.

ASM polytherapy was common. What constitutes rational polytherapy and how to maximize therapeutic benefits and minimize adverse effects is being discussed.[22,24,25] The development of precision medicine will make more precise, or even curative, treatments possible, based on diagnosed disease mechanisms.[26,27] At present, however, epilepsy surgery is the only potentially curative epilepsy treatment. The use of epilepsy surgery in only two cases (1.7%) is in line with two Scandinavian studies[1,9] but lower than in two North American reports with surgery rates of 4.8% and 5.5%, respectively.[3,11] It has been estimated that about 1 of 25 children (4%) with epilepsy, and most likely a higher ratio of infantile epilepsy, would benefit from epilepsy surgery.[28] A third of our study cohort had a structural etiology and surgery was probably underutilized. Two other nonpharmacological treatment options, VNS and ketogenic diet, were also used in a small number of patients in our cohort.

4.3 | Seizure outcome

Approximately half of the children in our cohort were in seizure remission for 2 years or longer at age 7, which is lower than the two thirds described in the overall pediatric age group.[1–3,5,6] Of the first year onset subgroup, 56% were in remission, in line with 48%–58% in comparable population-based studies.[1,9,10] Like a Finnish study,[10] we found no difference between first- and second-year onset, and the West syndrome subgroup also had a similar

	Seizure-free > 2 years		Seizure-free > 2 years and no ASM		No NDV and seizure - free > 2 years		Mainstream school	
p	RR (CI)	*p*	RR (CI)	*p*	RR (CI)	*p*	RR (CI)	*p*
.60	0.98 (0.70–1.36)	.88	0.94 (0.65–1.38)	.76	0.71 (0.42–1.18)	.19	1.01 (0.73–1.40)	.96
.37	1.40 (0.89–1.89)	.12	1.22 (0.67–1.81)	.46	1.07 (0.50–1.90)	.84	1.37 (0.88–1.85)	.14
.02	1.25 (0.60–1.80)	.46	1.32 (0.64–1.93)	.36	2.08 (0.98–3.24)	.054	1.75 (1.29–1.80)	.006
.45	1.08 (0.50–1.64)	.79	0.97 (0.37–1.66)	.93	0.96 (0.27–2.03)	.94	0.62 (0.18–1.20)	.20
.56	1.15 (0.52–1.76)	.66	1.05 (0.39–1.82)	.90	0.73 (0.13–1.90)	.59	0.42 (0.08–1.03)	.06
<.001	0.81 (0.52–1.16)	.27	0.80 (0.48–1.20)	.30	0.44 (0.19–0.83)	.009	0.67 (0.41–0.98)	.04
.07	0.49 (0.23–0.83)	.005	0.47 (0.20–0.86)	.01	0.71 (0.30–1.36)	0.34	1.00 (0.63–1.42)	.10
<.001	0.47 (0.27–0.72)	<.001	0.29 (0.13–0.52)	<.001	0.04 (0.00–0.17)	<.001	0.33 (0.17–0.54)	<.001
.03	0.9 0 (0.57–1.28)	.57	0.96 (0.59–1.43)	.86	0.73 (0.36–1.29)	.30	0.88 (0.56–1.25)	.49
<.001	0.54 (0.36–0.76)	<.001	0.43 (0.27–0.65)	<.001	0.18 (0.08–0.35)	<.001	0.42 (0.27–0.60)	<.001
.04	0.00 (NA-0.18)	<.001	0.00 (NA-0.20)	<.001	0.00 (NA-0.29)	<.001	0.4 1 (0.14–0.82)	.006
.34	1.08 (0.74–1.49)	.67	0.92 (0.57–1.36)	.69	0.36 (0.13–0.75)	.004	0.57 (0.33–0.87)	.006
<.001	0.58 (0.42–0.79)	<.001	0.51 (0.35–0.73)	<.001	0.29 (0.17–0.49)	<.001	0.46 (0.33–0.62)	<.001
<.001	0.42 (0.25–0.64)	<.001	0.31 (0.16–0.53)	<.001	0.22 (0.09–0.44)	<.001	0.46 (0.27–0.68)	<.001
.01	0.91 (0.57–1.30)	.61	0.87 (0.51–1.32)	.53	0.27 (0.08–0.60)	<.001	0.45 (0.22–0.75)	<.001
.002	0.53 (0.39–0.70)	<.001	0.45 (0.32–0.62)	<.001	0.27 (0.16–0.42)	<.001	0.58 (0.43–0.77)	<.001
<.001	0.74 (0.37–1.53)	.40	0.47 (0.20–1.06)	.07	0.09 (0.00–0.48)	.003	0.55 (0.28–1.07)	.08
.94	1.42 (0.92–2.13)	.11	1.06 (0.61–1.70)	.81	0.55 (0.20–1.18)	.13	0.73 (0.42–1.13)	.17

seizure outcome. Some specific etiologies of early onset epilepsy are known to have a worse prognosis than others, which is reflected in our cohort.

4.4 | Comorbidities

About half of our cases, similarly for onset before or after age 12 months, had intellectual disability at age 7. This is in line with a comparable study,[10] higher than in childhood epilepsy overall and higher than in two studies with intellectual disability in 30%–33% of children with infantile seizure onset.[4,9] One of these had an early last follow-up at age 2 years when mild to moderate cognitive impairments can be difficult to detect.[9] The other report included children after only one unprovoked epileptic seizure and excluded cases with previous neonatal seizures, acute symptomatic seizures at presentation, and cases with "acquired cerebral palsy," all measures that would be expected to improve overall outcome in the study cohort.[4] Intellectual disability tends to be more common in hospital-based cohorts.[13,14,16,29] For our West syndrome subgroup, the frequency of intellectual disability was just below the 75%–76% described in two previous studies.[30,31] Epilepsy due to perinatal asphyxia, cerebral malformations, TSC, and metabolic disease carry a poor prognosis for both cognitive development and seizure outcome. Of interest, in our study, genetic etiology without structural or metabolic abnormality had a seizure remission rate similar to unknown etiology (71% vs 77%) but a worse

TABLE 4 Results of multivariable log binomial regression analysis

Predictor →	First febrile seizure		DD at epilepsy onset		Daily seizure >4 weeks		Struct/Met/Inf etiology		Status epilepticus		Early EEG any abn	
Outcome↓	**RR (CI)**	***p***	**RR (CI)**	***p***	**RR (CI)**	***p***	**RR (CI)**	***p***	**RR (CI)**	***p***	**RR (CI)**	***p***
ID		ns	1.67 (1.17–2.81)	.001	2.56 (1.27–5.56)	.008	1.49 (1.09–2.44)*	.006		ns		ns
CP plus		ns	2.93 (1.69–6.48)	<.001		ns	13.78 (4.35–83.96)	<.001		ns		ns
Seizure-free 2 years	0.61 (0.32–0.88)	.003		ns	0.76 (0.52–0.96)	.02	0.53 (0.31–0.81)	<.001	0.00 (NA-0.26)	<.001		ns
Seizure-free 2 years, no ASM	0.56 (0.26–0.85)	.002	0.57 (0.25–0.96)	.03	0.71 (0.45–0.93)	.01	0.55 (0.26–0.94)	.02	0.00 (NA-0.37)	<.001		ns
No NDV, seizure-free		ns	0.08 (0.00–0.36)	<.001	0.57 (0.25–1.00)	.048		ns	0.00 (NA-0.81)	.03	0.55 (0.33–0.80)	.001
Mainstream school		ns	0.43 (0.22–0.73)	<.001	0.60 (0.38–0.86)	<.001		ns		ns	0.81 (0.63–0.95)	.01

Note: Of the eight outcome variables in the initial univariable analysis, see Table 3, two were excluded due to small numbers of "positive" cases (*Deceased* 11 and *ASD [autism spectrum disorder]* 13). Of the initial 18 predictors, only those showing univariable significance for any of the remaining six outcomes were considered for the multivariable analysis. Of these, *MRI abnormality* was excluded because less than half (57/116) of the cohort had an MRI and these cases are included in the predictor *Structural/metabolic/infectious etiology*. *Febrile seizure in FDR* was excluded due to a small number (7). As a first step in the multivariable analysis, the three partly overlapping etiology predictors were analyzed together against each outcome variable. *Structural/metabolic/infectious etiology* was the strongest for all outcomes except for *ID* and was selected to represent etiology in the final multivariable analysis. This left nine potential predictors for the multivariable analysis, of which the six in the table showed significance for one or more outcomes.

Abbreviations: ASM, antiseizure medication; 95% CI, 95% confidence interval; CP plus, cerebral palsy and similar motor symptoms in metabolic disease; DD, developmental delay; Early EEG, electroencephalogram within 6 months from onset; FDR, first-degree relative; ID, intellectual disability; ns, not significant; NDV, any neurodevelopmental problem; RR, relative risk.

*For *ID, Known etiology* had a higher predictive value. Selecting *Known etiology* for the multivariable analysis against *ID* resulted in the same three significant predictors but with a higher predictive value for etiology (RR: 3.19, 95% CI: 1.57–8.76; $p < .001$).

cognitive outcome (71% vs 11% ID), as shown in Table 2. The high seizure remission rate was not due to genetic workup, being focused on self-limited cases. On the contrary, WES/WGS was offered patients with drug-resistant epilepsy, DEEs or significant neurological comorbidities, and not to more benign cases. Our interpretation is that genetic epilepsies, including DEEs, without structural or metabolic abnormalities actually do have a good chance of seizure remission at school age...but a worse cognitive outcome with current treatments. *STXBP1* epileptic encephalopathy exemplifies this.

Although not directly comparable due to differences in definitions and methods, a study of early onset (<age 2 years) focal epilepsy showed a higher proportion of structural/metabolic/infectious etiology (55% vs 45%), similar seizure remission rates (57% vs 53%), and worse cognitive outcome (68% IQ <80 vs 49% IQ <70).[12] Of the 20 children with normal development at epilepsy onset and unknown etiology, all were seizure-free and remained developmentally normal at follow-up. In our study, this association was less striking with 29 of 41 (71%) having an overall normal outcome.

4.5 | Educational support needs

The fact that just above half of the whole cohort and one third of the West syndrome cases attended mainstream school at age 7 might seem surprisingly good. We did not find directly comparable data in previous population-based studies on infantile epilepsy, and the exact figures will also depend on non-medical factors like school system, availability of individual support within mainstream school, and local attitudes. Some children in our cohort were dependent on individual pedagogical support and may have greater difficulty in meeting mainstream school standards later during school age when demands increase. Several studies have shown significant social and academic burden on adults with childhood-onset epilepsy, especially but not only on those individuals with intellectual disability or drug-resistant epilepsy.[32,33]

4.6 | Predictors of outcome

The finding of etiology as a main predictor of both seizure remission and cognitive development confirms the reports from previous population-based early onset epilepsy cohorts.[1,9–11] However, this is a complex association. Different specific etiologies, just as seen in this study, have different outcomes. The category "known etiology" analyzed as a predictor in older reports and recent studies[1,12] has traditionally implied "symptomatic" or "structural-metabolic" etiology, but as genetic diagnostics have developed, cases with known genetic etiology have become more common and the "known etiology" category will be even more heterogeneous. The more genetic workup is focused on severe cases like epileptic encephalopathies and less on self-limited epilepsy, as in our cohort, the worse the outcome for "known genetic etiology" will be. For the future, focus on outcome of specific etiologies will be necessary, especially when developing and evaluating etiology-specific precision treatments.

Developmental delay at epilepsy onset and age at epilepsy onset have been reported as associated with outcome in some reports, although mostly in univariable analysis, and are thought to be highly influenced by etiology.[1,4,8–10] However, developmental delay at onset remained a significant predictor independent of etiology in our study (with stronger association with intellectual disability than with seizure remission), and was reported as associated with DRE in a previous study.[11] The same study found age at onset of <12 months to be an independent predictor of DRE in a cohort of epilepsy onset <36 months, which we could not confirm. A hospital-based study on epilepsy onset <36 months found onset <12 months to be independently predictive of intellectual disability but not of DRE.[16]

We found two directly seizure-related variables of interest for outcome. A history of status epilepticus was the strongest negative predictor of seizure remission in our cohort. We did not find support for this independent association in comparable data on early onset epilepsy[1,11] and contradictory results in studies including children with seizure onset before age 16 years.[34,35] Daily seizures for >4 weeks showed independent association with five of the six outcome variables in the regression analysis. We chose this variable as a measure of maximum seizure frequency and possibly as a reflection of the dynamic component that is implied in the concept of developmental and epileptic encephalopathy: seizures and interictal epileptiform activity can affect outcome on top of what the underlying etiology entails. We did not find previous data on a directly comparable variable, but in a study including older children high initial seizure frequency was a predictor of intractability.[35] This was not confirmed in another report.[34]

Male sex showed a strong overrepresentation among cases being diagnosed with ASD (12/13 cases, 92%; relative risk [RR] 11.59, 95% CI 2.40–207.70) but was not included in the multivariable analysis due to a small case number. This gender difference in ASD, but at a lower ratio, is previously well described in both epilepsy (RR 1.67:1)[36] and nonepilepsy cohorts (odds ratio [OR] 3:1).[37] How much of this difference between genders and between epilepsy and nonepilepsy cohorts is explained by true prevalence differences due to biological factors or differences in diagnostics is a matter of debate.[36,37] Although a small sample,

our study suggests that the autism/ASD gender difference could be larger in early onset epilepsy.

5 | CONCLUSIONS

Our study confirms that approximately half of children with seizure onset during the first and second year of life will become seizure-free and half of them will be diagnosed with intellectual disability. West syndrome cases have similar seizure remission rates but worse cognitive outcome. Etiology is a major independent predictor of both seizure remission and cognitive outcome in our study as well as in comparable reports. For the other factors associated with outcome in our cohort, previous data are conflicting or not available. Some specific etiologies have a very poor prognosis, which underscores the need for more effective treatments. Nevertheless, half of the children in our cohort and one third of West syndrome cases attended mainstream school at age 7 years.

AUTHOR CONTRIBUTIONS

TS collected and analyzed patient data and drafted the manuscript for intellectual content. TT designed and ran the incidence registry and revised the manuscript for intellectual content. BMA contributed patient data and revised the manuscript for intellectual content. TA was responsible for statistical analyses and revised the manuscript for intellectual content. OH contributed with statistical analyses and revised the manuscript for intellectual content. PÅ analyzed patient data and revised the manuscript for intellectual content. AW conceptualized the study and revised the manuscript for intellectual content.

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CONFLICT OF INTEREST

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*Excluded from the following multivariable regression analysis due to small numbers or lack of univariable significance, see Table 3 and Tables S1 and S2.

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Additional supporting information can be found online in the Supporting Information section at the end of this article.

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