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Seizure-like events leading to hospital referrals in infants: A retrospective population-based study

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Abstract

Aim: To identify the aetiology and outcome of seizure-like events leading to hospital referrals in infants and to identify early predictors of epilepsy and delayed neurodevelopment.

Methods: This Norwegian population-based study focused on all children born in Sør-Trøndelag county, who were up to one year of age in 2014-2015. They were identified by diagnostic codes for seizure-like events and electroencephalography (EEG) examinations. Hospital records were examined up to 1.5 years of age.

Results: The one-year prevalence of seizure-like events was 1.5% (114/7430). Epilepsy was diagnosed in 17%, 57% had non-epileptic paroxysmal events (NEPE), 16% had febrile seizures, and 10% had other acute symptomatic epileptic seizures. Neurodevelopmental delay occurred in 21%. The cumulative incidence was 0.22% for epilepsy and 0.79% for NEPE. Abnormal brain magnetic resonance imaging, abnormal first EEGs and neonatal care increased the likelihood of epilepsy and delayed development. Identifying situation-related factors decreased the epilepsy risk. Occurrence at a younger age increased the risk of delayed development. Absence of unambiguous motor symptoms was less common in epilepsy than in NEPE.

Conclusion: Seizure-like events were common in infants and most were not caused by epilepsy. Specific anamnestic clues, and detailed descriptions of the entire event, helped to predict adverse outcomes.

KEYWORDS

aetiology, epilepsy, infants, neurodevelopmental outcome, paroxysmal events

1 | INTRODUCTION

Paroxysmal events are common in young children. They are often thought to be epileptic in origin, but a wide spectrum of underlying mechanisms has been reported.[1-3] The immature newborn brain is more vulnerable to developing seizures, and it has been shown that ictal symptoms differ in infants from older children and adults due to the immaturity of their central nervous system.[4,5] The clinical presentation can be similar in epileptic and non-epileptic attacks and infants are unable to communicate symptoms like auras and other ictal and postictal manifestations.[6-8]

Paroxysmal events are defined as episodes with suddenly occurring symptoms that alternate with periods without symptoms. They often last for a short period of time and manifest as altered consciousness, altered behaviour, involuntary movements, altered muscle tone and,

Abbreviations: EEG, electroencephalography; MRI, magnetic resonance imaging; NEPE, non-epileptic paroxysmal events.

or, changed breathing patterns. The prospective population-based Generation R study that started in early foetal life reported that the incidence of all paroxysmal events in 2860 infants in the first year of life was 8.9%.[9] A national Finnish register study and a national Norwegian mother and child study showed that the incidence of epilepsy varied with age and was highest in the first and last years of life.[10,11] The incidence in infants has been reported to be 0.07%-0.21%.[9,11]

Differentiating between epileptic and non-epileptic paroxysmal events can be difficult and children with seizure-like events can be incorrectly diagnosed at first.[12-14] A low inter-observer agreement is reported in identifying seizure on video recordings of paroxysmal movements in neonates and infants.[13,14]

In some cases, paroxysmal events in infants can easily be recognised as benign. In other cases, it can be challenging to distinguish between benign events and symptoms that indicate the infant has a serious illness. As a result, such infants may need specialist paediatric evaluations, various medical examinations and even hospital care. This could also affect the families' psychosocial situation. There have been a lack of epidemiological studies and neurodevelopmental outcomes with regard to infants whose paroxysmal events were not obviously benign and led to hospital referral.[9]

The aims of this study were to identify the aetiology and outcomes of infants under one year of age who had seizure-like events that led to hospital referral. We also aimed to identify predictors of epilepsy and, or, delayed neurodevelopment that were available at an early stage of their illness.

Key notes

- Our two-year population-based study found that 1.5% of infants experienced seizure-like events that led to hospital referrals.
- The cumulative incidence of epilepsy was 0.22% and it was 0.79% for non-epileptic paroxysmal events.
- Presence of situation-related factors and absence of unambiguous motor symptoms conveyed a low risk of epilepsy, while events at a younger age increased the risk of delayed development.

2 | PATIENTS AND METHODS

This Norwegian population-based cohort study was based on the 7,443 children who were born alive in 2014-2015 to mothers who lived in Sør-Trøndelag County. We excluded 13 infants who died before the age of one year[15] and this resulted in a total population of 7,430 children. The number of live-born infants had been stable during the preceding 10-year period, and the average live birth rate for that period was very similar to the study period.[15] On January 1, 2015, the region had 310,047 inhabitants.[16]

All children in the county with paroxysmal events and, or, suspicious neurodevelopmental delay requiring specialist assessments were referred to St Olavs Hospital, Trondheim, Norway, which was where this study was carried out. This was the only hospital in the area that offered paediatric care and EEG recordings. Our study comprised children who were referred to our department by their primary care family doctor or other hospital professionals after they had experienced seizure-like paroxysmal events. All children had either received a clinical diagnosis of a seizure-like event or had undergone an EEG examination at the hospital. The clinical diagnoses were made according to the International Classification of Diseases, Tenth revision: G40 (epilepsy), P90 (convulsions in newborn infant), R56.0 (febrile seizures), R56.8 (other and unspecified convulsions) and R25 (other involuntary movements). Codes for EEG procedures in 2014 and 2015 were used to identify cases that had been referred for EEG examinations. To ensure that the prevalence rate was as accurate as possible, we also included infants who were born in 2013, but had seizure-like events or EEG examinations in 2014, before they reached one year of age. The hospital's records for all children under one year of age were reviewed and those who fulfilled the following criteria were included in the study. They had to have had at least one seizure-like paroxysmal event reported in their medical records and at least one of those events had to have occurred between January 1, 2014, and December 31, 2015. In addition, the child had to be under one year of age and a resident of Sør-Trøndelag County at the time of one of the seizure-like events (Figure 1).

The information collected from the medical records is shown in Table 1. All the available information in the medical records was examined up to the age of 1.5 years, and the two authors reached a consensus on the children's final diagnoses, somatic health and neurodevelopment outcomes. A severe somatic disorder was defined as a serious or life-threatening or chronic somatic disease that needed medical intervention and, or, long-term follow-up. Mild disorders included other diseases that had an assumed low impact on daily living. Neurodevelopment outcome was classified as normal, suspected delayed or obviously delayed. Children were classified with a suspected developmental delay if they had been assessed but the results had been inconclusive.

Seizure-like events were categorised into three major groups: epileptic seizures, non-epileptic paroxysmal events (NEPE) with an identified cause and NEPE with unknown aetiology. Epileptic seizures were sub-classified as epilepsy, acute symptomatic epileptic seizures or febrile seizures, according to the most plausible aetiology.[17,18] Epilepsy was further classified according to the current definitions of the International League Against Epilepsy.[18] The classifications in the NEPE group with an identified cause for the event were performed according to the most likely cause in a two-step process.[9,19] The sub-classification of NEPE with unknown aetiology was based on the symptomatology of the events. Details of the classifications are shown in Table 2.

The overlapping ictal symptomatology of NEPE and epileptic seizures, and the polymorphic features of infantile seizures

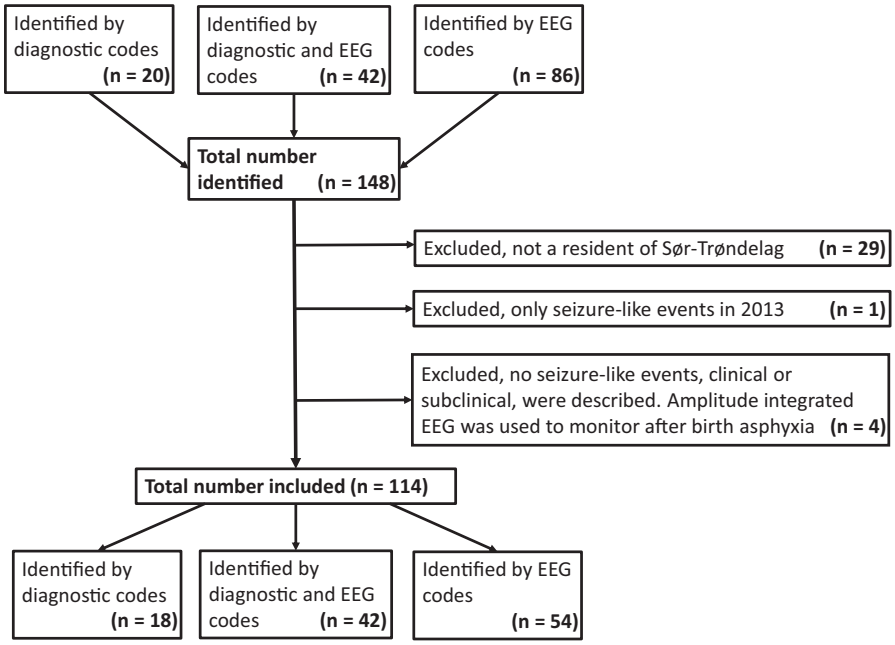

FIGURE 1 Flow chart of study population

that differ from those of older children and adults,[4-6] makes the International League Against Epilepsy classification difficult to apply.[2] Therefore, we used the adjustments proposed by the League's Task Force on Neonatal Seizures.[20] Only three broad symptom categories for all seizure-like events were used: unambiguously motor, non-motor and unclassified. Non-motor events included those with behaviour arrest and absences. Unclassified events included those with a combination of symptoms or where a clear description was lacking.

Acute symptomatic epileptic seizures were defined as those that occurred at the time of a systemic insult or in close temporal association with a documented brain insult.[17] Febrile seizures were associated with febrile illness and were diagnosed as such. A situation-related factor was defined as any particular circumstance, such as a trigger, situation or state, which had a clear temporal relationship to the event and had been identified in association with the event. This included factors that caused acute symptomatic seizures, such as asphyxia and cerebral infections and fever, and also precipitants such as gastroesophageal reflux and infections. It also included situations well within physiological limits, such as falling asleep.

2.1 | Statistical methods

The period prevalence was defined by the fraction of all infants who had seizure-like events and the population estimate of all infants aged 0-1 years in the defined region during the two-year study period. The cumulative incidence was calculated using the same fraction, but excluded those who had their first event in 2013.[15]

Binary logistic regression was used to identify the variables that could predict an increased risk of epilepsy or delayed or suspected neurodevelopment delay. The possible predictive variables were selected in advance and were estimated to be available at an early stage of the illness. These included gender, neonatal risk factors, the age when the events occurred—namely before or after 90 days of life—symptomatology, identifiable situation-related factors, epileptiform activity during the infant's first EEG and abnormalities seen on the magnetic resonance imaging brain scan. The results are presented as odds ratios with 95% confidence intervals (95% CI).

It was important to highlight the differences between the two groups that we considered were most difficult to separate at an early stage, namely epilepsy and NEPE. Fisher's exact test was used to evaluate the differences in binary outcomes, and the Mann-Whitney *U* test was used for ordinal variables.

Statistical analyses were performed using SPSS Statistics, version 24 (IBM Corp, New York, USA), and a P value of $<.05$ was considered to be statistically significant.

Data were collected using the WebCRF web-based system, which was developed and administered by the Unit of Applied Clinical Research at the Norwegian University of Science and Technology.

The Regional Committee for Medical and Health Research Ethics in Central Norway approved the study and stated that parental consent was not required as our research assessed the quality of clinical practice (registration number 2015/725).

3 | RESULTS

We found that 148 infants had experienced seizure-like events that needed a hospital referral. Of these, 114 fulfilled all the inclusion criteria (Figure 1) and that gave us a one-year prevalence of 1.5% in the defined population of 7,430 infants. The cumulative incidence was 1.4%, as nine infants had their first event in 2013. Table 2 shows the different types of seizure-like events and their distribution in the 114 patients. Epilepsy was diagnosed in 19 (17%), 12 (11%) had acute symptomatic epileptic seizures, and 18 (16%) had febrile seizures.

TABLE 1 Description of the cohort and subgroups, and comparison of those with epilepsy versus those with non-epileptic paroxysmal events

			Group 1	Group 2	Group 3	Group 4	Group 5	
		All (n = 114)	Epilepsy (n = 19)	Acute symptomatic epileptic seizures (n = 12)	Febrile seizures (n = 18)	Non-epileptic paroxysmal events with identified causes (n = 29)	Non-epileptic paroxysmal events with unknown causes (n = 36)	Epilepsy (group 1) versus non-epileptic paroxysmal events (groups 4 and 5)
	Category	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	*P* value
Total		114 (100. 0)	19 (16.7) [a]	12 (10.5) [a]	18 (15.8) [a]	29 (25.4) [a]	36 (31.6) [a]	
Sex	Boy	62 (54.4)	11 (57.9)	6 (50.0)	8 (44.4)	21 (72.4)	16 (44.4)	>.99[b]
Neonatal risk factors [c]	Yes	48 (42.1)	12 (63.2)	11 (91.7)	2 (11.1)	11 (37.9)	12 (33.3)	.04[b]
Number of days when first seizure-like event occurred after birth	0-28 d	42 (36.8)	8 (42.1)	8 (66.7)	0 (0.0)	12 (41.4)	14 (38.9)	.70[d]
	29-90 d	20 (17.5)	4 (21.1)	2 (16.7)	0 (0.0)	5 (17.2)	9 (25.0)	
	91-180 d	22 (19.3)	5 (26.3)	1 (8.3)	5 (27.8)	6 (20.7)	5 (13.9)	
	181-270 d	20 (17.5)	1 (5.3)	1 (8.3)	8 (44.4)	5 (17.2)	5 (13.9)	
	271-365 d	10 (8.8)	1 (5.3)	0 (0.0)	5 (27.8)	1 (3.4)	3 (8.3)	
Symptomatology	Unambiguous motor	78 (70.2)	17 (89.5)	9 (75.0)	18 (100.0)	21 (72.4)	13 (36.1)	.003[b,e]
	Non-motor	15 (11.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)	14 (38.9)	
	Unclassified[f]	21 (18.4)	2 (10.5)	3 (25.0)	0 (0.0)	7 (24.1)	9 (25.0)	
Identified situation-related factor[g]	Yes	51 (44.7)	2[h] (10.5)	12 (100.0)	18 (100.0)	19 (65.5)	0 (0.0)	.14[b]
All EEGs[i]	Performed	97 (85.1)	19 (100.0)	10 (83.3)	6 (33.3)	29 (100.0)	33 (91.7)	>.99[b]
24-hour EEGs[i]	Performed	21 (18.4)	10 (52.6)	1 (8.3)	0 (0.0)	3 (10.3)	7 (19.4)	.002[b]
Epileptiform activity on at least one EEG[i]	Yes	18 (15.8)	16 (84.2)	2 [g] (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	<.001[b]
Epileptiform activity on the first EEG[i]	Yes	14 (12.3)	12 (63.2)	2 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	<.001[b]
Brain MRI[j]	Performed	35 (30,7)	18 (94.7)	11 (91.7)	0 (0.0)	2 (6.9)	4 (11.1)	<0.001[b]
	Abnormal	16 (14.0)	8 (42.1)	6 (50.0)	0 (0.0)	1 (3.4)	1 (2.8)	<.001[b]
Genetic tests	Performed	17 (14.9)	11 (57.9)	1 (8.3)	0 (0.0)	1 (3.4)	4 (11.1)	<.001[b]
	Abnormal	10 (7.0)	6 [k](26.3)	1 (8.3)	0 (0.0)	1 (3.4)	2 [k] (2.8)	.006[b]
Total number of hospital admissions	0	19 (16.7)	0 (0.0)	0 (0.0)	5 (27.8)	7 (24.1)	7 (19.4)	<.001[b]
	1-2	67 (58.8)	6 (31.6)	10 (83.3)	11 (61.1)	16 (55.2)	24 (66.7)	
	>2	28 (24.5)	13 (68.4)	2 (16.7)	2 (11.1)	6 (20.7)	5 (13.9)	

(Continues)

TABLE 1 (Continued)

		All (n = 114)	Group 1 Epilepsy (n = 19)	Group 2 Acute symptomatic epileptic seizures (n = 12)	Group 3 Febrile seizures (n = 18)	Group 4 Non-epileptic paroxysmal events with identified causes (n = 29)	Group 5 Non-epileptic paroxysmal events with unknown causes (n = 36)	Epilepsy (group 1) versus non-epileptic paroxysmal events (groups 4 and 5)
	Category	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	*P* value
Somatic health up to 1.5 y of age	Significant disorder[l]	27 (23.7)	9 (47.4)	4 (33.3)	2 (11.1)	5 (17.2)	7 (19.4)	.03[b]
	Borderline	11 (9.6)	1 (5.3)	2 (16.7)	1 (5.6)	3 (10.3)	4 (11.1)	
	Healthy	76 (66.7)	9 (47.4)	6 (50.0)	15 (83.3)	21 (72.4)	25 (79.4)	
Neurodevelopmental outcome at 1.5 y of age	Obvious delay[l]	20 (17.5)	10 (52.6)	2 (16.7)	0 (0.0)	3 (10.3)	5 (13.9)	<.001[b]
	Suspected delay	4 (3.5)	1 (5.3)	2 (16.7)	0 (0.0)	0 (0.0)	1 (2.8)	
	Normal	90 (78.9)	8 (42.1)	8 (66.7)	18 (100.0)	26 (89.7)	30 (83.3)	

[a]Distribution within the total cohort.

[b]Fisher's exact test.

[c]Any recorded stay in the neonatal intensive care unit, regardless of the cause.

[d]Mann-Whitney *U* test.

[e]Comparison between children with motor events and those with non-motor and unclassified events.

[f]Multiple combined symptoms or symptoms that were too vaguely described to be classified.

[g]An identified situation-related factor when a certain and known stimulus (triggering factor, situation or state) had a clear temporal relationship to the event and had been identified early. All symptomatic epileptic seizures are included: 8/12 with benign sleep myoclonus with events with a certain relationship to falling asleep, gastroesophageal reflux, airways infection, emotional changes, flatulence, pulmonal hypertensive crisis, necrosis of small intestines and sleep terror-attack.

[h]Three children with a final epilepsy diagnosis and symptomatic epileptic seizures were described: three had fever and one also had hypoglycaemia. In two cases these situation-related factors were identified at the time of the first seizure-like event.

[i]EEG, electroencephalography.

[j]MRI, magnetic resonance imaging.

[k]Expanded genetic investigations planned before 1.5 y of age discovered pathology after 1.5 y of age in one patient.

[l]Two patients died before 1.5 y of age and were categorised with significant somatic disorders and obvious neurodevelopmental delay. One had severe epileptic encephalopathy, and one had significant hypoxic ischaemic encephalopathy

TABLE 2 Categorisation of seizure-like events and distribution of cases

Type of seizure-like event	(n)	Sub-classification	(n)	Division based on aetiology/symptomatology	(n)
Epileptic seizures	49	Epilepsy (group 1)	19	Epilepsy with verified genetic aetiologies [a]	5
				Epilepsy syndromes [b]	5
				Other epilepsies	9
		Acute symptomatic seizures (group 2)	12	Acute symptomatic seizures [c]	12
		Febrile seizures (group 3)	18	Simple febrile seizure	13
				Complex febrile seizure	5
Non-epileptic paroxysmal events with identified cause (group 4)	29	Physiological events	4	Normal behaviour	1
				Jitteriness in newborn infant	2
				Other physiological events[d]	1
		Apnoea	4	Breath-holding spells	3
				In association with upper respiratory infection	1
		Parasomnia	13	Benign sleep myoclonus	12
				Sleep terror	1
		Other non-epileptic events	5	Gastroesophageal reflux	3
				Cyclic vomiting	1
				Cardiovascular events	0
				Shuddering attacks	1
		Events associated with other diseases	3	Genetic disorder[e]	1
				Other severe disease[f]	2
Non-epileptic paroxysmal events with unknown cause (group 5)[g]	36	Unambiguous motor	13	Clonic, tonic or myoclonic	10
				Jitteriness	3
		Non-motor	14	Isolated apnoea	1
				Behaviour arrest and absences	13
		Unclassified	9	Multiple combined symptoms and/or unclear symptomatology	9
Total	114				

[a]Five were found: one each with 2q24.2q31 deletion, SCN1A mutation and SCN2A mutation and two with a KCNQ2 mutation. Four had severe epileptic encephalopathy with delayed development and one infant with the KCNQ2 mutation had normal development at 1.5 y of age.

[b]Three with infantile spasms of unknown aetiology, one with self-limited familial neonatal convulsions and one with self-limited neonatal epilepsy.

[c]Five with birth asphyxia, three with either brain haemorrhage or infarction, two with hyponatremia and dehydration, one with opiate and benzodiazepine withdrawal and one with hypoglycaemia.

[d]Motor symptoms related to defecation/flatulence.

[e]Rare genetic disorder with paroxysmal eye movements.

[f]One with congenital heart disease and pulmonary hypertension and one with intestinal necrosis.

[g]Sub-classification based on the most dominant symptom.

NEPE with an identified cause was found in 29 (25%), and 36 (32%) had NEPE of unknown aetiology. The cumulative incidence of epilepsy in the first year of life was 0.22%, excluding three of the 19 children with epilepsy who had their first epileptic seizure in 2013. The cumulative incidence of NEPE with an identified or unknown cause was 0.79%, excluding six children with NEPE who had their first event in 2013 (Table 1). Febrile seizures were also described in three children who received a final epilepsy diagnosis and one

TABLE 3 Predictors of epilepsy and delayed neurodevelopment early in the course of seizure-like events

	Epilepsy			Delayed neurodevelopment at 1.5 y of age		
Predictors	OR[a]	95%-CI[b]	*P* value	OR[a]	95% CI[b]	*P* value
Sex, male	1.19	0.44-3.21	.74	0.80	0.33-1.97	.63
Neonatal risk factors[c]	2.81	1.01-7.79	.047	3.63	1.40-9.39	.008
Early occurrence of the seizure-like event (before 90 d of life)	1.54	0.56-4.26	.40	3.14	1.14-8.63	.03
Symptomatology, motor symptoms	4.31	0.94-19.8	.06	1.36	0.49-3.78	.56
Identified situation-related factor	0.11	0.02-0.51	.004	0.43	0.16-1.14	.09
Epileptiform activity in the first EEG[d]	51.6	9.67-274.9	<.001	10.2	2.77-37.6	<.001
Abnormal MRI of the brain[e]	7.91	2.47-25.3	<.001	7.11	2.30-22.0	.001

Note: In the analysis, all children with seizure-like events are included (n = 114).

[a]OR, odds ratio.

[b]95%-CI, 95% confidence interval.

[c]Any stay in neonatal intensive care unit, regardless of the cause.

[d]EEG, electroencephalography.

[e]MRI, magnetic resonance imaging.

had hypoglycaemia at the same time. These events were the first seizure-like event in two of the three children.

Table 1 presents selected data for the whole cohort and separately for each subgroup, namely the populations, events, investigations that were performed and the results, any need for inpatient hospital care and somatic health and neurodevelopmental outcomes up to 1.5 years of age. Neurodevelopmental delay was identified in 24 children (21%), including two children who died. Developmental delay was found in 11/19 with epilepsy (58%) and in 6/36 with NEPE with an unknown aetiology (17%).

The early predictors of epilepsy and delayed neurodevelopment for the entire cohort, which included all 114 children, are shown in Table 3.

In the separate comparison, where those with acute symptomatic and febrile seizures were excluded, motor symptoms were described in 17/19 with an epilepsy diagnosis (90%) compared to 34/65 in the NEPE groups (52%) ($P = .003$). The differences in identified situation-related factors disappeared in this analysis (Table 1).

EEGs were carried out for 97/114 (85%) infants (Table 1). At least one 24-hour EEG recording without video was performed for 21 patients. Amplitude integrated EEG was performed on 21 infants during the neonatal period and 12 of these also had 24-hour EEG recordings. A total of 257 EEG recordings were performed: 138 (range 1-17) on the 19 patients with epilepsy and 119 (range 0-5) on the 95 patients with other causes ($P < .001$). Epileptiform activity was found in the initial EEG recording in 12/19 patients with epilepsy (sensitivity 63%), and epileptiform activity was identified in another four children after repeated EEG recordings (Table 1). Ictal EEG recordings were available for 13 infants with epilepsy and for two neonates who had acute symptomatic seizures. These two neonates had amplitude-integrated EEG recordings.

All but one infant with epilepsy had been treated with antiepileptic drugs. The child who did not receive treatment had recurrent unprovoked clinical seizures and ictal findings on the amplitude-integrated EEG in the neonatal period.

We found that 24-hour EEG, magnetic resonance imaging and, or, genetic investigations were performed in 43/114 (38%) cases and inpatient hospital care was needed in 95/114 (83%).

4 | DISCUSSION

This population-based study found that 1.5% of all infants had seizure-like events that led to paediatric referrals. Extensive resources, including a high degree of inpatient hospital care and large number of investigations, were used to evaluate these infants. A wide range of causes and diagnoses were identified, from physiological phenomena to brain disorders with fatal outcomes. Non-epileptic events were much more common than epilepsy, as epilepsy was only diagnosed in one out of six cases. At the age of 1.5 years, one out of five who had experienced seizure-like events had delayed neurodevelopment and this rose to more than a half of those diagnosed with epilepsy. Specific anamnestic clues can be helpful to identify those at increased risk of epilepsy and, or, developmental delay, at an early stage. Presence of situation-related factors and absence of unambiguous motor symptoms conveyed a low risk of epilepsy, while events at a younger age increased the risk of delayed development. Abnormal first EEG was a strong predictor

of epilepsy, and a necessary examination in selected infants was infantile epilepsy syndromes cannot be ruled out. The risk of delayed development increased with occurrences of seizure-like events at a younger age.

The term seizure-like event has been poorly defined. This study included all infants with potentially serious paroxysmal events. This was defined by the need for a paediatric hospital referral following a clinical diagnosis of a seizure-like event or a referral for an EEG examination. Obviously, we did not include benign paroxysmal events and many patients with simple febrile seizures, who were only assessed by primary care doctors or only observed by caregivers. This can probably explain the large differences between our study and the findings reported by Visser et al, who carried out a community-based questionnaire study of all paroxysmal events and found a cumulative incidence of 8.9%.[9] We believe that all children with a potentially serious paroxysmal disorder in the geographical study area were included, as paediatric services and EEG facilities were only available in the hospital where the study was performed.

The cumulative incidence of epilepsy was 0.22% in our study, which was similar to the figure reported for the same age group by a Norwegian nationwide cohort study carried out by Aaberg et al[11] The figures in the literature vary substantially, and our results, which were at the higher end of the range, might be explained by several factors.[9,11] It can be difficult to differentiate between epileptic seizures and other paroxysmal events and this can lead to both underdiagnosis and overdiagnosis.[21] Some studies have used voluntary-based retrospective questionnaires, which could risk self-selection and recall bias.[9] Other studies have been based on national diagnostic registries.[11] The access to the children's complete hospital medical records from birth to 1.5 years might have increased the accuracy.[22] This allowed us to include one child who died and two children with self-limited neonatal epilepsy syndromes. We also noted that three children with recurrent stereotypical ictal features that were consistent with epilepsy had repeatedly normal interictal EEG recordings and this emphasised that epilepsy is a clinical diagnosis. However, the small number of children diagnosed with epilepsy in this study makes it difficult to calculate the exact incidence and distribution of specific aetiologies and syndromes.

Many infants had associated medical needs and disorders that needed repeated hospitalisation, including admissions to the neonatal intensive care unit. In addition, many had delayed neurodevelopment at the age of 1.5 years. The highest figures were seen among those with epilepsy. An increased risk of paroxysmal events has previously been described in children born preterm, or with low Apgar scores, and so has an increased risk of neonatal seizures in those born with a low gestational age or low birthweight.[9,23] It is well known that children with early onset epileptic seizures have an increased risk of developmental delay and somatic disorders.[24] An increased risk of developmental delay and neurological deficits has also been shown in children with NEPE.[25] This might be explained by the fact that children have increased vulnerability to seizure-like events if they have concomitant diseases or cerebral dysfunction.[9,23] They may also be observed more closely by caregivers and medical teams because of their health issues.

It is essential to correctly diagnose infants with seizure-like events at an early stage and to distinguish those with epilepsy and, or, an increased risk of delayed development. This can enable early diagnosis and treatment of epilepsy and may minimise unnecessary investigations and hospital admissions in those with benign causes.[3] The difficulties in using clinical evaluation to differentiate between epileptic seizures and just non-epileptic movements in infants have been acknowledged.[13,14] The less distinctive, and frequently more subtle, symptomatology in immature children increases the difficulties of describing paroxysmal symptoms in detail.[5] Our study's retrospective design, which used information from hospital medical records, may have increased the risk of inadequately describing events. We have nevertheless showed that the absence of unambiguous motor symptoms conveyed a low risk of epilepsy, while the presence of motor symptoms did not help to establish the cause of the seizure-like events. This study also underlines the value of identifying any situation-related factor, both those causing acute symptomatic seizures and those associated with NEPE. The increased risk of epilepsy and delayed development in those with neonatal risk factors, epileptiform activity on their EEGs and abnormal brain magnetic resonance imaging (MRI) were expected.

In 18% of the infants, it was not possible to reach a clear symptom classification. Unknown is included as an entity in the International League Against Epilepsy classification of seizure types and in other epidemiological studies on paroxysmal events.[26,27] This indicates that classifying seizure-like events can be difficult. In some cases, it may be due to insufficient information and difficulties in placing in specified categories.

The necessity of using ictal EEG to diagnose epileptic seizures has been emphasised by the International League Against Epilepsy.[20,28] However, it is probably not possible for most hospitals to offer long-term EEGs to all children who display seizure-like events leading to hospital referral. Nor is it desirable. The aim of our study was to identify predictors that were available at an early stage of the illness. The lack of ictal EEG was not considered necessary, or crucial, for interpreting the main results. However, this might have affected diagnostic accuracy to some extent, and for example, children with benign infantile epilepsy may have been incorrectly categorised to the group of NEPE with unknown causes.

Home videos have been shown to be a cost-effective contribution to the diagnosis of paroxysmal events in infants.[29] They were not used systematically in this study, but should be noted as a valuable supplement to clarify descriptions of paroxysmal events.[29]

Further research is needed to determine whether using home videos, together with the findings of this study, could reduce overall health care need including advanced examinations in infants with paroxysmal events.

The lack of clinical neurodevelopmental assessments of the entire population at the age of 1.5 years was a limitation of the study.

The fact that we identified cases based on a set diagnosis and specific examination codes may also have affected the results. In particular, we may not have been able to identify infants with acute symptomatic seizures if the cause was easily identified but the seizure code was missing.

5 | CONCLUSION

It is common for infants to experience seizure-like events that lead to hospital referral. Extensive resources are used to evaluate infants with these symptoms. The events are caused by a wide spectrum of aetiologies, from physiological phenomena to brain disorders with fatal outcomes. The vast majority do not have epilepsy. Specific anamnestic clues can be helpful, at an early stage, to identify those at increased risk of epilepsy and, or, developmental delay. Presence of situation-related factors and absence of unambiguous motor symptoms convey a low risk of epilepsy, while events at a younger age increase the risk of delayed development. Abnormal first EEG is a strong predictor of epilepsy and a necessary examination in selected infants. The risk of delayed development increases with occurrences at a younger age.

We believe that our findings can help to improve clinical practice by reducing the overall need for health care and examinations in some infants with paroxysmal events.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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