Neurodevelopmental outcomes of neonatal non-epileptic paroxysmal events: a prospective study

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ABBREVIATIONS				
HINE	Hammersmith Infant			
	Neurological Examination			
HNNE	Hammersmith Neonatal			
	Neurological Examination			
NEPE	Non-epileptic paroxysmal event			

AIM To report on psychomotor development and outcomes in term born neonates with non-epileptic paroxysmal events (NEPEs).

METHOD From October 2017 to March 2019 we enrolled 38 consecutive term born neonates (22 males, 16 females; aged between 0–28d), born at the University Hospital San Marco in Catania, Italy, with NEPEs. We performed the Hammersmith Neonatal Neurological Examination scale (at enrolment), the Hammersmith Infant Neurological Examination (HINE) scale (at age 3, 6, 9, and 12mo), and the Griffiths scale (at age 12mo).

RESULTS The age at onset of first paroxysmal manifestations ranged from birth to 4 days. We recorded a suboptimal global score in 18 out of 38 patients at enrolment and in 10 out of 38 patients at age 3 months (>70% of these infants were male); all events disappeared within 6 months of life. At age 6, 9, and 12 months, all infants scored within normal values on the HINE and Griffiths scale.

INTERPRETATION Patients with NEPEs achieve neurodevelopment optimal scores within their first year of life.

Neonates may present with different types of non-epileptic paroxysmal events (NEPEs). These events are relatively frequent in the neonatal period. In fact, neonates have reduced inhibitory control of their motor system.¹ NEPEs are paroxysmal and time limited; unlike epilepsy, NEPEs are not caused by ictal epileptiform activity.² In contrast to epileptic seizures, which are a manifestation of excessive and hyper-synchronous discharges in the brain, NEPEs have psychological underpinnings and causes.³

Tremor in newborn infants is the most frequent NEPE, usually occurring within the first 28 days of life⁴ and has been described in infants with a low level of vitamin D,⁵ neonatal paroxetine withdrawal syndrome,⁶ or maternal administration of selective serotonin reuptake inhibitor.⁷ In this regard, an accurate clinical and neurological examination is mandatory to distinguish pathological conditions from physiological conditions.⁸ Other NEPEs in neonates include jitteriness (recurrent tremors),⁴ myoclonus (that can involve one muscle or a group of muscles)⁹ with benign neonatal sleep myoclonus being the most frequent manifestation in this age group,¹⁰ startles,¹¹ and ocular movements: in particular, paroxysmal tonic upgaze or

downgaze and opsoclonus can also be observed in neonates.⁹

Herein, we present a 1-year prospective study of term born infants with NEPEs referred to our neonatal accompaniment unit and diagnosed in our neonatal intensive care unit at the Hospital San Marco (Azienda Ospedaliero-Universitaria Policlinico), University of Catania, Italy. This study underlines the importance of determining a correct diagnosis of NEPEs in neonates and performing appropriate follow-up by using the Hammersmith Neonatal Neurological Examination (HNNE), the Hammersmith Infant Neurological Examination (HINE), and the Griffiths scale to observe the neurodevelopmental trajectory of NEPEs, which has not been previously reported.

The aim of the present study is to report on the different types of NEPEs and to correlate the psychomotor development of patients with NEPE to determine whether they tend to have a risk of atypical neurodevelopment on follow-up.

METHOD

We performed a prospective observational study on 38 consecutive term born neonates (22 males, 16 females;

aged 0–28d; born at \geq 37wks gestational age) with a diagnosis of NEPEs, born from October 2017 to March 2019 in the neonatal accompaniment unit at the Hospital San Marco (Azienda Ospedaliero-Universitaria Policlinico), University of Catania, Catania, Italy.

In Table 1 we summarize the perinatal features of the newborn infants enrolled. In Table S1 (online supporting information), we summarize the main clinical data of these infants with NEPEs, including sex, family history, neurological examination with HINE scores, type of NEPEs, triggering stimulation, behavioural state of appearance, and frequency. In all patients, ictal video-electroencephalograms (video-EEGs) according to the guidelines of the American Clinical Neurophysiology Society for neonates¹² were within normal limits, as were cranial ultrasound scans. We did not perform brain magnetic resonance imaging (MRI) in any of these 38 infants.

We excluded patients with the following features: physiological self-limited tremors that disappeared within the first 24 hours of life; tremors of metabolic origin; major diseases involving the main organs or systemic diseases at

What this paper adds

 Neonates experiencing non-epileptic paroxysmal events (NEPEs) can be examined with the Hammersmith Neonatal Neurological Examination, Hammersmith Infant Neurological Examination, and Griffiths scale at follow-up.

 Newborn infants with NEPEs achieve optimal scores within the first year of life.

diagnosis; history of maternal drug ingestion; alterations of glucose and electrolyte metabolism; alteration of the expanded newborn (metabolic) screening according to the Italian national 'Taverna's law' established by the Ministerial Decree of 16th October 2016, which includes 43 metabolic diseases screened by means of blood samples testing (taken from heel between 48–72h of age and placed on a tissue paper); NEPEs related to genetic mutation.

We diagnosed NEPEs according to the classification by Facini et al.¹ At T0, we administered the HNNE. We considered an HNNE global score of under 27 as suboptimal.¹³

All included patients underwent a clinical and diagnostic evaluation at 3 months (T1), 6 months (T2), 9 months (T3), and 12 months (T4) by means of HINE testing¹⁴ (3,

		Gestational age,	Birthweight,	Birth length,	Birth head circumference,	Mode of deliv-	Apgar score (1st/5tł
Patient	Sex	wks+d	g	cm	cm	ery	minute)
1	М	37+5	3000	50	35	Caesarean	8/10
2	Μ	40+0	3650	51	36	Vaginal	9/10
3	F	41+1	3545	50	34.5	Vaginal	9/10
4	F	39+3	3250	49.5	34	Vaginal	910
5	F	38+6	3440	52	36.5	Caesarean	8/10
6	Μ	38+5	2980	49	34	Vaginal	8/9
7	Μ	37+4	2890	50	36	Caesarean	9/10
8	Μ	39+0	3120	50	34.5	Vaginal	8/10
9	F	40+3	3090	51	35	Vaginal	8/9
0	Μ	40+2	3460	50.5	36	Vaginal	7/10
1	F	41+0	3220	50	35	Caesarean	8/9
2	F	39+6	3095	49	34	Vaginal	9/10
3	Μ	39+4	3360	50	36	Vaginal	910
4	Μ	38+5	3180	50.5	35.5	Vaginal	8/10
5	Μ	38+0	3520	50	34.5	Vaginal	9/10
6	Μ	41+2	3040	49	35	Vaginal	9/10
7	F	38+2	2995	49	34.5	Caesarean	8/9
8	М	39+4	3530	49.5	34	Caesarean	9/10
9	F	38+3	3280	50	36	Vaginal	9/10
0	F	40+6	3050	50	35.5	Vaginal	9/10
1	М	37+6	2970	49	34.5	Vaginal	8/10
2	F	40+4	3510	51	36.5	Vaginal	8/10
3	F	39+6	3050	49	34	Caesarean	10/10
4	M	41+1	3430	50	35.5	Vaginal	9/10
5	M	38+3	3330	50.5	36	Vaginal	9/10
6	M	41+0	3285	50	34.5	Vaginal	8/10
7	M	40+5	3690	52	37	Vaginal	8/9
8	M	40+4	3450	51	35.5	Vaginal	9/10
9	M	39+3	3150	51	36	Caesarean	7/9
0	F	38+6	3500	52	37	Vaginal	9/10
1	F	40+5	3280	51.5	35.5	Vaginal	8/10
2	F	39+5	3560	52	37	Vaginal	9/10
3	M	39+2	3020	51	36.5	Caesarean	9/10
4	F	37+5	2990	49	35	Vaginal	8/9
5	M	41+0	3395	50.5	36	Vaginal	9/10
6	M	39+0	3435	50.5	34.5	Vaginal	9/10
7	M	41+1	3700	51	36.5	Vaginal	8/9
8	F	38+4	3290	51	36	Vaginal	9/10

6, 9, and 12mo) to assess psychomotor development, and the Griffiths scale score system¹⁵ (12mo; Fig. S1, online supporting information) to assess development quotient, especially in patients with alteration of HINE score.

We considered a HINE global score of under 62 as suboptimal;¹⁶ a Griffiths scale score of under 70 was considered very low, 70 to 79 low, 80 to 89 low to average, 90 to 109 average, 110 to 119 high to average, 120 to 129 high, and a score above 129 was considered very high.¹⁷

Ethical statement

The authors declare that the present research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Ethical approval was not required. Parents of patients have given written informed consent to the research and to publication of the results.

RESULTS

A total of 38 term born neonates were diagnosed with NEPEs and enrolled (Video S1, online supporting information). All newborn infants presented adequate birthweight, height, head circumference, and normal Apgar score. Twenty-nine out of 38 neonates were born by vaginal delivery and 9 out of 38 by caesarean delivery (Table 1).

The 38 newborn infants with NEPEs consisted of 22 males and 16 females, and were aged between 0 and 28 days: 18 presented with tremors, six with startles, four with jitteriness, four with paroxysmal ocular movements, four with sleep myoclonus, and two with myoclonus (Table 2).

The age at onset of symptoms ranged from birth to the fourth day of life. In 10 newborn infants, the abnormal clinical manifestations persisted after the first week of life and disappeared within 6 months of life.

The HNNE performed at T0 showed suboptimal values in 18 out of 38 newborn infants (mean 28.94, SD 3.97; range 12; median 31.5; mode 32; Table 2). Of these 18 infants with suboptimal scores, four presented with tremors, two with jitteriness, two with myoclonus, four with paroxysmal ocular movements, and six had startles triggered by acoustic stimuli, according to Facini et al.¹ None of the infants with sleep myoclonus showed suboptimal values. Of these 18 infants with suboptimal scores, 13 out

Table 2:	Clinical features,	sex distribution,	and neurological	examination
at the fir	st evaluation (<i>n</i> =3	38)		

Paroxysmal motor phe- nomena	n (%)	Male	Female	HNNE score <27
Tremors	18 (47.3)	10	8	4
Jitteriness	4 (10.5)	2	2	2
Myoclonus	2 (5.2)	_	2	2
Sleep myoclonus	4 (10.5)	2	2	_
Paroxysmal ocular movements	4 (10.5)	4	-	4
Startles	6 (15.7)	4	2	6

HNNE, Hammersmith Neonatal Neurological Examination.

of 18 were male. Infants with a suboptimal global score presented with the following: tone item and tone pattern in 8 out of 18 cases, reflexes and abnormal signs in 15 out of 18, movements in 18 out of 18, behaviour in 2 out of 18. In two infants, all areas were involved.

We acquired the HINE score at 3, 6, 9, and 12 months of age and the Griffiths scale score at 12 months of age. At 3 months of age, we recorded a suboptimal global score in 10 out of 38 infants: eight were male and two were female; six presented with startles and four with paroxysmal ocular movements. The areas involved in the 10 infants with suboptimal global scores were posture, movements, tone and reflexes, and cranial nerves. At 6, 9, and 12 months of age, all infants had normal values on the HINE scale with full remission of their clinical manifestations and reaching normal neurological exam within 6 months of age. At 12 months, 14 out of 38 infants had low to average Griffiths scale scores, 23 out of 38 had average scores, and 1 out of 38 had high to average scores. None of the 38 infants had low or very low scores (Table 3).

DISCUSSION

NEPEs are occur frequently in neonates. In 1989, Rothner affirmed that 'not everything that shakes is epilepsy', a relevant hypothesis especially in reference to the neonatal period.¹⁸ The differential diagnosis between epileptic and non-epileptic events is difficult to achieve, especially if we consider the differential diagnosis between non-epileptic events underlying a pathological condition and those not associated with diseases. Nonetheless, the differential diagnosis between epileptic forms is crucial to establish a correct therapeutic management and for a mid-long-term prognosis.^{19,20} A video-EEG study is often required for a more accurate assessment²¹ since it represents the criterion standard for distinguishing epileptic versus paroxysmal non-epileptic events.²²

In the present study, we reported the clinical, laboratory, ultrasound, and neuropsychological findings in 38 neonates with NEPEs whose onset of abnormal manifestations ranged from birth to the fourth day of postnatal life. The most frequent paroxysmal motor event was tremor (n=18), followed by startles (n=6), jitteriness (n=4), sleep myoclonus (n=4), paroxysmal ocular movements (n=4), and myoclonus (n=2). At diagnosis, almost half of these infants (n=18) had a suboptimal HNNE score. Among these patients, most presented with startles, followed by tremor, paroxysmal ocular movements, jitteriness, and myoclonus. No infants with sleep myoclonus showed suboptimal values. The areas involved in infants with suboptimal global scores included tone items, tone patterns, reflex, movements, abnormal signs, and behavioural items. Almost all were males, confirming the data from Chen et al., who inferred that NEPEs are more commonly seen in males than females.²³

During their follow-up, only 10 out of 38 neonates had suboptimal HINE scores at 3 months of age, whereas at 6

Table 3: Hammersmith Neonatal Neurological Examination (HNNE), Hammersmith Infant Neurological Examination (HINE),	and Griffiths score at enrol-
ment and follow-up	

Patient	Sex	HNNE T0 global score	HINE T1 global score	HINE T2 global score	HINE T3 global score	HINE T4 global score	Griffiths T4 general quotient
1	Μ	32	65	75	75	76	102.7
2	Μ	25	54	65	66	67	85.3
3	F	33	67	76	76	77	97.3
4	F	32	63	70	71	72	92.5
5	F	31	65	77	78	78	108.5
6	М	26	53	69	70	71	83.3
7	Μ	32	64	69	70	71	83.3
8	Μ	33	64	69	70	70	80.8
9	F	32	67	73	73	74	89.2
10	Μ	33	65	72	73	74	89.2
11	F	32	65	73	74	74	93.3
12	F	32	64	71	71	71	87.1
13	M	33	64	65	69	70	93.9
14	M	23	46	67	75	75	98.3
15	M	33	62	65	65	67	92.5
16	M	32	63	67	68	69	86.7
17	F	33	63	72	73	74	116.0
18	M	25	51	68	69	70	91.7
19	F	23	47	66	67	68	87.7
20	F	34	65	68	69	69	100.0
21	M	26	52	64	64	66	86.3
22	F	24	67	68	69	69	97.6
23	F	24	65	67	67	67	96.1
24	M	33	65	67	67	67	99.1
25	M	26	54	64	66	67	87.7
26	M	34	65	68	68	68	94.1
27	M	26	66	69	70	71	84.0
28	M	25	64	70	71	71	92.2
29	M	25	64	69	70	70	95.7
30	F	25	65	67	68	71	93.3
31	F	33	62	65	67	67	97.7
32	F	32	63	65	67	67	98.2
33	M	22	46	63	64	66	94.1
34	F	32	66	68	68	68	92.5
35	M	26	63	67	67	67	86.7
36	M	26	66	67	67	67	109.3
37	M	26	53	64	65	67	93.0
38	F	26	49	67	69	70	89.1

and 9 months, none presented with anomalies in the tone, posture, cranial nerves, movements, or reflex areas, indicating a spontaneous remission of these events, which in turn led to normal scores on the HINE scale. At 12 months of age, all infants presented with normal values on the HINE scale, and none showed low or very low values on the Griffiths scale. A diagnosis of these phenomena is possible after careful exclusion of the underlying pathological conditions.¹

Retrospective studies on NEPEs in childhood have been reported. Canavese et al. described 63 individuals with NEPEs, of which NEPEs were the only neurological manifestations in 18 (primary), while in the remaining 45 individuals, NEPEs were associated with other neurological conditions (secondary) due to static encephalopathy (24/45 individuals) or progressive encephalopathy (21/45 individuals).²¹ Bye et al. analysed 285 children with non-epileptic events, and compared their results with those of other studies.^{24–27} They showed that a significant percentage of children who had epilepsy and an epileptiform EEG and

used anticonvulsant medication at some time were developmentally delayed or neurologically impaired, but the authors did not add findings regarding their follow-ups.²²

In a prospective study, Shuper et al. reported on 13 out of 22 infants aged 1 to 12 months, all born at term, with repeated spells and normal interictal EEG recordings. The initial physical and neurological examination was normal, and all the spells disappeared completely over the followup period,²⁸ thus confirming the benign nature and the regression of NEPEs over time. Leone et al. assessed 84 low risk term born neonates with tremors at birth and persisting after 10 days who underwent a longitudinal neurological assessment of the evolution of tremors and increased resistance to passive movement. Their results confirmed that outcome was always normal in all children, but the rate of resolution of the signs was variable with a consistent number still having signs at 9 months and a few even at 12 months.²⁹

Recent reviews on neonatal NEPEs have demonstrated the importance of distinguishing them from neonatal seizures.^{19,30} In 2013, Cross³¹ published a review discussing various physiological mechanisms and the pathological significance of NEPEs with similar clinical features. The author showed the importance of a detailed clinical examination, video-EEG recordings, and a detailed clinical history to the differential diagnosis between NEPEs and epileptic events in order to avoid overtreatment and incorrect management of these newborn infants. Orivoli et al.⁹ published an extensive review of the most frequent paroxysmal non-epileptic motor events in newborn infants, describing a diagnostic-therapeutic approach to the disease. Facini et al.¹ provided an extensive overview of the clinical features of neonatal paroxysmal motor events of both epileptic and non-epileptic origin.

To our knowledge, little data have been published on neonates with NEPEs, and there are scant data in the literature on follow-ups and outcomes of these neonates.

Furthermore, to the best of our knowledge, this is the first prospective study on term newborn infants with NEPEs focused on outcomes with patient examination and HINE and Griffiths scale testing.

Given that all infants in our study did not present alterations on the HINE or Griffiths scale scores at the end of their follow-ups, we emphasize that a correct diagnosis and follow-up are indispensable to avoid unnecessary therapeutic treatment because NEPEs and associated neurological alterations tend to regress within the first months of life. Although 18 of our patients showed a positive neurological examination, neurological follow-up at 3 months showed anomalies in 10, whereas at 6 and 12 months of life, all infants had normal HINE scores, and none had low or very low Griffiths scale scores.

The aim of our study was to highlight the importance of a correct diagnosis of motor paroxysmal non-epileptic events in neonates and the need to obtain interictal and ictal video-EEGs of these patients to avoid inappropriate pharmacological treatment and management. We recommend adequate follow-up, including administration of the HINE and Griffiths scales, until 12 months of life.

During the first year of life, infants may present with a wide spectrum of movement patterns that mimic epilepsy. These spells may appear in typically developing infants and do not interfere with further typical development. They are also limited in duration, and a significant number of these spells will resolve spontaneously.

Moreover, we believe that further studies should be performed to obtain data on these disorders in the neonates.

Our study has several limitations: (1) the sample of patients is relatively small, and thus additional studies in larger cohorts are recommended to further study the neurological developmental in newborn infants with NEPEs; (2) we studied infants until 12 months of life; other studies should be performed to assess neuromotor and cognitive development until school age; (3) future research in this area of enquiry should include the analysis of genetic profiles and stratify analysis by sex to identify an eventual correlation between genetic/genomic features and neurological development.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

SUPPORTING INFORMATION

The following additional material may be found online:

Table S1: Clinical data of patients with non-epileptic paroxysmal events

Figure S1: Study design.

Video S1: NEPE in a term-born infant.

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