Transient benign paroxysmal movement disorders in infancy

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Introduction. Transient benign paroxysmal movement disorders in infancy encompass a group of disorders that appear during the neonatal period and in the first years of life, and that spontaneously disappear without leaving consequences. This article aimed to review the main transient benign paroxysmal movement disorders in infancy, focusing on recognition and diagnostic approach.

Development. Overall, it includes entities such as: jitteriness, benign neonatal sleep myoclonus, shuddering, benign myoclonus of early infancy, transient idiopathic dystonia in infancy, spasmus nutans, paroxysmal tonic upgaze of infancy, and benign paroxysmal torticollis.

Conclusion. Transient benign paroxysmal movement disorders are non-epileptic paroxysmal episodes, and their diagnosis is eminently clinical. The correct recognition of these entities is crucial to avoid anxiety, unnecessary complementary exams, and treatments.

Key words. Dystonia. Infant. Movement disorders. Myoclonus. Neurodevelopmental disorders. Spasmus nutans.

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Introduction

Transient benign paroxysmal movement disorders (TBPMD) in infancy encloses a group of entities that appear in the neonatal period, and in the first year of life, and that spontaneously disappear without leaving consequences. This group includes entities, such as: jitteriness, benign neonatal sleep myoclonus, shuddering, benign myoclonus of early infancy, transient idiopathic dystonia in infancy, spasmus nutans, paroxysmal tonic upgaze of infancy and benign paroxysmal torticollis [1,2]. TBPMD are defined by non-epileptic paroxysmal episodes and by the following principles: a) no change in consciousness during episodes; b) normal neurological examination between episodes; c) normal psychomotor development; d) spontaneous remission; and e) normal auxiliary diagnostic tests [1,3].

Evidence supporting the neurophysiopathology of these disorders is still scarce, but functional changes in the immature cortex and their genetic basis may be involved. Globally, TBPMD represents a group of underdiagnosed or even misdiagnosed entities, whose prevalence is unknown [1,4]. Epilepsy is the main differential diagnosis and consequently the number one reason for referral to the neuropediatrics unit. A detailed description of the episodes and their observation on video are essential for proper diagnosis and clinical guidance.

This article aimed to review the main transient benign paroxysmal movement disorders in infancy, focusing on recognition and diagnostic approach.

Disorders description

Jitteriness

Jitteriness is observed in 50% of healthy term newborns within the first few days of life, which corresponds to the most common movement disorder observed in the neonatal period [5,6]. It is a bilateral, symmetric, high-frequency, low-amplitude rhythmic tremor that can involve the chin and/or extremities. It is elicited by crying, the Moro reflex and stress. It is highly stimulus-sensitive and can be easily suppressed by gentle restraint.[7,8]. Essential jitteriness usually disappears throughout the neonatal period. However, it can persist until two months of age and may recur after a symptom-free interval of up to six weeks. Despite this, it is always resolved until the age of one year [9].

The pathogenesis remains unclear, but it may be secondary to endocrine-metabolic imbalances (hypoglycemia, hypocalcemia, hypomagnesemia, and hyperthyroidism), hypoxic-ischemic encephalopathy, intracerebral hemorrhage, and drug withdrawal. Epilepsy is the main differential diagnosis, especially when jitteriness appears after a symptom-free interval, and an electroencephalogram (EEG) is recommended. These movements are not accompanied by paroxysmal activity in the EEG. There is no specific treatment for essential jitteriness, and the neurological outcome is good [5].

Benign neonatal sleep myoclonus

Benign neonatal sleep myoclonus often begins during the first two weeks of life, decreases in the second month, and disappears in 95% of the cases by the sixth month. It is characterized by sudden repetitive myoclonic movements, during sleeping (non-rapid eye movement sleep) or in the sleep-wake transition periods, and ceases with arousal [1,5,10]. Myoclonus is bilateral, diffuse and synchronous (less often unilateral). Distal upper limbs are predominantly affected (flexion of the fingers, wrist and/or elbow). It may also be generalized. However, facial muscle involvement is less frequent. It is not associated with abnormal eye movements, apnea, color changes or crying [11,12]. Myoclonic jerks mostly occur in clusters, with a frequency of 1-5 per second, lasting several seconds or minutes, although recurrence with irregular intervals and localization may be possible. Some of the triggers described in literature include rocking motion, tactile stimulation and car riding [13]. Benzodiazepines may exacerbate myoclonic jerks. There is also a higher incidence of benign neonatal sleep myoclonus in opioid-dependent mothers [11]. Both the neurologic examination and the EEG are normal. The differential diagnosis of benign neonatal sleep myoclonus includes benign neonatal seizures, neonatal status epilepticus, jitteriness, and motor automatisms (pedaling, stepping and rotary arm movements) [7,14,15]. Treatment is not required, and the neurologic outcome is good.

Shuddering

Shuddering appears in the first year of life and consists of a brief (5-15 seconds) motor movement, in the form of shivering involving head, shoulders and, sometimes, trunk [1,16]. It can occur daily, with a frequency between five to more than 100 times a day, but it does not happen while sleeping [1,17]. The main triggering factors are food, head movements and certain specific movements such as pressing two objects against each other [17]. The pathogenesis of this movement is still unknown, and a possible association with essential tremor has been proposed. However, this relationship remains uncertain [18]. Epilepsy may be excluded through a complete and detailed clinical history, episode video recording and EEG. Routine brain magnetic resonance imaging (MRI) is not recommended [17]. Shuddering movements may also be an expression of benign myoclonus of early infancy (see below) and may even correspond to the same nosological entity [19,20]. The prognosis is favorable with complete resolution by the age of four.

Benign myoclonus of early infancy

Benign myoclonus of early infancy, also called non-epileptic infantile spasms, usually starts within the first year of life (frequently after six months). Benign myoclonus of early infancy is characterized by sudden and brief contractions of the neck and/or upper limbs, resulting in head flexion or rotation movements and limb extension and abduction. It has a broad clinical spectrum [19], and it may be observed in different forms, namely spasms, brief tonic contractions, shuddering, or atony (cervical or axial). Most episodes occur while awaking (but they may also be present during sleep), usually in clusters with intervals of three to four minutes [21,22]. They may happen several times a day, but they do not always occur on a daily basis. Triggering factors include states of excitement or frustration. There is still no consensus in the literature regarding its pathogenesis. Nonetheless, transient changes in neurotransmitters (GABA, glycine, serotonin or glutamate) may occur and familial forms have been described, suggesting a possible genetic factor [19,21]. The main differential diagnosis is made with epileptic syndromes starting in the first year of life, particularly West syndrome, benign childhood epilepsy and reflex childhood tonic seizures. Brain MRI and EEG should be included in the initial diagnostic approach. Interictal EEG shows a hypsarrhythmic pattern in West syndrome, whereas it may be normal in benign childhood epilepsy [19]. A detailed semiology of the episodes and the association or not with wakefulness, and respective triggering factors, provide important clues for the diagnosis. The frequency of episodes will gradually decrease in the following months after the first episode, un-

til it spontaneously resolves by the age of two (up to three years old) [21].

Transient idiopathic dystonia in infancy

Transient idiopathic dystonia in infancy is characterized by dystonic unilateral posture of the upper limb (rarely both) that may be associated with trunk or lower limb dystonia [23]. Transient idiopathic dystonia in infancy usually begins between five and ten months of age. The typical posture is an abducted arm with pronation of the forearm and flexion of the wrist; feet can assume an echinovaro posture [24]. These episodes are intermittent, lasting from seconds to hours, but, in some infants, they can persist longer, even though they attenuate during sleep [1,23]. The disappearance of dystonia with the change of position and during voluntary movements in the absence of functional limitation is the diagnostic clue for transient idiopathic dystonia in infancy [23]. Orthopedic pathology and brachial plexus paresis should be excluded. Pathophysiology is still unknown. Transient idiopathic dystonia in infancy has a favorable prognosis, with spontaneous resolution by the age of four to five [23].

Spasmus nutans

Spasmus nutans is a rare paroxysmal disorder, characterized by a clinical triad: head nodding, nystagmus and torticollis. Nodding movements and nystagmus are present in most cases, 87% and 80% respectively, while torticollis appears in about 40% [1]. It starts between four and 18 months of age, but, in some cases, it can start later, between 18 months and three years. Head movements correspond to slow cephalic tremor, usually no-no, yes-yes, or rotary, with a low frequency (2-3 Hz) and variable amplitude (2-25º), and do not occur during sleep [1,25]. Nystagmus is asymmetrical, unconjugated, horizontal and pendular, with low amplitude and high frequency (up to 15 Hz). With fixation, both the nystagmus and nodding may cease or, paradoxically, may be triggered. As with other movement disorders, pathogenesis is unknown. It has been suggested that it may result from an immaturity/instability of the ocular motor control mechanisms in the first months of life. Electronystagmography studies suggest that the nodding movements and torticollis are a form of compensation for the nystagmus [25]. Familial forms have been described, suggesting the involvement of genetic factors in the pathogenesis of spasmus nutans. It occurs more frequently in children with a history of prematurity, low birth weight, in families of low socioeconomic status, and in children with parents with psychiatric pathology or drug abuse [25]. The differential diagnosis includes congenital idiopathic nystagmus (persistent) and entities clinically similar to spasmus nutans but with central nervous system involvement, like opsoclonus-myoclonus and the bobble-head doll syndrome [26]. Other pathologies may cause a spasmus nutans-like condition (secondary spasmus nutans), such as ophthalmological disorders (severe refractory errors, optic nerve and chiasm gliomas, and retinal pathology) and neurological disorders (cerebellar vermis hypoplasia, brain tumors, Pelizaeus Merzbacher disease, and Leigh's disease) [25,26]. Spasmus nutans is a diagnosis of exclusion, based on normal neurological and ophthalmic examination. The diagnostic approach should include brain MRI, visual evoked potentials, and electroretinography. It has a favorable prognosis, with spontaneous resolution in one to two years after the onset of clinical symptoms. The nystagmus decreases in intensity as the child grows, but subclinical nystagmus may persist until twelve years of age [26].

Paroxysmal tonic upgaze of infancy

Paroxysmal tonic upgaze of infancy is characterized by prolonged episodes of sustained or intermittent upward deviation of the eyes, with compensatory cervical flexion. The average age of onset is five months, with a minimum age reported of one week and a maximum of seven years. The combined deviation of looking downwards is hampered, resulting in downwards saccades movements. The horizontal movements are normal [27]. Paroxysmal or persistent ataxia may be associated and may persist after the resolution of the ocular disorder. These episodes may last seconds to hours (rarely days) and may be triggered by fatigue, immunization or febrile infectious intercurrence [28]. Daytime fluctuation may exist, and alleviation with sleep is typical. However, the relationship with sleep can be paroxysmal and a tonic deviation of the eye can occur immediately after waking up [17,27,28]. Pathogenesis is controversial and speculative but despite that familial cases have been reported suggesting an autosomal recessive inheritance. There are reports of improvement after treatment with dopamine, suggesting that defects in the mechanisms of dopamine synthesis may be involved. Additionally, it may depend on the immaturity of the

Table. Transient benign paroxysmal movement disorders in infancy.

	Age of onset	Age of resolution	Secondary causes	Consider performing some further diagnostic testing
Jitteriness	< 2 weeks	< 1 month (2 months-1 year)	Yes	Biochemical tests, EEG
Benign neonatal sleep myoclonus	< 2 weeks	< 6months	Yes	EEG
Shuddering	< 1 year	< 4 years	No	EEG
Benign myoclonus of early infancy	6 months (< 1 year)	< 2 -3 years	No	EEG, brain MRI
Transient idiopathic dystonia in infancy	5-10 months	< 5 years	No	Brain MRI
Spasmus nutans	4-18 months (18 months- 3 years)	1-2 years after onset	Yes	Brain MRI; ophthalmological evaluation (visual evoked potential and electroretinography)
Paroxysmal tonic upgaze of infancy	5 months (1 week -7 years)	< 4 years	Yes	EEG, brain MRI; ophthalmological evaluation (visual evoked potential and electroretinography), and CACNA1A sequencing
Benign paroxysmal torticollis	< 3 months (1 week-3 years)	< 4 years	No	EEG, brain and cervical MRI, and CACNA1A sequencing

EEG: electroencephalogram; MRI: magnetic resonance imaging.

corticomesencephalic control mechanisms of the vertical eye movement. Other studies point to a possible association between paroxysmal tonic upgaze and benign paroxysmal torticollis, raising the possibility that both are channelopathies, namely CACNA1A-related disease and PTU has also been identified in patients with GRID2 mutations and as a SCN8A-intermediate phenotype [17,27,28]. Absence seizures and oculogyric crises are the main differential diagnoses. Secondary causes of paroxysmal tonic upgaze in infancy should also be considered, such as brain malformation, brain tumors, white matter disorders, chromosomal disorders, dopamine blockers, and retinal pathology. Pharmacological treatment is usually unnecessary and ineffective, although a levodopa trial (150 mg/day) may be considered [27,28]. The frequency of episodes progressively decreases and usually disappears until four years of age. Although the episodes are transient and eventually resolve within childhood, the mono-symptomatic course is rare. Despite the resolution of the oculomotor manifestations, about 40% might have learning difficulties or mild cognitive impairment, which can be moderate to severe in 10% of patients. Residual ataxia may persist in one quarter of the patients, and changes in ocular mobility (strabismus or nystagmus) may occur in 20-25% [27,28].

Benign paroxysmal torticollis

Benign paroxysmal torticollis is characterized by recurrent and painless episodes of latero, retro or torticollis, often associated with homolateral trunk torsion and unilateral extension of the lower limbs. It can also be accompanied by external eye rotation, homolateral ptosis and hypotoni [1,29,30]. It starts before the age of three months in half of the cases, but it may range from the first week to 30 months [1,17,29]. Two distinct forms are described, periodic and paroxysmal. The most common is the periodic form, lasting several hours to days. In the paroxysmal form, episodes last a few minutes and are usually accompanied by oculomotor signs [29]. Both forms are more common on awaking and can be triggered by febrile illness and postural changes [29]. Irritability, pallor, nausea, vomiting and ataxia are commonly associated. Ataxia may be the dominant or the only feature, particularly after several episodes of torticollis and in older children [17,29]. Pathophysiology is still unknown, notwithstanding mechanisms of vestibular dysfunction (labyrinthitis or vestibulo-cerebellar), immaturity of the central nervous system, and genetic factors may be involved. Long-term follow-up demonstrated that benign paroxysmal torticollis may be an equivalent of migraine. One third of children later develop a periodic childhood syndrome (recurrent abdominal pain, paroxysmal vertigo, or cyclic vomiting) and classic migraine in adolescence [29,31]. The episodic character, the presence of a triggering factor, and the absence of structural cause, reinforce the association of benign paroxysmal torticollis and migraine and are suggestive of channelopathy, as the CACNA1A and SCN8A mutations [32]. There have been reports of benign paroxysmal torticollis in families with hemiplegic migraine caused by the CACNA1A variants, framing it in the same clinical spectrum [31]. Differential diagnosis should include epilepsy, posterior fossa tumors, Sandifer's syndrome, cervical spine pathology and iatrogenic dystonia [33]. Brain and cervical MRI and EEG should be performed. The episodes are initially frequent, occurring on a reg-

ular basis, but, subsequently, there is a progressive reduction in the number of episodes until its resolution, which frequently happens by the age of four [29,31].

Conclusion

Transient benign paroxysmal movement disorders are non-epileptic paroxysmal episodes, and their diagnosis is eminently clinical. In the table, there is a summary of all the clinical and diagnostic features of each disorder. Previous studies highlight a high percentage (~20%) of misdiagnosis of epilepsy, which were in fact non-epileptic seizures. The diagnosis can be challenging at the initial presentation and due to the growing number of patients referred to the Neuropediatrics unit, it is essential to have a high index of suspicion in its identification. The correct recognition of these entities is crucial to avoid anxiety, unnecessary complementary exams, inappropriate use of anti-seizure medications and subsequent needless side effects, and for cost effectiveness treatments. Further diagnostic testing should be performed directed towards the exclusion of secondary causes.

References

1. Fernández-Alvarez E. Transient benign paroxysmal movement disorders in infancy. Eur J Paediatr Neurol 2018; 22: 230-7.
2. Temudo T, Carrilho I. Movement disorders in children. Mov Disord Curricula 2017; 415-26.
3. Nagy E, Hollody K. Paroxysmal non-epileptic events in infancy: five cases with typical features. Epileptic Disord 2019; 21: 458-62.
4. Singer HS, Mink JW, Gilbert DL, Jankovic J. Transient and developmental movement disorders in children. In Singer H, Mink J, Gilbert D, Jankovic J, eds. Movement disorders in childhood. 2 ed. Philadelphia: Elsevier; 2016. p. 69-78.
5. Blackburn JS, Mink JW. Movement disorders of infancy. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF, Finkel RS, Gropman AL, et al, eds. Swaiman's pediatric neurology: principles and practice. 6 ed. Chicago: Elsevier Inc.; 2017. p. 724-7.
6. Huntsman RJ, Lowry NJ, Sankaran K. Nonepileptic motor phenomena in the neonate. Paediatr Child Health 2008; 13: 680-4.
7. Hahn JS, Sanger T. Neonatal movement disorders. Neonreviews 2004; 5:321-6.
8. Garone G, Capuano A, Travaglini L, Graziola F, Stregapede F, Zanni G, et al. Clinical and genetic overview of paroxysmal movement disorders and episodic ataxias. Int J Mol Sci 2020; 21: 3603.
9. Luat AF, Kamat D, Sivaswamy L. Paroxysmal nonepileptic events in infancy, childhood, and adolescence. Pediatr Ann 2015; 44: e18-23.
10. John B, Patnaik S. Benign neonatal sleep myoclonus: is it so uncommon? Med J Armed Forces India 2006; 62: 186-7.
11. Maurer VO, Rizzi M, Bianchetti MG, Ramelli GP. Benign neonatal sleep myoclonus: a review of the literature. Pediatrics 2010; 125: e919-24.
12. Kaddurah AK, Holmes GL. Benign neonatal sleep myoclonus: history and semiology. Pediatr Neurol 2009; 40: 343-6.
13. Suzuki Y, Toshikawa H, Kimizu T, Kimura S, Ikeda T, Mogami Y, et al. Benign neonatal sleep myoclonus: our experience of 15 Japanese cases. Brain Dev 2015; 37: 71-5.
14. Sing GJ, Singla G, Mahey H. Benign neonatal sleep myoclonus: frequently misdiagnosed as neonatal seizures. Indian Pediatr 2015; 52: 713-4.
15. Turanli G, Şenbil N, Altunbaşak Ş, Topçu M. Benign neonatal sleep myoclonus mimicking status epilepticus. J Child Neurol 2004; 19: 62-3.
16. Thabit MN, Sadek AA, Motawe ES, Ali RAE, Mohamed MM. Non-epileptic paroxysmal events in paediatric patients: a single tertiary centre study in Egypt. Seizure 2021; 86: 123-8.
17. Bonnet C, Roubertie A, Doummar D, Bahi-Buisson N, De Cock VC, Roze E. Developmental and benign movement disorders in childhood. Mov Disord 2010; 25: 1317-34.
18. Caraballo RH, Capovilla G, Vigevano F, Beccaria F, Specchio N, Fejerman N. The spectrum of benign myoclonus of early infancy: clinical and neurophysiologic features in 102 patients. Epilepsia 2009; 50: 1176-83.
19. Ghossein J, Pohl D. Benign spasms of infancy: a mimicker of infantile epileptic disorders. Epileptic Disord 2019; 21: 585-9.
20. Vigevano F, Specchio N. Benign myoclonus of early infancy. J Pediatr Neurol 2010; 8: 23-4.
21. Calado R, Monteiro JP, Fonseca MJ. Transient idiopathic dystonia in infancy. Acta Paediatr Int J Paediatr 2011; 100: 624-7.
22. Davico C, Sotgiu F, Canavese C. Transient idiopathic dystonia in infancy: a clinical case and video description. Mov Disord Clin Pract 2016; 3: 318-9.
23. Papageorgiou E, McLean RJ, Gottlob I. Nystagmus in childhood. Pediatr Neonatol 2014; 55: 341-51.
24. Kartal A. Paroxysmal tonic upgaze in children: three case reports and a review of the literature. Pediatr Emerg Care 2019; 35: e67-9.
25. Blumkin L, Leshinsky-Silver E, Michelson M, Zerem A, Kivity S, Lev D, et al. Paroxysmal tonic upward gaze as a presentation of de-novo mutations in CACNA1A. Eur J Paediatr Neurol 2015; 19: 292-7.
26. Humbertclaude V, Krams B, Nogue E, Nagot N, Annequin D, Tourniaire B, et al. Benign paroxysmal torticollis, benign paroxysmal vertigo, and benign tonic upward gaze are not benign disorders. Dev Med Child Neurol 2018; 60: 1256-63.
27. Solazzi R, Castellotti B, Canafoglia L, Messina G, Magri S, Freri E, et al. Paroxysmal tonic upgaze in a child with SCN8A-related encephalopathy. Epileptic Disord 2021; 23: 643-7.
28. Shin M, Douglass LM, Milunsky JM, Paul Rosman N. The genetics of benign paroxysmal torticollis of infancy. J Child Neurol 2016; 31: 1057-61.
29. Gur-Hartman T, Berkowitz O, Yosovich K, Roubertie A, Zanni G, Macaya A, et al. Clinical phenotypes of infantile onset CACNA1A-related disorder. Eur J Paediatr Neurol 2021; 30: 144-54.
30. Blumkin L. Paroxysmal torticollis of infancy: a benign phenomenon? Dev Med Child Neurol 2018; 60: 1196-7.
31. Danielsson A, Anderlid BM, Stödberg T, Lagerstedt-Robinson K, Klackenberg Arrhenius E, Tedroff K. Benign paroxysmal torticollis of infancy does not lead to neurological sequelae. Dev Med Child Neurol 2018; 60: 1251-5.
32. Rosman NP, Douglass LM, Sharif UM, Paolini J. The neurology of benign paroxysmal torticollis of infancy: report of 10 new cases and review of the literature. J Child Neurol 2009; 24: 155-60.
33. Mindlina I. Diagnosis and management of Sandifer syndrome in children with intractable neurological symptoms. Eur J Pediatr 2020; 179: 243-50.

Trastornos paroxísticos del movimiento de carácter benigno y transitorio en la infancia

Introducción. Los trastornos paroxísticos del movimiento de carácter benigno y transitorio en la infancia engloban un grupo de trastornos que aparecen durante el período neonatal y en los primeros años de vida, y que desaparecen espontáneamente sin dejar secuelas. El objetivo de este artículo fue revisar los principales trastornos paroxísticos del movimiento de carácter benigno y transitorio en la infancia, centrándose principalmente en el enfoque utilizado para su reconocimiento y diagnóstico.

Desarrollo. En general, estos trastornos presentan entidades como temblores, mioclonías neonatales benignas del sueño, estremecimientos, mioclonías benignas de la infancia temprana, distonía transitoria idiopática del lactante, espasmo *nutans,* desviación tónica paroxística de la mirada hacia arriba en la infancia y tortícolis paroxística benigna.

Conclusiones. Los trastornos paroxísticos del movimiento de carácter benigno y transitorio son episodios paroxísticos no epilépticos, cuyo diagnóstico es eminentemente clínico. Es crucial reconocer correctamente estas entidades para evitar los estados de ansiedad y la necesidad de realizar exámenes complementarios y tratamientos innecesarios.

Palabras clave. Distonía. Espasmo *nutans.* Infantil. Mioclono. Trastornos del desarrollo neurológico. Trastornos del movimiento.