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Review article

Transient benign paroxysmal movement disorders in infancy

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ABSTRACT

This review summarizes the current empirical and clinical literature on benign paroxysmal movement disorders in infancy most relevant to practitioners. Paroxysmal benign movement disorders are a heterogeneous group of movement disorders characterized by their favourable outcome.

We pay special attention to the recognition and management of these abnormal motor conditions strongly suggestive of epileptic disorders. They include: neonatal jitteriness; benign neonatal sleep myoclonus; benign paroxysmal tonic upgaze; paroxysmal tonic downgaze, benign paroxysmal torticollis and benign polymorphous movement disorder of infancy.

Contents

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1. Introduction

Transient benign paroxysmal movement disorders (TBPMD) can be defined as those abnormal paroxysmal movements that spontaneously stop over time without leaving residua.

The aim of this paper is to provide a practical approach to the recognition of the more common TBPMDs in the first year of life. The following conditions will be discussed: neonatal jitteriness, benign neonatal sleep myoclonus, paroxysmal tonic upgaze of childhood, paroxysmal tonic downgaze of newborn and infancy, and benign paroxysmal torticollis. Particularly, we will focus on the group of benign, brief, sudden infantile abnormal movements historically known as terms such as shuddering attacks or benign myoclonus of early infancy that can be grouped under the umbrella term: "benign polymorphous movement disorder of infancy' (BPMDI).[41,48]

Their clinical picture is sometimes so distinctive that no investigations are required. In other cases recognition allows a limitation of what otherwise could be a very extensive diagnostic work-up.

2. Neonatal jitteriness

Jitteriness is a common clinical finding during the examination of healthy neonates within first days of life mainly when crying, stressed or electing the Moro reflex. It is a particular tremor of high frequency and low amplitude involving jaw and symmetrically the extremities.[73] Their severity is variable. In the mild forms this occurs only during asleep or startle response (half of cases), in the moderate forms this occurs also during alertness or crying. In severe cases the tremor persists in almost all the arousal states.

'Essential' jitteriness markedly diminishes during the first 2 weeks and disappears without sequel before the child is one-year-old.[85] In a follow-up study, jitteriness resolved at a mean age of 7.2 months.[62] In addition, in some infants, essential jitteriness may reappear after an interval of up to 6 weeks but also disappears at the typical age. Jitteriness can also occur in infants with hypoxic ischaemic encephalopathy, hypocalcaemia, hypoglycaemia, congenital heart defect, maternal use of cannabis, and drug withdrawal[73] ('secondary' jitteriness).

2.1. Diagnosis

Jitteriness can be misdiagnosed as an epileptic phenomenon especially when it reappears after an interval. Differential features included precipitation by crying or by sudden movement in jitteriness, abolition by restraint or change of position of the affected limbs and absence of abnormal eye movements. In jitteriness, critical EEG shows no paroxysmal activity. However, secondary jitteriness and seizures can occur coincidentally and can be difficult to differentiate.

2.2. Pathophysiology

This is unclear. Jitteriness could be regarded as a spontaneous clonus triggered by the infant's sudden movements.

Prognosis of jitteriness in healthy babies is good. In secondary jitteriness, the prognostic significance is also unclear; the associated signs, rather than the tremor itself, are the major determinants of the ultimate prognosis.

There are no specific treatments for essential neonatal jitters apart from support, and familial reassurance.

3. Benign neonatal sleep myoclonus (BNSM)

In 1982 Coulter and Allen reported three infants with sleep myoclonus that began in the first month of life and coined the term 'benign neonatal sleep myoclonus' (BNSM). Myoclonic jerks were described as bilateral, repetitive, confined to sleep and stop with arousal. Neurological examination and critical EEG were normal and remained normal during follow-up.

During the following years some series of BNSM had been reported[26,29,31,32,66,74,77,92] emphasising the importance of differential diagnosis with epileptic neonatal seizures.

3.1. Clinical features

BNSM appears in term newborn infants during the first weeks of life. The earliest onset has been registered in a 5 h old neonate.[24] Because intensity and frequency of jerks increase up to the 3rd week of life, more subtle myoclonus appearing in the early days may go unnoticed.

Myoclonic jerks in BNSM are present during quiet sleep.[29] They may appear in the transition from sleep to wakefulness.[57] The myoclonic jerks take on many forms and can be localised or bilateral, synchronous or asynchronous, subtle or

violent, rhythmical or arhythmical, and even migratory or multifocal. In some infants, repeated multifocal jerks continue for 30 min or more.[57,95] In most cases jerks are predominant in the upper limbs, especially distally, but myoclonus in the face, axial, and abdominal muscles has also been reported.[26,29,77] Bouts of myoclonic jerks usually recur irregularly in series lasting 20–30 min[29] or up to 90 min[9] so BNSM can mistaken for convulsive status.[4,95] Waking up always stops the jerks. Occasionally BNSM was shown to be stimulus sensitive, elicited for instance, by noises.[24] Its appearance after rocking the crib has been described as a diagnostic manoeuvre. [4,66] Benzodiazepines were found to increase the intensity of BNSM.[76]

BNSM fades spontaneously from the second month onwards, and usually disappears in 95% before the 6th month of life.[66] Interictal and ictal EEG are normal. At follow-up in one study, 8 of 38 children were found to have mild abnormalities in axial muscle tone,[74] but the general view is that most children with BNSM are normal in the long term.

3.2. *Aetiology*

Genetic factors may be involved in the genesis of BNSM as affected siblings have been reported[32,92,96] and, in addition, a history of jerks during sleep in one of the parents was also suggested in several cases.[3] Afawi et al.[1] did not find linkage with the KCNQ2 and KCNQ3 potassium channel genes that are mutated in benign familial neonatal seizures.

The origin of the myoclonus is not clear. In the study of Daoust-Roy and Seshia,[26] polygraphic recordings showed EMG bursts of greater than 100milliseconds making a cortical form of myoclonus unlikely. Fokke et al.,[42] using sophisticated neurophysiological techniques, suggest the myoclonus may arise from a spinal generator.

3.3. *Differential diagnosis*

Often BNSM is misdiagnosed as epileptic seizures. The relationship of the attacks with quiet sleep, normal clinical and developmental status of the infant and the normality of the EEG are important clues to BNSM diagnosis. Other misdiagnoses include physiological myoclonus, jitteriness and motor automatisms. Motor automatisms such as pedalling, stepping, rotary arm movements, and complex purposeless movements in the newborn are also not associated with EEG seizure discharges but they are not related to sleep state. Benign myoclonus of early infancy never starts in newborn infants and generally occurs in the waking state.[39]

4. Benign paroxysmal tonic upgaze of childhood (PTU)

The essential sign of this complex disorder with onset in the first months of life is prolonged episodes of sustained or intermittent tonic conjugate upward deviation of the eyes with down-beating nystagmic jerks during attempts to look downward. The horizontal movements are normal. Throughout the episode the children typically adopted a neck flexion causing a chin down position. These episodes last hours, rarely days.[28,45] They frequently aggravate with fatigue or infections and disappear or are alleviated with sleep but a case where the symptoms were more severe following sleep has been reported.[5] Usually, the frequency of observed episodes of upward deviation is between 2 and 10 events per day.[82] The frequency and duration of the episodes usually spontaneously remits between 1 month and 6 years. Recurrences in a modified form have been reported.[51]

PTU was first reported in 1988 by Ouvrier and Billson. Soon after, other cases were reported[2,14,28,37,45,49,81,90,91] including one large series.[51] Considered to be a benign, transient disorder, long-term follow-up showed that, in fact, permanent neurological problems such as ataxia and mild ocular abnormal movements are quite common. In a study of 16 children, developmental and/or language delay are present in up to 60–70 percent of cases and only three of them had normal development and neurological findings.[51]

Some patients[28,70,71] start, in addition, with ataxia that may persist during the episodes.[5,14,37]

Laboratory, neurophysiologic and neuroimaging examinations are normal. Ataxia was also noted in multiple different reports.[14,49,64] Rare cases of structural abnormalities of the brain have been reported: MRI images suggestive of periventricular leukomalacia in spite of a normal perinatal history,[91] hydrocephalus associated with a vein of Galen malformation,[51] pinealoma,[90] and demyelination.[84] In two of the previously-mentioned 16 cases of Hayman et al.,[51] MRI creates the 'impression' of mild delay in cerebral myelination but was not confirmed in later repeated MRI exams. Pathological study of one infant, who died accidentally, was normal.[70] Moreover, cases where the mothers were taking valproate during pregnancy[14,37,71] have been reported. The term 'paroxysmal tonic upgaze plus' has been suggested for the patients who have structural and other abnormalities associated with episodes of tonic upgaze.[105]

4.1. *Physiopathology*

Physiopathology of PTU is unknown. Both autosomal dominant[14,49] and recessive inheritance[51] have been suggested. Episodes of tonic upward eye deviation in children have been associated with chromosomal abnormalities,[56] Beckwith–Wiedemann syndrome,[88] CACNA1A mutations,[11,78] and GRID2 mutations.[52] Considering the well known clinical reports of abnormalities of tonic upgaze in patients with lesions in mesencephalic region it is possibly that PTU results from an age-related neurotransmitter dysfunction, mainly affecting the supranuclear pathways that control vertical eye movements. Another possibility is abnormal cerebellar dysfunction, particularly of the flocculus.[52] But, in any case it is difficult to explain the paroxysmal nature of the disorder.

4.2. *Differential diagnosis*

Seizures come into the differential diagnosis, but are usually easily separated from PTU. Oculogyric crises need to be considered, as the episodes of tonic epileptic upgaze are not clinically distinguishable from brief episodes of PTU. Oculogyric crises occur in treatable conditions such as tyrosine hydroxylase deficiency, where severe neurological abnormalities may be completely reversed with L-dopa therapy, and it is

therefore of the greatest importance that they be recognised. Mesencephalic tumours, opsoclonus-myoclonus syndrome or alternating hemiplegia can be easily excluded by anamnesis, normality of the EEG and neuroimaging studies. In retinal disease preserving the lower visual fields the abnormal upward gaze deviation is permanent.

4.3. *Treatment*

No treatment of PTU has been shown to be consistently effective. In a few cases L-Dopa treatment[14,70] resulted in disappearance of the episodes in 15 days and 3 months in the two cases of[14] but has been ineffective in others.[51,81]

5. Paroxysmal tonic downgaze of newborn and infancy

A few cases of infants with paroxysmal self-limited downgaze ('setting sun sign') as the only neurological abnormality in otherwise healthy infants have been reported.[21] The eyes quickly return to primary gaze after the short downward position. Associated downward nystagmus has been occasionally reported.[8] These movements can be provoked by abruptly raising and lowering the infant's head in the vertical plane or suddenly removing a light source the 'eye-popping' reflex of.[75] In 5 of 242 prospectively examined healthy newborn infants, tonic downward eye deviation was observed while awake[54] This phenomenon has been also reported in preterm infants born between 22 and 28 weeks age gestation.[60] Usually the sign is observed shortly following birth and is resolved before the age of 6 months[68] but cases beginning at the age of 5 months have been reported.[102] In a personal case episodes start at age of 2 months, reach a peak at 3 months (with 2–3 episodes per hour) to then slowly improve. In another personal case the father had had identical episodes when he was an infant. In both cases neuroimaging and development are normal.

Secondary paroxysmal downgaze is frequent in kernicterus and hydrocephalus. Yokochi[104] described 13 children with spastic quadriplegia or diplegia, intellectual disability, and cortical visual impairment, who had paroxysmal episodes of downward deviation of the eyes lasting several seconds. In five infants these episodes stopped by the age of 2 years. Congenital stationary night blindness may present tonic downgaze, and a chin-up head posture between the ages of 3–5 months to 2–3 years.[86]

Although paroxysmal tonic downgaze can be a benign and transient phenomenon, investigations including neuroimaging, and careful ophthalmological examination and follow-up are required.

6. Benign paroxysmal torticollis (BPT)

6.1. *Clinical signs*

BPT was initially reported in 1969 by Snyder who described 12 affected children. Recurrent episodes of painless latero, retro or torticollis are the hallmark of this disorder. In half of these children episodes appear on awakening[34,50] or may be precipitated by changes in posture.[20] Abnormal eye movements may herald an attack. Most episodes are accompanied, at onset of the episode, by irritability, pallor, vomiting and ataxia. Then the infant remains quiet in the abnormal posture. In rare cases, ataxia may be the dominant feature[27] and sometimes may become the only manifestation after several episodes of torticollis.[50] Even if torticollis is the major feature, lateral curvature of the trunk and extension of one lower limb are sometimes associated.[23,27,83] The duration of attacks may vary from minutes to several days and, on rare occasions, up to 2 weeks.

Cases of very short episodes of sudden turning of the head and eyes to one side and rapid blinking when the patient is moved from an upright to a supine position have been reported.[20,35] This short-lived and 'paroxysmal' form, lasting only minutes, and accompanied by ocular signs that are usually not seen in the 'periodic' form is very difficult to differentiate from the benign polymorphous movement disorder of infancy to be discussed later.

In more than half the cases the episodes began before 3 months of age, sometimes as early as in the first week of life,[83,50] personal case or as late as the age of 30 months.[89] Attacks tend to occur frequently at onset (1–2 monthly) and often with strikingly regular occurrence. They disappear spontaneously before the age of 5 years.

6.2. *Pathophysiology*

Pathophysiology is unclear. EEG and neuroimaging are normal. Kimura and Nezu[59] performed surface EMG recordings during an episode of torticollis, and concluded it was a dystonic phenomenon. A few cases are familial.[27,63,79,83] Auditory function and vestibular tests have been found to be abnormal by Snyder,[89] but others[12,27,80] found that in contrast to Snyder's original paper, caloric and audiometric testing were normal. Possibly BPT is a clinical syndrome of multiple different aetiologies. Deonna and Martin[27] followed patients with BPT in whom the episodes of torticollis were replaced by typical migraine or who developed migraine years after BPT and, moreover some children later remember having had a headache during the episodes of torticollis.[79] Familial antecedents of migraine are frequent.[27,69,79] Some patients later develop benign paroxysmal vertigo[7,36] suggesting a vestibular disturbance and a possible pathogenetic link with migraine.[38] The view of many authors is that BPT is an early manifestation of migraine, or a part of the periodic syndromes of childhood. Familial and sporadic cases of BPT with mutations in the CACNA1A gene have been reported.[46,78,100] Some of these patients also had shown benign paroxysmal vertigo of childhood, benign paroxysmal tonic upgaze and/or migraine as associated disturbances.

6.3. *Differential diagnosis*

Differential diagnosis may be difficult in the first attack, especially if the disorder starts in the newborn period, because BPT is not usually considered at this age. The differential diagnosis is wide and includes seizures, vertigo, dystonic reactions to drugs,[19] posterior fossa tumours,[94] cervical spine

abnormalities,[101] ocular co-ordination defects, ocular abnormalities such as fourth cranial nerve palsies and Sandifer syndrome. When the episodic nature is confirmed and the child is neurologically normal between attacks, the diagnosis becomes easier.

BPT is a benign disorder. A transient motor delay can coexist but it improves with the resolution of the attacks of BPT. However three of the 10 children of the Rosman et al.[80] series were left with ongoing motor problems.

6.4. *Treatment*

Yaghini et al.[103] have described four children with BPT whose attacks responded well to topiramate but unless irritability and vomiting require symptomatic treatment, no drug therapy is necessary. Clear explanation of the good prognosis of the disorder to the parents is necessary.

7. Benign polymorphous movement disorder of infancy (BPMDI)

Vanasse et al.,[97] and, Lombroso and Fejerman[65] reported two new selflimiting paediatric paroxysmal nonepileptic conditions, respectively named shuddering attacks (SA) and benign myoclonus of early infancy (BMEI). According to these reports, SA should consist of brief bursts of rapid tremors (5–15 s) of the head and arms reminiscent of a shiver; on the other hand, BMEI should comprise repeatedly myoclonic jerks of the head and/or of the upper limbs mimicking infantile spasms. Further reports of cases showing these phenomena have been published under the terms of BMEI,[18,43,44,67,72] SA[55,58,93] or different names such as benign nonepileptic infantile spasms,[33,47] tonic reflex seizures of early infancy,[98] sleep-related infantile tremor,[30,87] and "benign infantile shaking body attacks".[16] Fernández-Alvarez[41] hypothesized that in fact these phenomena are polymorphic expression of the same nondisease condition and, moreover, proposes a new descriptive umbrella term 'benign polymorphous movement disorder of infancy' (BPMDI). Fernández-Alvarez[41] lists the main characteristics of BPMDI: (1) paroxysmal events with abrupt onset, sometimes in clusters[58,67,72] separated by 3–4 min; (2) short duration (usually few seconds); (3) no alteration of consciousness during the spells; (4) often appear multiple times per day (sometimes, even more than 100); (5) usually triggered by excitement, frustration, or postural changes; (6) onset in the first year of life, mainly between 4 and 7 months; (7) normal development and neurological examination; (8) normal ictal and interictal EEG; and (9) self-limited, usually stopping the episodes before the age of 2 years, but not uncommonly they continue into childhood. In 12 successive children followed by Jan,[55] complete cessation of the episodes was noted by between 3 and 7 years (mean 5.6 years) of age.

These movements can be grouped as follows:

(1) fine tremor that consists of low-amplitude (of 8–10 Hz) tremors primarily of the head, arms, shoulders and, occasionally, only the trunk.[72] These peculiar paroxysmal movements were creatively termed shuddering. According to Vanasse et al. (1976) the parents describe the movements "as if water was poured down the child's back," "as if the child had gone into the cold," or "as if he needed to move his bowels".

(2) coarse tremor with an approximate frequency of 4–6 Hz of head, arms, and hands (always in this order). This kind or tremor has been reported as 'sleep-related infantile tremors'[30,87] because it occurs when the child is about to sleep while breast-feeding.

(3) Brief tonic contractions. In their seminal paper, Lombroso and Fejerman[65] refer to the movements as "tonic/myoclonic seizures," but others prefer using the term "spasms".[33,47] These movements consist of episodes of shoulder and/or limb stiffening, occurring frequently in short clusters ranging from minimal elevation of the shoulders while moving the head downward to a more sustained tonic contraction. The episodes are sometimes so light that they are recognized only by the parents.[13,72] A peculiar form of these movements are the cases published by Vigevano and Lispi[98] as "'tonic reflex seizures of early infancy" where the paroxysmal phenomenon was described as diffuse tonic extension of four limbs lasting 3–10 s associated with apnoea and cyanosis. These episodes occurred only when the child is awake, held in a vertical position, and triggered by a shaking or a tactile stimulation. Nodding head can be an associated movement in the tonic contractions, but it can be the only movement in some cases.[67,72]

(4) Atonic or negative myoclonus. Head drops imitating epileptic atonia has been found in approximately 4% of the BPMDI cases.[17,18,99] In a personal observation, brief episodes of nodding were followed by a sudden head drop.

(5) Diffuse movements ('shaking body'). Episodes of brief and abrupt side-to-side trunk movements associated with asynchronous involvement of different muscles of both sides of the entire body have also been reported. These movements could be accompanied by the crying of the infant.[16]

(6) Infants with more than one type of the episodes coexist[18] and, more importantly, there are cases that move from one type to another.[18,58,72] However, the analysis of the literature shows some interesting aspects. Usually, the paroxysms are complex: in some cases, individuals with spasms are also described as having fine tremor (shuddering) of the head and the trunk during the episodes; in others, shivering is "sometimes associated with stiffening of the upper extremities,"[53] "clear nodding of the head,"[72] "posturing of face and trunk before or during a shiver," or "minimal movement of the head" following tonic spasms.[13] This means that in some studies, the description of the paroxysms does not match the name and, moreover, the episodes can combine movements of varied morphology. For instance, fine tremors (shuddering) are sometimes accompanied, before, during, or after the episodes, by symmetrical stiffening in flexion of the head and adduction of the elbows and knees[6,10,13,33,53,55,58] or in cases where the tonic contractions predominate, they are often superimposed by axial shudder or minimal tremors of the upper

extremities ("jerky tremors").[53,65,72] All these movements may be associated with facial grimacing,[65,87] clenched of the teeth, and/or crying.[44,58,65,67,72] In four of the fourteen available videos of the cases of Bye et al.,[13] the children close their eyes during the event and one child rolls their eyes upward after the shudder.

7.1. *Neurophysiologic studies*

In the majority of cases, intercritical, and in some cases critical EEG have been performed. According the necessary criteria the results are normal. However, artefacts caused by EMG contamination may be erroneously considered as epileptic by professionals with insufficient experience.[17] In cases of predominant "myoclonic" movements, the polygraphic tracings of the motor phenomenon is a tonic contraction lasting from 2 to 4 s[33,67,72,98] a duration longer than 50–200 ms considered the longest duration of myoclonus. So, for these episodes, the term myoclonus is not accurate; instead, spasms or brief tonic events seems more precise terms. By contrast, in cases reported as SA, Kanazawa[58] founded EMG discharges with frequencies similar to those seen in essential tremor. In conclusion, the neurophysiologic characteristics of these episodes are dissimilar and probably as varied as their phenomenology.

7.2. *Prevalence*

The prevalence of BPMDI is unknown. The condition was very likely underdiagnosed, because of the short duration of the episodes and of the interictal normality of the infant.

In two studies of children with paroxysmal non-epileptic events referred for video-EEG monitoring, 7 and 10% were respectively diagnosed as shuddering attacks.[13,22] Non-epileptic myoclonus (two cases) and shuddering (one case) have been found in a series of 25 nonepileptic paroxysmal events between the age of 2 months and 5 years, studied with prolonged video EEG monitoring.[61] In another EEG-polymyographic study of 18 cases of nonepileptic paroxysmal motor events 10 were classified as SA (5) or BMEI (5).[15]

7.3. *Differential diagnosis*

Diagnosis of BPMDI relies on a detailed history and a careful observation. Home video recordings can be an important tool. Recording an event remains the gold standard when the interictal EEG is normal. However, as access to videoEEG monitoring is not always possible, a clear-cut history of typical development, normal examination, as well as a normal interictal EEG and home video of the episodes may be enough for suspicious BPMDI and for monitoring their evolution before carrying out complex exams and/or using antiepileptic drugs. . There should be suspiciousness in infants (1) who are younger than 18 months; (2) with typical development, normal EEG; and (3)with episodes with the characteristics described previously.

Because of their paroxysmal character, more than half of the patients with BPMDI episodes are erroneously considered as epileptic, most commonly as West syndrome or myoclonic infantile epilepsy. A detailed analysis of the differences between BPMDI and different types of infantile epilepsy are beyond the scope of this article. Sandifer syndrome[40] and non neurological disorders, such as infection of the urinary tract causing sensation of urethral "burning," have been evoked.[16]

7.4. *Management*

Reassurance of families is crucial because relatives are often frightened by the unexpected appearance and, often, by the high frequency of the attacks. It is important to insist on the nondisease conditions that these attacks represent and on their non equivalence to other processes such as epilepsy. Considering that they are not pathologic conditions, the dominant opinion is that no drug therapy should be recommended.

In conclusion, TBPMD represents a group within the paroxysmal non-epileptic motor conditions of infancy which considering the favourable outcome and spontaneous remission must be recognized and differentiated from other paroxysmal conditions. Most of these non-epileptic events should be diagnosed clinically by history alone. Other studies than EEG are often not indicated. Reassurance of families that these attacks are benign and do not represent other disorders such as epilepsy, is central to the management of these patients. They are age-related and probably associated with a stage in the maturation of the central nervous system.

Conflict of interest

None.

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