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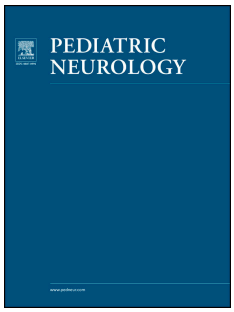

Ocular motor paroxysmal events in neonates and infants: a review of the literature

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Ocular motor paroxysmal events in neonates and infants: a review of the literature

Raffaele Falsaperla [1,2], Marco Andrea Nicola Saporito [1], Francesco Pisani [3], Janette Mailo [4], Piero Pavone [5], Martino Ruggieri [5], Agnese Suppiej [6], Giovanni Corsello[7]

[1] *Neonatal Intensive Care Unit [NICU], AOU "Policlinico", PO "San Marco", University of Catania, Catania, Italy.*

[2] *Unit of Pediatrics and Pediatric Emergency, AOU "Policlinico", PO "San Marco", University of Catania, Catania, Italy.*

[3] *Unit of Child Neuropsychiatry, Department of Neuroscience, University of Parma, Parma, Italy.*

[4] *Division of Pediatric Neurology, University of Alberta, Edmonton, Alberta, Canada.*

[5] *Unit of Rare Diseases of the Nervous System, Department of Clinical and Experimental Medicine, Section of Pediatrics and Child Neuropsychiatry, University of Catania, Catania, Italy.*

[6] *Department of Medical Sciences, Section of Pediatrics, University of Ferrara, Ferrara, Italy.*

[7] *Neonatal Intensive Care Unit [NICU], Department of Maternal and Child Health, University of Palermo, Palermo, Italy*

Corresponding author

Marco Andrea Nicola Saporito, MD
Neonatal Intensive Care Unit [NICU]
AOU "*Policlinico - Vittorio Emanuele*",
PO "*San Marco*"
Viale Carlo Azeglio Ciampi
95125 - Catania - Italy
Phone: ++39 095 4794069;
Fax: ++39 095 4795562;
E-mail: marcosaporito@hotmail.com

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Abstract

Background: Ocular Paroxysmal Events (**OPEs**) can accompany a variety of neurological disorders. Particularly in infants, OPEs often present a great diagnostic challenge for pediatric neurologists and neonatologists. Distinguishing between epileptic and non-epileptic events, or physiological and pathological paroxysmal events can be challenging at this age, since clinical history and physical examination are often limited. Continuous polygraphic video-EEG monitoring can be very helpful in these situations.

Methods: We provide a comprehensive review of OPEs in newborns and infants. The aim is to improve clinical recognition of OPEs and provide neonatologists and pediatricians with necessary knowledge to guide further management. We used the PubMed database. We reviewed studies focused on all ocular motor paroxysmal events that could occur in neonates and infants.

Results: Fifty-eight study researches were found and selected on the topic. We summarized and divided these studies into non-epileptic OPEs and epileptic OPEs.

Conclusions: OPEs can be challenging to diagnose, however, they are important to recognize and manage appropriately due to the variety of associated etiologies that neonatologists and pediatric neurologists need to be aware of, including central nervous system disorders. The distinction between epileptic vs. non-epileptic OPEs often cannot be done on the clinical grounds alone, and polygraphic video-EEG is required for diagnosing epileptic events. For non-epileptic events, further testing can then identify pathological ocular movements. To determine the etiology and prognosis of OPEs, a multimodal approach is required, including full history, thorough clinical exam coupled with ophthalmologic examination, polygraphic video-EEG monitoring, neuroimaging, and a careful follow up plan.

Keywords: ocular motor paroxysmal events, epileptic phenomena, non-epileptic phenomena, newborn, infant.

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Background

Paroxysmal motor events are sudden brief involuntary movements that could involve various parts of the body [1]. In newborns, physiological paroxysmal movements are common due to the

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immaturity of the corticospinal system [1]. Ocular Paroxysmal Events (**OPEs**) are paroxysmal motor events involving muscles of the eyes and eyelids. Although episodic uncoordinated eye movements are common phenomena in newborn infants, the distinction between physiological and pathological, and epileptic and non-epileptic ocular movements can be challenging for neonatologists and pediatric neurologists alike [2,3].

There is no clear definition of ocular paroxysmal events in newborns. The prevalence of pathological paroxysmal motor events is unknown, mostly due to their brief duration but also due the variety of underlying etiologies [3].

In newborns with OPEs, the first step is distinguishing between non-epileptic OPEs, such as paroxysmal tonic upgaze, paroxysmal tonic downgaze, opsoclonus, infantile nystagmus, and epileptic OPEs, such as ictal ocular phenomena, epileptic nystagmus, or ictal blinking. This distinction is the key for an initiation of an appropriate diagnostic work-up and, consequently, an appropriate management. Polygraphic video-EEG is necessary to confirm an electro-clinical correlation between ictal discharges and non-epileptic ocular phenomena, as well as to classify electroclinical seizures [3,5]. In some situations, OPEs could be strongly suspected to be epileptic in origin clinically, however; if they are no clear electrographic correlations [6] a prolonged video EEG monitoring and careful and systematic assessment for other etiologies is required.

In this comprehensive review of paroxysmal eye movements in newborns, the authors provide a detailed description of paroxysmal non-epileptic and epileptic ocular motor events, including non-epileptic and epileptic nystagmus. The aim is to guide neonatologists, pediatricians and pediatric neurologists to a prompt and correct diagnosis, management and treatment.

We summarized in Table 1 non-epileptic OPEs and in Table 2 epileptic OPES, focusing on their onset, etiology, clinical manifestations, associated pathologies, and related electrographic findings [Table 2].

Methods and results of search

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We provide a comprehensive review of OPEs in newborns and infants with the aim to improve their recognition, and to guide neonatologists to a correct diagnostic approach and subsequent management. We used PubMed database. The search terms used were as follows: ocular motor paroxysmal events, ocular motor events, ocular movements, ictal blinking. No limit was imposed on the year of publication of the studies or languages. The included age groups were newborns and infants.

Fifty-eight study researches were found and selected on the topic. We evaluated for each entity clinical manifestations, etiology, pathophysiology, electrophysiological studies (polygraphic video-EEG) and outcome. Tables 1 and 2 summarize our search.

Ophthalmic examination

A comprehensive eye examination is the key step in assessment of all conditions that could cause OPEs in newborn/infant, even before performing neuroimaging. The ophthalmic examination should pay special attention to vision, visual behavior, pupillary reactions, and the presence of anterior or posterior segment abnormalities. The clinician should evaluate both external and internal eye structures, look for eye asymmetries, globe abnormalities, eyelids abnormalities or periocular masses. Ophthalmoscopy will assess ocular structures and confirm the presence or absence of red reflex, congenital cataracts, corneal opacity (congenital glaucoma, anterior segment dysgenesis, corneal dystrophies) or retinoblastoma. [7] Visual function evaluation is part of any neurological examination in newborn/infant; the clinician should evaluate pupillary reaction to light, abnormal pupillary constriction, the type of ocular movements, visual alertness in response to a red ball or black and white target, the ability to fix and follow the same target horizontally, vertically or in a complete arc, acuity, color discrimination and attention at distance [8].

An ophthalmic examination is crucial for an early diagnosis of nystagmus and strabismus that are common in infancy. Early-onset nystagmus needs to be noticed, as this could also be a marker of visual impairment [9]

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A best attempt at funduscopic examination should be made to look for retinal anomalies. A funduscopic examination may appear normal in infancy. This however, does not preclude the presence of a retrobulbar optic nerve problem, as optic pathway glioma, or a retinal dystrophy as Leber congenital amaurosis. Ancillary testing including Optical Coherence Tomography, Electroretinography and/or visual evoked potentials can help with the diagnosis.

Paroxysmal non-epileptic ocular motor events

Paroxysmal tonic upgaze

Paroxysmal tonic upgaze (**PTU**) is a benign self-limited ocular movement disorder of heterogeneous origin characterized by episodes of sustained upward deviation of the eyes [1,3,4,10]. Ouvrier and Billson first described it, in 1988 [2,11]. The etiology of PTU is not completely understood, but at least some cases are associated with genetic disorders. Disorders with autosomal dominant and autosomal recessive inheritance [12,13], as well as chromosomal abnormalities have been described in newborns with PTU. Specifically, association with Beckwith-Widemann syndrome and anomalies of chromosome 15 has been reported in the literature [14,15]. CACNA1A [12] and GRID2 [16] should be considered in infants with tonic upgaze who later start developing cerebellar signs and symptoms. Pathophysiology is not completely clear, but immature cortico-mesencephalic control of vertical gaze and a failure of cortical compensation during a stressor event have been proposed. Other hypotheses suggest cerebellar dysfunction, or neurotransmitter disorder affecting supranuclear pathways that control vertical eye movements [2,12,13]. The onset is usually within the first 6-12 months of life, followed by a spontaneous remission at around 3-4 years of age [10,11,17,18,19,20]. Spontaneous remission might be a result of progressive cerebral maturation and myelination [2]. PTU can be exacerbated by fatigue, infections, vaccinations or febrile illnesses [2,18]. PTU can last from a few minutes to several hours. Clinically, PTU is best described as an incomplete movement of the eyes on attempted downward gaze, and/or presence of downbeat nystagmus [1,3,4,10]. Neuroimaging should be

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considered, especially if any other neurological signs or symptoms are present. Although brain imaging can be normal, abnormal myelination, periventricular leukomalacia, hydrocephalus, vein of Galen malformation and pinealoma have been reported in infants with PTU [2,13,20]. Ictal polygraphic video-EEG monitoring is normal, confirming non-epileptic nature of the eye movements [2,3]. Although PTU generally appears in neurologically normal newborns and infants, some will later develop other neurological symptoms such as abnormal ocular movements, ataxia, learning disability, intellectual disability, developmental or language delay [2,13,20]. Ongoing follow up is therefore strongly suggested for infants presenting with PTU.

Paroxysmal tonic down gaze

Paroxysmal tonic downgaze (PTD) is an ocular motor disorder characterized by episodic downward deviation of the eyes, typically lasting for seconds and occurring several times per day [4,10]. Sudden movements, feeding or stimulation have been shown to trigger these episodes in some infants [4,10]. PTD can occur as isolated finding or it can be associated with horizontal strabismus [4,10]. PTD has been described in term and preterm infants, both healthy and neurologically impaired [1,4,10]. In most newborns PTD is a benign phenomenon that spontaneously resolves [21,22]. The resolution is typically seen within the first 6 months in term infants, but it can take up to 3 years in preterm infants for PTD to resolve [4,10,13,23,24,25]. In healthy infants, the pathophysiology of PTD is thought to be an immaturity of the extrageniculocalcarine visual pathways, or disorder of their maturation [10,23]. PTD can also be seen in infants with kernicterus, hydrocephalus, congenital stationary night blindness, gliosis, and encephalomalacia of the optic pathways and occipital cortex [10,13,25].

Opsoclonus

Opsoclonus (Op) is an ocular motor disorders characterized by irregular chaotic, rapid, involuntary bursts of high amplitude, back and forth multidirectional oscillations of both eyes [3,4,26]. It has

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been rarely reported in infancy [26]. It was first described by Orzechowski in 1927 [26,27]. There is no pause intervals or rhythmicity [26,28] of opsoclonus. Op generally starts at the beginning or at the end of voluntary eye movements and it can persist during sleep [28,29]. If it's purely horizontal it is defined as ocular flutter [26].

Op is different from nystagmus because of the lack of regularity and rhythmicity [26,30]. Exact pathophysiologic mechanism is not known; however; the hypotheses include cerebellar dysfunction and altered function of inhibitory neurons [31,32]. It can be seen as a benign transient phenomenon in healthy infants, and those cases are thought to be secondary to immaturity of the central nervous system [29]. It has been rarely reported following immunizations. However; presence of Op can also be associated with serious etiologies such as neural crest tumors (neuroblastoma, ganglioneuroblastoma), paraneoplastic conditions, myoclonus, craniofacial dysmorphism cerebellar ataxia, herpes simplex encephalitis, meningitis, hypoxic-ischemic encephalopathy, para-infectious conditions, posterior encephalocele and hydrocephalus [2,3,26,28,32]. When Op is associated with neural crest tumors, the proposed pathophysiology is an immunological cross-reactivity between tumor cells and healthy cerebellar neurons [26]. Depending on its etiology, Op can persist, or it can gradually disappear within 1-6 months [28,29,34]. However, in the long-term, the affected infants are at risk of developing visual loss, strabismus, cognitive and neurologic disabilities [26,28]. Therefore, detailed examination and focused investigations are recommended to rule out serious pathology in newborns and infants presenting with opsoclonus. When diagnosed in neonates, an early stage neuroblastoma must be excluded; and a long-term follow-up is required [26].

Infantile (congenital) nystagmus

Nystagmus could be physiological or pathological phenomena [35e]. The main types of physiological nystagmus are vestibular nystagmus, optokinetic nystagmus and eccentric gaze evoked nystagmus [35e]. Vestibular nystagmus occurs during body rotation [36].

Optokinetic nystagmus is often seen physiologically in the first days of life, but it can persist beyond 6 months of life [35,37]. Vestibular nystagmus consists of an intial slow-phase pursuit

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response to movement of the visual surroundings, followed by a corrective saccade, a quick phase [37]. In neonates it can be evoked by a head movement towards a stimulus in the temporal-to-nasal direction of the viewing eye [37]. In infants it can occur naturally during head and eye movements or by looking out of the window of a moving car [37].

Infantile nystagmus (IN) is a pathological event characterized be a gaze-dependent, involuntary, repetitive, rhythmic oscillation of one or both eyes [36,38]. It can be present at birth or occur at any time thereafter, but it is typically diagnosed within the first 6 months of life. It can be transitory, or it can persist throughout the life [3,38].

IN can be idiopathic, or associated with retinal or optic nerve pathology, hydrocephalus, trisomy 21, cerebral vascular diseases, Chiari malformation or Central Nervous System tumors [38,39].

Transitory forms of IN are very rare and resolve by 8-9 months of life [40]. IN more frequently persists throughout life with or without neurological impairments. In a child with IN, a detailed history and physical examination will help to identify presence of other abnormalities and help to decide whether brain imaging or referral to ophthalmologist are needed [38].

Nystagmus could be secondary to visual impairment (sensory deficit nystagmus). In neonates this is could be difficult to distinguish clinically from idiopathic infantile nystagmus, however; poor or absent pupillary responses to light could point to an underlying visual impariment. Sensory deficit nystagmus canbe seen with albinism, Leber's congenital amaurosis and achromatopsia [7].

Paroxysmal epileptic ocular motor events

Ictal ocular phenomena of neonatal seizures

Ictal Ocular phenomena were reported to be the one of most frequent clinical manifestation of seizures in newborns, occurring in up to 70% of neonatal seizures [41]. Common ictal ocular phenomena include tonic horizontal eye deviation, rhythmic eye flickering, tonic epileptic upgaze and sustained eye opening with ocular fixation. Ictal Ocular phenomena can be associated with ictal

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orolingual automatism, autonomic manifestations and tonic seizures [41]. Electrographically, seizures with ocular features were associated with frontocentral, paracentral or temporal onset [41,42]. Tonic horizontal eye deviation has been consistently associated with ictal EEG discharges [43]. Eye deviation is considered a reliable lateralizing sign, with the direction of version consistently contralateral to the epileptogenic focus [41,42,44].

Epileptic nystagmus

Epileptic nystagmus (EN) is a rare seizure manifestation characterized by a rapid repetitive eye oscillation associated with ictal epileptic discharges [45,46]. It was first described in infants by Giove in 1960 [47]. Ictal discharges generally arise from temporal-parietal-occipital region, contralateral to the direction of nystagmus, suggesting a subcortical origin [46,48,49]. The International League Against Epilepsy has not yet proposed specific EN ictal EEG pattern. EN is usually characterized by jerk, horizontal and conjugate nystagmus, which can be associated with head and tonic horizontal eye deviation [46]. Two types of EN have been described; one confined to the contralateral side without crossing the midline, the other of larger amplitude that crosses the midline [50,51,52]. Proposed pathogenic mechanism is a stimulation of cortical saccade centers by ictal discharges for the first type; and a stimulation of the cortical smooth pursuit centers, or cortical optokinetic centers and subcortical structures for the second type [46,49].

Ictal blinking

Ictal blinking (IB) is an electroclinical seizure manifesting clinically as smooth blinking of the eyes not associated with facial spasms, and time-locked to ictal epileptic discharges [53]. It was first described by Bartholow in 1874 [54]. IB is caused by activation of trigeminal fibers during seizures. IB can be unilateral or bilateral; it can occur as the only clinical seizure manifestation or it can be associated with other ictal motor manifestations. IB have occasionally been described in infancy

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[53,55,56,57]. Ictal Video-EEG pattern is characterized by a rhythmic activity arising from occipital area most frequently ipsilateral to IB. Less frequently ictal discharges arise from contralateral occipital cortex, characterized by slow wave complexes and superimposed fast activity. The specific IB EEG pattern has not been yet recognized by the International League Against Epilepsy. Although the pathogenesis has not been completely understood, the hypotheses include a stimulation of ipsilateral cerebellum, frontal and basal region of the temporal lobe, occipital areas and basal hemisphere structures [53,56,58]. IB may be associated with central nervous system pathologies such as stroke, hemispheric porencephalic cyst, cerebral cyst, and cortical dysplasia [53,58].

Polygraphic video-EEG monitoring

We recommend considering a polygraphic video-EEG monitoring in every infant with OPEs of unclear etiology. Polygraphic video-EEG monitoring is the gold standard for differentiation between epileptic and non-epileptic events, since it allows to correlate paroxysmal motor events with electrographic changes [59]. EEG can be done using full montage of 21 electrodes or reduced neonatal montage of 10 electrodes according to 10-20 International System. Ocular activity is recorded by additional electrodes positioned above and below both eyes (electro-oculography) [4]. Ideally, two cameras should be used during video-EEG recording, one focused on the whole body, and the other zoomed on eyes.

The distinction between epileptic and non-epileptic events is essential for the correct management, and to avoid over or under treatment with anti-epileptic medications. Polygraphic video-EEG has be interpreted by a neurophysiologist with expertise in neonatal EEG. [60]. Unfortunately, polygraphic video-EEG monitoring is not always readily available in many Neonatal Intensive Care Units.

Conclusions

OPEs represent a challenge for neonatologists, pediatricians and pediatric neurologists. When present, they deserve particular attention because they may be a sign of central nervous system pathology. It is essential to distinguish epileptic from non-epileptic phenomena, in order to avoid inappropriate use of antiepileptic medications. This distinction often cannot be done on the clinical grounds alone, and polygraphic video-EEG is may be needed. To determine the etiology and prognosis of the OPEs, a multimodal approach is required, including full history, thorough exam, neuroimaging, polygraphic videoEEG monitoring, ophthalmological examination and a careful follow up plan.

Disclosure

The authors report no conflicts of interest in this work.

Ethical statement

The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki as revised in 2000.

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Paroxysmal motor event	Onset	Etiology	Clinical manifestations	Associated pathologies	Electrophysiological studies (EEG)	Outcome
Paroxysmal tonic upgaze	First 6-12 months	-uncertain -autosomal dominant/recessive inheritance -immature corticomesencephalic control of vertical gaze -failure of cortical compensation during a stressor event -dysfunction of cerebellum -neurotransmitter dysfunction affecting supranuclear pathways that control vertical eye movement	-episodes of prolonged upward eye deviation -last minutes or several hours -exacerbated by fatigue and intercurrent episodes - associated with incomplete downward movement on attempted downward or downbeat nystagmus	-deficient myelination -periventricular leukomalacia -hydrocephalus -vein of Galeno malformation -pinealoma -Beckwith syndrome -anomalies of chromosome 15	Normal	spontaneous remission in 3-4 years -mild ocular abnormal movements -ataxia -learning disability -mental retardation -developmental delay -language delay
Paroxysmal tonic downgaze	First months	immaturity or dysfunction of the extrageniculocalcarine visual pathways maturation	-sudden downward deviation of the eye -last several seconds -several time per day -triggered by movements, feeding or stimulations -isolated or associated to horizontal strabismus	-benign -kernicterus -hydrocephalus -congenital stationary night blindness -gliosis -encephalomalacia of the optic pathways and occipital cortex	Normal	-spontaneous remission within 6 months of life in term infants, 3 years of life in preterm infants -neurological impairments
Opsoclonus	First months	-cerebellar dysfunction -alteration of function of inhibitor neurons -immaturity of central nervous system -immunological cross-reactivity between tumoral cells and healty cerebellar neurons	-irregular chaotic, rapid, involuntary bursts of high amplitude, back and forth multidirectional oscillations of both eyes -no pause intervals or rhythmicity -start at the beginning or at the end of a voluntary eye movement -could persist during sleep	-neural crest tumors -paraneoplastic conditions -myoclonus -facial tics -craniofacial dysmorphism -cerebellar ataxia -herpes simplex encephalitis -meningitis -hypoxic-ischemic encephalopathy -para-infectious conditions -posterior encephalocele -hydrocephalus -follow episodes of immunizations	Normal	-persistence -gradual resolution after 1-6 months -visual loss -strabismus -mental and neurologic disabilities
Infantile nystagmus	First 6 months	-idiopatic -secondary	involuntary repetitive rhythmic oscillation to and of one or both eyes transitory (very rare) persistence throughout life (more frequent)	-retinal or optic nerve pathologies -hydrocephalus -trisomy 21 -cerebral vascular pathologies -Chiari malformation -Nervous Central System tumors	Normal	-resolution at 8-9 months of life (transitory form) -persistence throughout life with or without neurological impairments

Table 1: non-epileptic paroxysmal ocular motor events

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Paroxysmal motor event	Onset	Etiology	Clinical manifestation	Associated pathologies	Electrophysiological studies (EEG)
Ictal ocular phenomena	First months	Epileptic	-tonic horizontal eye deviation -eye flickering -tonic epileptic upgaze and -sustained eye opening with ocular fixation -associated with orolingual, autonomic and tonic events		-ictal discharge arising from frontal, paracentral, temporal or occipital cortex
Epileptic nystagmus	First months	Epileptic	-rapid repetitive eye oscillation due to an epileptic discharge -jerk, horizontal and conjugate -associated with head and tonic horizontal eye deviation		-ictal discharge arising from contralateral temporal-parietal-occipital region after the nystagmus -subcortical origin?
Ictal blinking	First months	Epileptic	-smooth blinking of the eyes not associated with other facial spasms, due to an epileptic discharge -unilateral or bilateral -isolated or associated with other motor events	-stroke -hemispheric porencephalic hollows -cerebral cyst -cortical dysplasia	rapid wave activity arising from occipital area homolateral to IB or less frequently contralateral, followed by slow wave complex and superimposed fast activity

Table 2: epileptic paroxysmal ocular motor events

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