·专家讲座·
(Expert Lecture)

Non epileptic motor phenomena in the newborn

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Introduction

The newborn infant is prone to a variety of motor phenomena that are non epileptic in origin. Tremor, jitteriness and benign neonatal sleep myoclonus are frequently encountered, while other abnormal movements including neonatal hyperekplexia are less commonly seen. Many of these phenomena are benign and have no bearing on the neonate's eventual neurodevelopmental outcome. However, some such as jitteriness should alert the physician to possible pathology that may require specific investigations and treatment.

Alternately, epileptic seizures in the newborn are frequently associated with significant intracranial pathology and place the newborn at high risk for poor neurodevelopmental outcome. Differentiating non epileptic phenomena from epileptic seizures is important so as to avoid unnecessary parental anxiety, investigations and treatment with potentially harmful medications. This often can be done clinically. In some circumstances this can be difficult, such as differentiating subtle seizures from brain stem release phenomena. In these circumstances electroencephalogram (EEG) and other neuro-investigations are required.

In this paper, the authors will provide a review of the various non epileptic motor phenomena seen in neonates. The objectives of this paper are to provide physicians who care for neonates with a review of these non epileptic phenomena with special emphasis on differentiating them from epileptic seizures and offer information on treatment and prognosis wherever possible.

Tremor and jitteriness

Tremor can be defined as an involuntary, rhythmical oscillatory movement of equal amplitude around a fixed axis. It can be either fine with a high frequency (>6 Hz) and low amplitude (<3 cm) or coarse with low frequency and higher amplitude[1]. Jitteriness refers to recurrent tremor[2]. In this review the terms tremor and jitter are used interchangeably. Tremor is the most common abnormal movement encountered in the neonate. Up to two thirds of healthy newborns will have some fine tremor in the first 3 days of life and Parker et al[2-3] reported that up to 44% of newborns were jittery.

Although tremor in older children and adults usually denotes a lesion within the cerebellum, basal ganglia, red nucleus or thalamus, this does not appear to be the case in the neonate[4]. One theory is that neonatal tremor is due to immaturity of spinal inhibitory interneurons causing an excessive muscle stretch reflex. As the neonate gets older and the interneurons mature, the tremor resolves[5]. Another theory is that elevated levels of circulating catecholamines account for the tremor[6].

Tremor and jitteriness may be benign or pathological. Pathological conditions that may be associated with tremor include hypoglycemia, hypocalcemia, sepsis, hypoxic-ischemic encephalopathy, intracranial hemorrhage, hypothermia, hyperthyroid state and drug withdrawal[1-3]. In general, fine tremor is usually benign or secondary to metabolic disturbance such as hypoglycemia. Coarse tremor should raise suspicion of intracranial pathology such as hypoxic-ischemic encephalopathy

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and intracranial hemorrhage. Coarse tremor is frequently associated with the "neonatal hyperexcitability syndrome" in mildly asphyxiated neonates with increased tendon reflexes and excessive moro response[1].

The neurological outcome of neonates with tremor is good as long as there are no perinatal complications such as asphyxia identified. Two follow up studies showed that jittery infants without a history of perinatal complications had normal neurodevelopmental outcome regardless whether the tremor was fine or coarse[4,7]. Jittery neonates with a history of perinatal complications were at a thirty percent risk of adverse neurodevelopmental outcome in particular those with coarse tremor as part of the "neonatal hyperexcitability syndrome"[4,8].

Tremor can be differentiated from seizure if the following characteristics are observed: 1) Tremor can be brought on with stimuli and can be stopped with gentle passive flexion and restraint of the affected limb. 2) Tremor is not associated with ocular phenomena such as forced eye deviation. 3) Tremor is not associated with significant autonomic changes such as hypertension or apnea[9].

Investigation of the jittery neonate should depend on the perinatal history and physical examination. If the neonate appears well and has no history of perinatal complications, blood glucose measurement alone will suffice[2]. One can determine if the tremor is benign by placing the neonate supine with hands free at their side. A benign tremor will resolve when the neonate is allowed to suck on the examiner's finger[10]. Further investigations should be performed in those neonates that appear unwell, have coarse tremor, have a history of perinatal complications and whose tremor doesn't settle with soothing or suckling. Investigations performed ultimately depend on the clinical situation but consideration should be given towards doing a septic workup, urine drug screen, neuroimaging, thyroid screen and metabolic workup[2].

Special consideration should be given to tremor as part of a neonatal withdrawal syndrome. Excessive tremor and jitteriness has been reported in newborns of mothers who had been prescribed opiates[11] and selective serotonin reuptake inhibitors[12-13]. Maternal abuse of illicit substances such as marijuana, inhaled volatile substances and cocaine can also cause a withdrawal syndrome in which coarse tremor is prominent[3,14-15]. Interestingly tremor doesn't appear to be more common in neonates of alcoholic or nicotine dependent mothers[3].

Treatment of neonates with tremor and jitteriness should be aimed at correcting the underlying cause if identified. Those that appear unwell or have a history of perinatal complication should be observed in a NICU setting. Special care must also be paid to mother-newborn bonding as jittery neonates tend to have decreased visual attention and are more difficult to console[3].

A form of tremor that only involves the perioral muscles is familial trembling of the chin which is an autosomal dominant condition in which the cutaneous muscles of the chin will tremble. In the neonate it is frequently brought on by crying. Treatment with botulinum toxin injections into the perioral muscles is reserved only for cases where the trembling causes difficulty with eating, drinking or social embarrassment[16].

Myoclonus

Myoclonus is a brief shock like movement of a limb caused by muscle contraction. It can be either localized to one body part or generalized. It can be a single event but is often repetitive. Unlike tremor it is irregular and arrhythmic. Myoclonus also tends to have higher amplitude than tremor. Myoclonus can originate from any level of the central nervous system in particular the cortex, brainstem and spinal cord[17]. In the neonate, epileptic myoclonus is uncommon and infrequently associated with synchronous discharges on the EEG. This has provoked much debate whether myoclonus in the absence of synchronous EEG discharges can be epileptic or non epileptic[9,18-19]. Epileptic myoclonus should not be provoked by stimulus, and cannot be suppressed by restraining the affected body part[18].

Non epileptic myoclonus may be benign or denote severe CNS pathology. Neonates with pathological non epileptic myoclonus have abnormal neurological examinations and abnormal EEG. The most common etiologies are severe intraventricular hemorrhage, hypoxic ischemic injury and glycine encephalopathy[20-21]. Myoclonus has also been reported in premature neonates after receiving intravenous benzodiazepines[22-23]. Non epileptic pathological myoclonus most likely represents brainstem release phenomena in which cortical inhibition of normally suppressed brainstem activity is lost due to diffuse cerebral injury[18,21,24].

Benign neonatal sleep myoclonus is characterized by rhythmical myoclonic jerks seen only during sleep. It is common and frequently misdiagnosed as seizures. Benign neonatal sleep myoclonus can be distinguished

from epileptic myoclonus by the fact it only occurs in sleep, and stops abruptly and consistently when the child is roused. During the myoclonus the EEG is normal[25]. It tends to occur in healthy, full term newborns. While it can be seen in any stage of sleep, it tends to occur predominantly in quiet sleep[17,25]. Unlike sleep myoclonus in adults, which is usually an asymmetric single jerk, benign neonatal sleep myoclonus is bilateral and repetitive[26]. Onset is usually in the first few days of life and usually remits spontaneously by four months of age[17]. Unlike tremor and jitteriness, gentle restraint may worsen the myoclonus. As the myoclonus can last up to an hour it can be mistaken for status epilepticus leading to treatment with anticonvulsants which provide no benefit and often worsen the myoclonus[27]. Like many other forms of myoclonus, benign neonatal sleep myoclonus can respond to clonazepam (0.05-0.1 mg/kg/day) however, consideration towards treatment should only be given to the most severe cases.

The underlying mechanism behind benign neonatal sleep myoclonus is poorly understood. One proposed mechanism is immaturity of serotonergic pathways within the brainstem which normally suppress movement during sleep[17,26].

Benign myoclonus of early infancy which has usual onset between three to nine months has also been reported in the neonatal period[28]. In this condition, the infant will have recurrent clusters of myoclonic jerks when awake. Typically they are not provoked by stimulus. They resemble infantile spasms but are not associated with developmental decline and the EEG is normal even during events. Resolution is by nine months of age and there is no apparent effect on neurodevelopment. The underlying etiology is unknown[29-30]. Usually treatment is not required.

Stimulus provoked myoclonus resulting in myoclonic jerking of the extremities with handling or stimulation can occur in the newborn period. This is poorly described in the literature. Our recent experience with a newborn with severe stimulus provoked myoclonus revealed that the myoclonus is refractory to all anticonvulsants with the exception of clonazepam which aborted the myoclonic jerks at a low dosage (0.1 mg/kg/day). EEG was recorded during many of these events. The interictal background was normal and during the bouts of myoclonus showed rhythmic movement artifact only. No epileptiform discharges were seen. MRI of the brain and spine and extensive metabolic workup did not reveal an underlying cause for the myoclonus. By 3 months of age the myoclonnus had resolved and the medication was withdrawn successfully. Development to date has been normal. Although we did not find an underlying cause for the stimulus provoked myoclonus, we recommend that these newborns undergo neuroimaging of the brain and spine and metabolic workup to rule out conditions such as nonketotic hyperglycinemia.

Neonatal hyperekplexia

Also known as startle disease, hyperekplexia is a rare disorder characterized by generalized muscle rigidity in the neonate, nocturnal myoclonus and an exaggerated startle reaction to auditory, tactile and visual stimuli. The startle reaction is a normal response to stimuli that consists of facial grimace and blinking followed by flexion of the trunk. The startle response is exaggerated when it interferes with normal activities, causes apnea and frequent falls[31].

Hyperekplexia can present in either a minor or major form. The minor form has an exaggerated startle response only. The exaggerated startle response can consist of a generalized tonic spasm with tonic flexion of the limbs and trunk and clenching of the fists. The eyes often remain open in an anxious stare. Apnea is common during the spasms due to chest wall rigidity. The exaggerated startle response can be elicited by tapping the nasal bridge thus differentiating it from seizures for which it is often mistaken. In the major form, there is also a generalized muscle rigidity seen only when the infant is awake and nocturnal myoclonus[31-32].

During the first two years of life, the affected infant is at increased risk of sudden infant death syndrome due to central apnea secondary to brainstem dysfunction as well as apnea during the tonic spasms. For this reason, these infants should have home apnea monitoring. Although the muscle rigidity resolves by around three years of age, the exaggerated startle persists resulting in frequent falls and injury. In some cases, clonazepam (0.1 mg/kg) can be helpful in controlling the muscle rigidity and startle episodes[31].

Hyperekplexia is for the most part a familial condition inherited in an autosmal dominant fashion with variable expression. The genetic defect is linked to chromosome 5q33-35. This results in defective chloride conduction through the alpha-1 subunit of the glycine receptor in the caudal pontine reticular formation resulting in defective neuronal inhibition[31].

Other transient movement disorders

A movement disorder results from dysfunction within the basal ganglia circuitry. While many are transient and benign, some may result from permanent basal ganglia injury. Up to one third of the transient benign movement disorders of childhood can be seen in the first three months of life. Benign paroxysmal torticollis is characterized by episodes of painless lateral neck flexion or torticollis often associated with pallor, emesis and abnormal eye movements. The attacks may last up to several days. Fernandez-Alvarez[29] reports that two of thirteen patients had attacks in the first month of life.

A hyperkinetic movement disorder resulting in choreiform movements of the extremities and abnormal mouth and tongue movements similar to those seen in oral-buccal dyskinesia has been reported in premature infants with severe bronchopulmonary dysplasia. These movements seemed to worsen during periods of respiratory failure and are attenuated during sleep. The proposed pathophysiology is chronic hypoxic injury to the basal ganglia. The neurodevelopmental outcome of these infants was poor[33].

Subtle seizures and brainstem release phenomena

The neonate is prone to a variety of epileptic seizures including "subtle" and tonic seizures. Volpe[9] defines subtle seizures as paroxysmal alterations in the neonates' behavior or motor and autonomic function that are not associated with tonic, myoclonic or clonic activity. Frequently associated changes include abnormal eye movements (random, nystagmoid or sustained lateral gaze) and oral-buccal lingual movements such as sucking chewing or tongue protrusions. Tonic seizures can either consist of tonic extension of all four extremities mimicking decerebrate posturing or tonic flexion of the arms and extension of the legs mimicking decorticate posturing[9].

These events are frequently not associated with epileptic changes on the EEG and respond poorly to standard anticonvulsants. This has led to debate whether they represent epileptic seizures or non epileptic brainstem release phenomena[9,18-19]. Volpe[9] feels that these may represent seizures that are not detectable on standard EEG because they arise from deep subcortical structures such as the diencephalon or from deep within the limbic structures. While there is evidence derived from animal studies to support this theory, it has not been shown in humans. Mizhrahi and colleagues[18-19] argue that if these events are not associated with epileptic changes in the EEG and they have features of reflexive behavior such as being provoked by stimulation and suppressed by gentle restraint then they are not epileptic and represent brainstem release phenomena. Single photon emission computed tomographic (SPECT) imaging obtained in a neonate with severe hypoxic ischemic injury with recurrent episodes of tonic posturing showed that the posturing originated in the brainstem, thus supporting Mizhrahi's argument[21].

Both seizures and brainstem release phenomena occur in neonates who have abnormal neurological functioning and can occur concurrently in the same patient[18-19,21]. Differentiating between the two can be very difficult on clinical grounds alone making video-EEG necessary. Electrographic seizure activity in the neonate tends to be localized most commonly to the temporal and central head regions. Seizures arising from the occipital and frontal lobes are very uncommon. The EEG features of a seizure in the neonate can be quite subtle with features very different from those seen in adults or older children making them easy to miss[34]. Therefore the recording must be read by an electroencephalographer with experience in neonatal EEG. To optimize detection of seizure activity and interictal discharges, the neonatal montage should be used when recording the EEG. This montage maximizes recording in the temporal, central and vertex head regions[34]. To assist in interpretation of the EEG the technologist needs to record changes in head position, state changes or movement. Recently, cerebral function monitoring has been used with increased frequency to monitor the cerebral activity of asphyxiated newborns. Typically, a limited number of electrodes are placed on the newborn's scalp, thus limiting the ability to detect and interpret epileptic events. Therefore, in our opinion, cerebral function monitoring is not adequate to determine if an event is epileptic in origin or not.

A common interictal discharge encountered in the neonate is the sharp transient which is a sharply contoured wave that is clearly distinguished from the underlying background activity. These can be benign or pathological depending on their location, frequency and persistence. Whether pathological sharp transients should be used to determine that an event is epileptic or not is controversial[19,34-35].

Conclusions

Differentiating epileptic seizures from non epileptic motor phenomena is extremely important. While neonatal seizures are usually a sign of serious intracranial pathology, non epileptic motor events may be benign. If they are pathological, the underlying cause may be different from those that cause seizures requiring a different treatment approach.

While the neonatal brain may have an innate resistance to injury from a prolonged seizure, recurrent brief seizures are more common and may result in further brain injury in an already neurologically compromised neonate[9,36-37]. This has to be balanced with the fact that the standard anticonvulsants used in neonates have potentially harmful side effects. Acute anticonvulsant administration can cause hypotension, bradycardia and respiratory depression all of which can lead to further hypoxic or ischemic brain injury. There is also concern about the long term effects of anticonvulsants on the developing brain. Animal studies have shown that the most commonly used anticonvulsants including phenobarb, phenytoin and diazepam cause apoptic neurodegeneration at therapeutic levels. This however hasn't been extrapolated to humans and their effect on long term neurodevelopmental outcome is debatable[19].

Consequently, anticonvulsants should only be used in the neonate when the likelihood that the events are truly epileptic is high. Features that increase the likelihood that the events in question are epileptic would be the presence of associated autonomic changes, abnormal ocular phenomena and whether they can be brought on by stimulating the neonate and suppressed by restraining the affected body part. In the case of benign neonatal sleep myoclonus the events should cease when the neonate is awoken. If there is any clinical uncertainty, an EEG recorded in the neonatal montage and interpreted by an experienced electroencephalographer is vital. If the events are deemed to be non epileptic, treatment with agents such as with clonazepam should only be considered if they are severe enough to cause apnea, feeding difficulties or interfere with normal neonatal care.

[References]

[1] Rosman NP, Donnelly JH, Braun MA. The jittery newborn and infant: a review[J]. Dev Behav Pediatr, 1984, 5(5):263-273.

[2] Armentrout DC, Caple J. The jittery newborn[J]. J Pediatr Health Care, 2001, 15(3):147-149.

[3] Parker S, Zuckerman B, Bauchner H, Frank D, Vinci R, Cabral H. Jitteriness in full-term neonates: prevalence and correlates[J]. Pediatrics, 1990, 85(1):17-23.

[4] Futagi Y, Suzuki Y, Toribe Y, Kato T. Neurologic outcomes of infants with tremor within the first year of life[J]. Pediatr Neurol, 1999, 21(2):557-561.

[5] Shuper A, Zalzberg J, Weitz R, Mimouni M. Jitteriness beyond the neonatal period: A benign pattern of movement in infancy[J]. J Child Neurol, 1991, 6(3):243-245.

[6] Sims M, Artal R, Quach H, Wu PY. Neonatal jitteriness of unknown origin and circulating catecholamines[J]. J Perinatal Med, 1986, 14(2):123-126.

[7] Berger A, Sharf B, Winter ST. Pronounced tremors in newborn infants: Their meaning and prognostic significance. A long-term follow-up study of 30 such infants[J]. Clin Pediatr, 1975, 14(9): 834-835.

[8] Prechtl HFR. The observation period[M]//The Neurological Examination of the Full Term Infant. 2nd ed. London: William Heimemann, 1991:12-16.

[9] Volpe JJ. Neonatal seizures[M]//Volpe JJ. Neurology of the Newborn. 4th ed. Philadelphia: WB Saunders, 2001:178-214.

[10] Linder N, Moser AM, Asli I, Gale R, Livoff A, Tamir I. Suckling stimulation test for neonatal tremor[J]. Arch Dis Child, 1989, 64(1 Spec No): 44-46.

[11] Meyer FP, Rimasch H, Blaha B, Panditt P. Tramadol withdrawal in a neonate[J]. Eur J Clin Pharmacol, 1997, 53(2):159-160.

[12] Zeskind PS, Stephens LE. Maternal selective serotonin reuptake inhibitor use during pregnancy and newborn neurobehaviour[J]. Pediatrics, 2004,113(2):368-375.

[13] Spencer MJ. Fluoxetine hydrochloride (Prozac) toxicity in a neonate[J]. Pediatrics, 1993, 92(5):721-722.

[14] Tenenbeim M, Casiro OG, Seshia MM, Debooy VD. Neonatal withdrawal from maternal volatile substance abuse[J]. Arch Dis Child, 1996, 74(3):F204-F207.

[15] Chiriboga CA, Brust JCM, Bateman D, Hauser WA. Dose-response effect of fetal cocaine exposure on newborn neurologic function[J]. Pediatrics, 1999, 103(1):79-85.

[16] Fernandez-Alvarez E, Aicardi J. Disorders with tremor[M]// Movement Disorders in Children. London: Mac Keith Press, 2001:43-62.

[17] Cohen R, Shuper A, Straussberg R. Familial benign neonatal sleep myoclonus[J]. Pediatr Neurol, 2007, 36(5):334-337.

[18] Mizrahi EM, Kellaway P. Neonatal seizures[M]// Pellock JM, Dodson WE, Bourgeois BFD. Pediatric Epilepsy Diagnosis and Therapy. 2nd ed. New York: Demos Medical Publishing, 2001: 145-162.

[19] Mizrahi EM. Neonatal seizures[M]// Swaiman KF, Ashwal S, Ferriero D. Pediatric Neurology Principles and Practice. 4th ed. Philadelphia: Mosby Elselvier, 2006:257-277.

[20] Scher MS. Pathological myoclonus of the newborn: electrographic and clinical correlations[J]. Pediatr Neurol, 1985,1(6):342-348.

[21] Alfonso I, Papazian O, Litt R, Meyer K, Paez J. Single photon emission computed tomographic evaluation of brainstem release phenomenon and seizure in neonates[J]. J Child Neurol, 2000, 15(1):56-58.

[22] Magny JF, d'Allest AM, Nedelcoux H, Zupan V, Dehan M. Midazolam and myoclonus in neonate[J]. Eur J Pediatr, 1994,153 (5):389-392.

[23] Lee DS, Wong HA, Knoppert DC. Myoclonus associated with lorazepam therapy in very-low-birth-weight infants[J]. Biol Neonate, 1994,6(6):311-315.

[24] Kakisaka Y, Haginoya K, Togashi N, Kitamiura T, Vematsu M,

Hino-Fukuyo N, et al. Neonatal-onset brainstem reticular reflex myoclonus following a prenatal brain insult: generalized myoclonic jerk and a brainstem lesion[J]. Tohuku J Exp Med, 2007, 211(3):303-308.
[25] Daoust-Roy J, Seshia SS. Benign neonatal sleep myoclonus. A differential diagnosis of neonatal seizures[J]. Am J Dis Child, 1992, 146(10):1236-1241.
[26] Turanli G, Senbil N, Altunbasak S, Topcu M. Benign neonatal sleep myoclonus mimicking status epilepticus[J]. J Child Neurol, 2004, 19(1):62-63.
[27] Ramelli GP, Sozzo AB, Vella S, Bianchetti MG. Benign neonatal sleep myoclonus: an under-recognized, non-epileptic condition [J]. Acta Pediatr, 2005, 94(7):962-963.
[28] Fernandez-Alvarez E, Aicardi J. Disorders with myoclonus[M]// Movement Disorders in Children. London: Mac Keith Press, 2001:170-191.
[29] Fernandez-Alvarez E. Transient movement disorders in children [J]. J Neurol, 1998, 245(1):1-5.
[30] Chaves-Carballo E. Syncope and paroxysmal disorders other than epilepsy[M]// Swaiman KF, Ashwal S, Ferriero D. Pediatric Neurology Principles and Practice. 4th ed. Philadelphia: Mosby Elselvier, 2006:1209-1233.
[31] Praveen V, Patole SK, Whitehall JS. Hyperekplexia in neonates [J]. Postgrad Med J, 2001, 77(911):570-572.
[32] Scarcella A, Coppola G. Neonatal sporadic hyperekplexia: a rare and often unrecognized entity[J]. Brain Dev, 1997, 19(3):226-228.
[33] Perlman JM, Volpe JJ. Movement disorder of premature infants with severe bronchopulmonary dysplasia: a new syndrome[J]. Pediatrics, 1989, 84(2):215-218.
[34] Clancy RR, Berquist AGC, Duglos DJ. Neonatal electroencephalography[M]// Ebersole JS, Pedley TA. Current Practice of Clinical Electroencephalography. 3rd ed. Philadelphia: Lippncott Williams and Wilkins, 2003:160-234.
[35] Clancy RR. Interictal sharp EEG transients in neonatal seizures [J]. J Child Neurol, 1989, 4(1):30-38.
[36] Scher MS. Neonatal seizures and brain damage[J]. Pediatr Neurol, 2003, 29(5):381-390.
[37] Zupanc ML. Neonatal seizures[J]. Pediatr Clin North Am, 2004, 51(4):961-978.

Non epileptic motor phenomena in the newborn
新生儿的非癎样运动(摘译)

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新生儿易出现各种非癎样运动如颤动、惊跳和良性新生儿睡眠性肌阵挛。而其他的异常运动如新生儿惊跳病就较为少见。然而这些运动的大多数预后良好,不会影响新生儿远期的神经发育。但临床医生对新生儿出现的一些惊跳现象仍需高度警惕,需与病理性惊跳鉴别,必要时行特殊的检查和治疗。

新生儿惊厥常与颅内疾患有关,且可影响新生儿的神经发育。因此鉴别癎性惊厥与非癎性惊厥非常重要,并可避免给父母带来不必要的焦虑,避免孩子免受不必要的检查及使用有潜在危害的药物治疗。临床通过体格检查即可鉴别。然而有时一些细微的惊厥与脑干释放运动较难区别,这种情况可行脑电图和其他神经系统方面的检查。

本文将介绍几种新生儿期常见的非癎样运动,其目的是帮助新生儿医师认识新生儿期的非癎样运动,便于与癎性惊厥鉴别,并探讨相关的治疗和预后等问题。

颤动和惊跳(tremor and jitteriness)

颤动为一种沿着身体的某个固定轴的不自主的、节律性的等幅振动。这种振动要为细小高频(>6 Hz)低幅(<3 cm)的振动,或低频高幅的粗大运动[1]。惊跳指反复发生的颤动[2]。本文中颤动与惊跳的提法是可互换的。颤动是新生儿期最常见的异常活动,约 2/3 生后 3 d 内的健康新生儿可出现细微的颤动。Parker 等[2-3]报道约 44% 的新生儿可出现惊跳。

尽管儿童期和成人出现的震颤均提示小脑、基底节、红核和丘脑的病变,但新生儿的颤动则无上述病变[4]。有研究认为新生儿颤动是由于脊髓抑制型中间神经元的不成熟致过度的肌牵张反射。随着小儿的生长发育及中间神经元的成熟,颤动可自发消退[5]。另一个研究则认为颤动可能与机体循环中儿茶酚胺的水平升高有关[6]。

颤动和惊跳可为良性,也可为病理性。病理性的颤动见于低血糖、低血钙、败血症、缺氧缺血性脑病、颅内出血、低体温、甲状腺功能亢进和撤药综合征等[1-3],一般情况下细小的颤动通常为良性或继发于电解质紊乱如低血糖等。对于粗大的颤动应警惕颅内病变如缺氧缺血性脑病和颅内出血。通常粗大的颤动与轻度窒息新生儿活跃的腱反射和拥抱反射所致的“新生儿过度兴奋综合征”有关[1]。如果没有合并围产期并发症如明确的新生儿窒息等,出

现颤动的新生儿一般远期神经发育预后良好。

两个随访研究也表明:没有围产期窒息史的新生儿即使临床上出现一些细小或是粗大的颤动,其远期神经发育也是正常的[4,7]。但对有围产期合并症的新生儿如出现颤动,则有 30% 的患儿有神经发育异常的风险,尤其是那些临床表现为粗大颤动的患儿,属于"新生儿过度兴奋综合征"临床表现的一部分[4,8]。

颤动与惊厥的鉴别在于:1)颤动多于刺激后出现,如予轻微的被动屈曲和颤动肢体的制动即可停止;2)一般不伴有眼球的偏斜;3)一般不伴高血压或呼吸暂停等表现[9]。

明确新生儿惊跳或颤动的原因需要详细地询问围产期病史和进行细致的体格检查。如果检查无异常发现,也无围产期并发症,检测患儿血糖即可[2]。下述简单的方法能鉴别颤动是否属于良性。将新生儿仰卧,其双手自如地置于身体两侧,如果颤动为良性,当新生儿吸吮检查者的手指时,颤动即可消失[10]。然而对粗大颤动的患儿,如体格检查有异常,并伴有围产期的合并症,颤动经安抚或予安慰奶嘴吸吮后不能消失者,需要作进一步的检查如血常规、血培养、尿毒物筛查、神经影像学、甲状腺功能和代谢病检查等[2]。

对一些临床上出现颤动的新生儿,需要注意是否为戒断综合征。据报道如果母亲曾经使用过阿片类麻醉药物[11]和选择性 5-羟色胺再摄取抑制剂[12-13],新生儿可出现过度的颤动。如果母孕期有大麻、可卡因等吸毒史,患儿也可因撤药综合征表现为粗大颤动等[3,14-15]。

因此对新生儿的颤动,临床上首先应明确原因。对有围产期并发症或体格检查有异常的新生儿应留新生儿重症监护病房观察,因为颤动的新生儿其注意力下降且难以安抚[3]。

有一种形式的颤动如家族性的下颌震颤属于常染色体显性遗传,仅表现为下颌肌肉的微颤,常因患儿哭闹诱发。如果这种颤动影响患儿吸奶、喝水及社会交往时,可予肉毒杆菌毒素口周注射[16]。

肌阵挛

肌阵挛是一种快速的由于肌肉收缩引起的肢体运动,可为局灶性,也可为全身性,反复或孤立性的出现。与颤动不同,肌阵挛的发作无规律性和节律性,且幅度较颤动大。肌阵挛冲动可源于任何水平的中枢神经系统尤其是皮质、脑干和脊髓[17]。新生儿癫性阵挛不常见,EEG 上也很少有同步放电。对于癫性与非癫性肌阵挛是否根据脑电图上有同步放电进行鉴别,目前存在较大的争议[9, 18-19]。但癫性肌阵挛一般不会因刺激而诱发,也不会因限制肢体的运动而终止[18]。

非癫性肌阵挛可为良性,也可与严重的中枢神经系统的病变有关。新生儿如出现病理性非癫性肌阵挛可有异常的神经系统体征或 EEG 的异常。最常见的病因为严重的颅内出血,缺氧缺血性脑损伤,甘氨酸脑病等[20-21]。据报道早产儿在静注地西泮后可出现肌阵挛[22-23]。非癫性病理性肌阵挛可能为脑干的释放现象,这种现象是由于弥漫性脑损伤致皮质对脑干活动的正常抑制受影响引起[18, 21,24]。

良性新生儿睡眠性肌阵挛多见于健康的足月儿,是新生儿睡眠中出现的一种节律性的肌肉抽动,较为常见,但常被误认为惊厥。良性新生儿睡眠性肌阵挛可出现在睡眠的任何时相,但多发生在安静睡眠时[17,25]。与癫性肌阵挛的鉴别是前者仅出现在睡眠中,当患儿被唤醒时阵挛可突然停止,EEG 无异常[25]。成人睡眠性肌阵挛为非对称单一的抽动不同,新生儿良性肌阵挛为对称性反复发作[26],多发生在生后的头几天,一般在 4 个月龄时症状自发消失[17]。但与颤动不同,即使轻微的限制也可使肌阵挛加重。由于肌阵挛可持续 1 个多小时,有时也可被误认为癫痫持续状态而予抗癫痫药治疗,这种治疗不但无任何作用,反而会加重阵挛[27]。另外与其他类型的肌阵挛一样,良性新生儿睡眠性肌阵挛也可用氯硝安定(每日 0.05 ~0.1 mg/kg)治疗,但药物治疗仅限于重症病例。新生儿良性睡眠性肌阵挛的发生机制尚不清楚,有学者提出可能与脑干内 5-羟色胺通路未成熟有关,因为正常情况下该通路抑制睡眠期间的运动[17,26]。

据报道,婴儿早期的良性肌阵挛(通常在婴儿 3 ~9 个月时出现)同样也可在新生儿期观察到[28]。这种阵挛一般在婴儿处于觉醒状态时出现,为反复发作的肌阵挛,一般不会因刺激而诱发,临床表现与婴儿痉挛症类似,但不会影响神经发育,EEG 即使在发作期也无异常。多在婴儿 9 月龄时消退,神经发育不受影响。病因尚不清楚[29-30],一般不需治疗。

在新生儿期刺激诱发的阵挛可引起肢体阵挛样的颤动,尤其是在护理新生儿的时候,但这种现象文献少有报道。最近我们诊治的一名新生儿因受到严重的刺激而诱发阵挛,用所有的抗惊厥药都不能控制,但应用氯硝西泮仅每天0.1 mg/kg后就停止了阵

挛。阵挛发作期间对患儿行 EEG 监测发现:发作间期的背景波是正常的,但阵挛发作期间的 EEG 仅提示节律性的运动伪影,未见癎性放电。脑、脊柱 MRI 检查及全面的代谢化验也未发现导致阵挛的潜在诱因。到患儿 3 月大时,阵挛自行停止,并停服抗癫癎药,至今患儿发育正常。虽然我们仍然没有找到刺激诱发阵挛的潜在原因,但我们仍建议对这些患儿进行脑、脊柱的 MRI 检查及全面的实验室检查排除非酮性高甘氨酸血症。

新生儿惊跳病(hyperekplexia)

新生儿惊跳病较为罕见,临床表现为新生儿受到声音、触觉及视觉等刺激后出现全身肌肉强直、夜间肌阵挛及过度的惊跳反应。惊跳反应表现为当患儿受到上述刺激时,出现面部鬼脸、眨眼及躯体的屈曲,属于正常现象。而惊恐反应为机体受到刺激后,正常的反应被夸大,还可致患儿呼吸暂停和频繁跌倒[31]。

新生儿惊跳病主要有两种形式:一种仅表现为夸张的惊恐反应如肢体和躯干的全身性强直痉挛和屈曲、握拳,双眼张开呈焦虑状态,发作时由于胸壁肌肉僵硬常致患儿出现呼吸暂停,惊恐反应还可通过轻弹患儿鼻梁引出,据此可与惊厥鉴别,但这种形式较为少见。另一种常见的形式是患儿在清醒和夜间肌阵挛时出现的全身肌肉强直[31-32]。

本病患儿在生后的头两年,由于疾病发作时脑干功能的失调,致患儿出现中枢性的呼吸暂停和由于发作时的全身强直引起的呼吸暂停,均可使患儿发生猝死。因此这些患儿应进行呼吸暂停的家庭监护。尽管到患儿 3 岁时肌肉强直可自行缓解,但发作时夸张的惊跳常使患儿频繁跌倒和摔伤。对一些患儿,氯硝安定(0.1 mg/kg)治疗可控制肌肉强直和惊跳发作[31]。

惊跳病属于常染色体显性遗传,有家族史,有不同的表现形式。致病基因定位在染色体 5q33-35,由于氯离子通过位于脑桥网状结构尾部的甘氨酸受体上的 α-1 亚单位传导时受影响,从而影响神经元的抑制作用[31]。

其他短暂的运动障碍

指由于基底节的功能失调引起,许多这种运动障碍是短暂的,预后一般良好。但也有一些运动障碍可能与永久性的基底节损伤有关。约有 1/3 的儿童期这种短暂的、良性的运动障碍见于 3 月左右的婴儿。良性阵发性的颈部偏斜表现为无痛性的颈部侧屈并伴面色苍白、呕吐、异常眼球运动为特征的发作,可持续数天。据 Fernandez-Alvarez [29] 报道,13 名患儿中 2 名在生后的头 1 个月发作。

另外运动亢进可致肢体的舞蹈样运动和异常的口、舌运动,类似于严重支气管肺发育不良早产儿的口颊运动障碍。这些运动在呼吸衰竭时加重,但睡眠时好转。其发生机制可能与基底节的慢性缺氧损伤有关,患儿的远期神经发育预后不良[33]。

微小发作和脑干释放现象

新生儿易发生各种癎样惊厥,包括“微小”和“强直性”发作。Volpe[9] 定义微小发作为一种新生儿行为、运动和自主神经功能的阵发性改变,与强直性、肌阵挛或阵挛性活动无关。常伴有异常的眼球运动如不自主的眼球震颤、持久的眼球偏斜和凝视以及口颊舌的运动如吸吮、咀嚼或伸舌等。强直性惊厥包括四肢强直,与去大脑强直类似,或手臂的强直屈曲及腿的强直伸展与去皮质强直类似[9]。

但这些癎样惊厥在行 EEG 检查时并未发现癎样放电,且抗癫癎药物治疗效果不好。因此神经病学专家对此现象存有争议:这些惊厥是属于癎样惊厥或是非癎样的脑干释放现象[9,18-19]。Volpe[9] 分析认为这些活动为标准 EEG 检测不出的惊厥,因为这些电活动起源于深部的皮质下结构如间脑或深部的边缘结构,上述现象在动物实验中也得到证实,只是目前尚无临床研究结果。Mizhrahi 等[18-19] 对此解释有不同看法,他们认为如果这些惊厥不伴有 EEG 的癎样改变,且这些发作在受到刺激后可诱发,而予轻微的制动可停止等,这些特点都提示这种发作不是癎样惊厥,而可能是脑干的释放现象。如一个严重的新生儿缺氧缺血性脑病患儿反复的强直样发作的单光子发射计算机断层成像(SPECT)结果表明:强直样发作起源于脑干,从而支持 Mizhrahi 等的观点[21]。

惊厥和脑干释放现象均可发生在神经系统功能异常的的新生儿,并且可同时发生在一个患儿[18-19,21]。如果仅凭临床对两者进行鉴别较为困难,因此必须借助于视频 EEG。新生儿的惊厥性电活动多为局灶性,且大多数集中在颞叶和中央脑部区域。起源于枕叶和额叶的电活动极为少见。与成人或年长儿相比,新生儿的癎样放电在 EEG 上极为不典型,因此易于漏诊[34]。因此新生儿 EEG 结果的分析必须由熟悉新生儿脑电特点的有经验的医师

进行。为了更好地记录惊厥发作和间期的异常放电,行 EEG 检查时可使用新生儿组合剪辑的方法。这种方法可最大程度地记录颞叶、中部脑区和顶部脑区的活动[34]。为了便于更准确地阅读 EEG 结果,技术人员还需要记录 EEG 检查期间患儿头的位置、精神及运动状态等。

新生儿常见的发作间期的电活动是一种短促的尖波,这种波形极易与背景活动鉴别。这种波形可为良性,也可是病理性的,主要取决于波形的位置、频率和持续的时间。是否应根据 EEG 上的这种尖波区别癎性或非癎惊厥学界尚有争议[19,34-35]。

结论

区别癎性惊厥和非癎性惊厥是非常重要的,因为新生儿惊厥常是严重颅内病变的表现,而非癎样活动则预后多良好。如果这些非癎样活动是病理性的,其潜在的病因可能与导致癎样惊厥的病因不同,因此需要采取不同的治疗。

虽然新生儿的大脑对于时程较长的惊厥发作可能有一个内在的抵抗,但反复发作的短暂惊厥在新生儿更为常见,且可进一步加重已有的脑损伤[9,36-37]。因此临床医师必须权衡惊厥对脑的损伤及抗癫癎药物的副作用后,决定是否需要对患儿进行抗癫癎治疗。因为急性的抗癫癎药物治疗可引起低血压、心动过缓和呼吸抑制等副作用,而这些副作用又可加重脑的缺氧缺血性损伤,同时临床医师还需注意抗癫癎药物对发育中大脑的远期影响。动物实验发现大多数常用的抗癫癎药物如苯巴比妥、苯妥英和地西泮等,即使用治疗剂量也可致神经细胞发生退行性改变。然而关于这些副作用及其对患儿远期神经发育的影响在临床上尚未得到证实,且仍存有争议[19]。

因此,临床上抗癫癎药物治疗仅用于癫癎可能性极大的新生儿。对癎样与非癎样惊厥的鉴别可根据患儿是否有意识的改变、异常的眼球活动、惊厥是否因刺激诱发、限制患儿活动惊厥是否会停止等。如果仅凭临床不能确定是否为癫癎,可行 EEG 检查,并由有丰富经验的 EEG 专家分析结果。如果确认为非癎性惊厥,一般只在惊厥发作引起患儿呼吸暂停、喂养困难或干扰了新生儿的正常看护时,才考虑使用药物如氯硝安定等治疗。

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