Neonatal Lethargy, Seizures, and Asphyxiation

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Neonatal lethargy and seizures in newborns are problems encountered in the NICU yet can also present once neonates have been discharged. Prompt recognition of the symptoms and understanding the possible differential diagnoses are essential to guide early evaluation and therapy. A lethargic infant typically presents with feeding difficulty, a poor suck reflex, and hypotonia and may be difficult to arouse The differential diagnosis for lethargy includes hypoxic-ischemic encephalopathy (HIE), infection/sepsis, asphyxiation, inborn errors of metabolism (IEMs), intraventricular hemorrhage (IVH), and hyperbilirubinemia. Hypoxic-ischemic encephalopathy occurs when there is diminished blood supply and hypoxemia to the brain and may be due to antepartum, intrapartum, or postnatal factors, although intrapartum events seem to be the most common cause. Sepsis occurs in approximately 1 to 5 per 1,000 live births, with a higher incidence in low birthweight infants. Poor feeding and lethargy are the earliest signs, requiring prompt physical examination and laboratory evaluation, even if fever is not present. Intrapartum asphyxiation presents with lethargy soon after birth if the ischemic insult is significant. Milder hypoxic events may initially show lethargy that can progress to jitteriness and/or seizures. In contrast, lethargy secondary to an IEM will usually follow a period of normal neurologic function. Associated laboratory abnormalities such as hyperammonemia, hypoglycemia, hypocalcemia, and lactic acidosis may be present. Severe IVH can present early with signs of hypotonia and lethargy. As with asphyxiation, infant presentation can vary widely depending on the degree of bleeding. Finally, significant hyperbilirubinemia can cause an encephalopathy, with the infant presenting with lethargy and feeding difficulty.

Neonatal seizures occur in 1% of all neonates. As with lethargy, prompt physical examination, laboratory evaluation, and neurologic evaluation guide treatment. The differential diagnosis for neonatal seizures is similar to that for neonatal lethargy and includes HIE, infection, intracranial hemorrhage, stroke, IEM, and familial epilepsy syndromes. Hypoxic-ischemic encephalopathy is the most common cause of neonatal seizures; approximately 65% of seizures can be attributed to some degree of hypoxic injury. Seizures caused by HIE generally present in the first day after birth and can be difficult to control. The presentation can vary from mild tremors to generalized tonic-clonic seizures, depending on the degree of encephalopathy. Contrasting this, seizures caused by infection may occur later in the neonatal period. Both bacterial and viral meningitis (especially herpes simplex virus) can cause seizures and lead to significant morbidity and mortality. It is, therefore, important to review the maternal infectious history to guide prompt antibiotic and antiviral drug therapy, although lack of risk factors would not rule out infectious causes. Prompt treatment with antibiotic agents and acyclovir may be lifesaving if bacterial or herpes simplex virus meningitis is present. Intracranial hemorrhage, including subarachnoid, intraventricular, and intraparenchymal bleeding, also causes

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Hypoxic-Ischemic Encephalopathy: Clinical Aspects. Volpe JJ. *Neurology of the Newborn*. 5th ed. Philadelphia, PA: Saunders Elsevier; 2008:400–465

The Current Etiologic Profile and Neurodevelopmental Outcomes of Seizures in Term Newborn Infants. Tekgul H, Gauvreau K, Soul J, et al. *Pediatrics*. 2006;117;1270–1280

Guidelines on Neonatal Seizures. Geneva, Switzerland: World Health Organization; 2011

seizures in the early neonatal period. Intraventricular hemorrhage is generally more common in preterm infants. In contrast, subarachnoid hemorrhage is more common in term infants and may be secondary to birth trauma or nonaccidental trauma once the infant goes home. Focal seizures in neonates are often caused by stroke, with the distribution of the middle cerebral artery being most commonly affected. Other important causes of seizures to recognize early are homeostatic disturbances (hypoglycemia, hypocalcemia, and hyponatremia) and IEMs (aminoacidopathies and urea cycle defects). Finally, if findings from initial laboratory and neurologic evaluations are normal, there are some familial epilepsy syndromes that can present in the neonatal period. Initial evaluation for neonatal seizures should always include serum electrolytes and a complete blood cell count. In addition, if infection is suspected, blood, urine, and cerebrospinal fluid should be cultured. Electroencephalography as well as neuroimaging with ultrasound or magnetic resonance imaging should also be performed.

Cases of HIE with seizures from fetal asphyxiation (umbilical cord prolapse, placental abruption, traumatic delivery, or fetal heart decelerations) can affect other organ systems. Kidney injury may be seen with only a mild insult, resulting in the inability to concentrate urine, but in more severe cases, acute tubular necrosis with complete loss of function can be seen. Measurement of serum creatinine levels, serum electrolytes, and urine output can help diagnose the initial injury and monitor kidney recovery. Myocardium may also become ischemic, which may result in impaired function and heart failure in some patients. Functional echocardiography has been used at the bedside to measure cardiac impairment secondary to hypoxic injury in real time. Regarding the pulmonary system, the injury may be primary or secondary due to cardiac failure. With coexisting heart failure, pulmonary edema may develop secondary to poor right-sided heart function. Persistent pulmonary hypertension and acute respiratory distress syndrome can also develop secondary to hypoxic injury with no discernible myocardial injury. Finally, feeding intolerance can develop secondary to underperfusion of the gastrointestinal tract. This can progress to necrotizing enterocolitis if the hypoxic injury is severe. Ischemic liver injury can also result in poor hepatic function, and if the synthesis of clotting factors is disrupted, bleeding disorders such as disseminated intravascular coagulation may develop.

COMMENT: The problems of neonatal lethargy, seizures, and asphyxia can be subtle in the newborn period but present with an incredibly broad differential diagnosis. The vigilant observations of the NICU staff and the parents are critical for rapid diagnosis. Physical examination findings may be subtle, but examination of the infant's level of consciousness, breathing pattern, pupillary response, and tone may provide additional cues. Although I feel that those of us in developed countries are fortunate to have at our disposal all the laboratory and neuroimaging modalities needed to make the correct diagnosis, I marvel at practitioners in developing countries where these modalities may not be available. These providers often need to treat based on clinical suspicions, enhancing the importance of reliance on observation and physical examination skills.

– Janet Serwint, MD
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Correction

An error was found in the April 2017 review "Pleural Effusions and Pneumothoraces" (Cashen K, Petersen TL. Pediatrics in Review. 2017;38(4):170-181, DOI: 10.1542/pir.2016-0088). On page 179, under the heading "Treatment," the first sentence should read, "Treatment is supportive, and isolated spontaneous pneumomediastinum generally resolves with a low recurrence rate." The online version of the article has been corrected; for the print edition, a correction will be published in the next available issue. The journal regrets the error.

ANSWER KEY FOR JUNE 2017 PEDIATRICS IN REVIEW

Heart Rate and Rhythm Disorders: 1. A; 2. D; 3. A; 4. E; 5. E.
Group B Streptococcal Infections: 1. D; 2. D; 3. A; 4. D; 5. E.
Environmental Risks to Children: Prioritizing Health Messages in Pediatric Practice: 1. D; 2. D; 3. C; 4. C; 5. D.

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