A 3-day-old male infant, whose birth-weight was 720 g and estimated gestational age at birth 24 weeks, has evidence of periventricular-intraventricular hemorrhage on cranial ultrasonography (Fig. 1). At 4 weeks of age, the infant has a bulging anterior fontanel, slight separation of cranial sutures, and a gain in head circumference of 1.2 cm during the preceding week. A cranial ultrasonograph reveals slowly progressive ventricular dilatation (Fig. 2).

Of the following, the MOST appropriate treatment for prevention of hydrocephalus and need for ventriculo-peritoneal shunt in this infant is the use of:

1. carbonic anhydrase inhibitor  
2. cerebrospinal fluid drainage  
3. head wrapping  
4. intraventricular fibrinolytic therapy  
5. osmotic agent

You selected 2, the correct answer is 2.

Periventricular-intraventricular hemorrhage (PIVH) is classified, as suggested by Papile, into 4 grades based on its severity. In grade I, the hemorrhage is localized to the germinal matrix region in the thalamocaudate groove and does not extend into the ventricular cavity (Fig. 3). In grade II, the hemorrhage extends into the ventricular cavity, covers less than 50% of the ventricular area, and does not cause ventricular distension (Fig. 4). In grade III, the hemorrhage extends into the ventricular cavity, covers more than 50% of the ventricular area, and causes ventricular distension (Fig. 4). And in grade IV, the hemorrhage extends beyond the ventricular cavity into the brain parenchyma (Fig. 1). The risk of death increases with the severity of PIVH and so does the risk of post-hemorrhagic hydrocephalus among the survivors.

The mortality rates in PIVH are approximately 5% in grade I, 10% in grade II, 20% in grade III, and 50% in grade IV. Among the survivors, the rates of post-hemorrhagic hydrocephalus needing ventriculo-peritoneal shunt are approximately 5% in grade I, 20% in grade II, 55% in grade III, and 80% in grade IV. The infant in this vignette, who has grade III PIVH in the left cerebral hemisphere and grade IV PIVH in the right cerebral hemisphere, is at substantial risk for the development of post-hemorrhagic hydrocephalus. The symptoms and signs of increased intracranial tension and the cranial ultrasonographic evidence of slowly progressive ventricular dilatation at 4 weeks of age in this infant suggest that spontaneous resolution of ventricular dilatation is unlikely and treatment for prevention of post-hemorrhagic hydrocephalus is warranted.

The most appropriate treatment for persistent and slowly progressive ventricular dilatation that does not resolve spontaneously within about 4 weeks of the occurrence of PIVH is the institution of cerebrospinal fluid (CSF) drainage. The rationale behind this treatment is that removal of blood products by early and repeated drainage of CSF may prevent or ameliorate the occlusion of arachnoid granulations to allow CSF absorption. Additionally, intermittent decompression of the ventricles from CSF drainage may improve cerebral blood flow and, at least temporarily, arrest the progression of ventricular dilatation to allow for the natural healing to occur. One of the methods of CSF drainage is the institution of sequential lumbar punctures. To be effective, the presence of communication between the ventricles and the lumbar subarachnoid space is critical. Also, a sufficient volume of CSF - estimated at approximately 10 mL/kg body weight - needs to be removed at each procedure. The frequency and duration of lumbar punctures are determined by the volume of CFS removed at each procedure, clinical evaluation of the infant for symptoms and signs of increased intracranial tension, cranial ultrasonographic evaluation of ventricular size, and other factors including the

stability of the infant during the procedure. The typical frequency of lumbar punctures is once at 24 hour intervals, and the typical duration is 2-3 weeks. The complications associated with sequential lumbar punctures include meningitis, ventriculitis, epidural abscess, vertebral osteomyelitis, and intraspinal epidermoid tumor. The latter is associated with the use of unstyleted needles while performing lumbar punctures. A large, multicenter, randomized trial, performed in mid-1980s, has shown a significant reduction in neuromotor disability among preterm infants who had PIVH with brain parenchymal involvement treated with sequential lumbar punctures as compared with those treated conservatively and expectantly. According to Volpe, sequential lumbar punctures performed under optimal conditions may prevent the development of post-hemorrhagic hydrocephalus and the need for ventriculo-peritoneal shunt in approximately 2/3rds of the survivors of PIVH with persistent and slowly progressive ventricular dilatation.

An alternative method of CSF drainage is the placement of a ventricular access device. This device is a small, flat-bottomed reservoir attached to a ventricular catheter. The reservoir is placed on the surface of the skull under the galea of the scalp. Percutaneous puncture of the reservoir with sequential aspiration of CSF serves to keep the ventricular system decompressed. The ventricular access device is used commonly as a temporizing measure pending the placement of a ventriculo-peritoneal shunt. The latter may be delayed to allow for infant growth as well as for clearance of CSF protein and cellular debris.

Head wrapping involves compression of the head by application of a tight bandage. Although historically documented, this approach does not have a sound rationale as a means for prevention of post-hemorrhagic hydrocephalus and is no longer implemented in clinical practice.

The rationale behind the use of a carbonic anhydrase inhibitor is that suppression of CSF production induced by this drug may control CSF accumulation and prevent or ameliorate ventricular dilatation. The carbonic anhydrase inhibitor, acetazolamide, causes a 50% reduction in CSF production, and when used in combination with a diuretic such as furosemide, can induce a nearly complete cessation of CSF production. The dosage of acetazolamide used in clinical trials has been 100 mg/kg/d, and that of furosemide 1.0 mg/kg/d. The total duration of treatment has been 6 months. The complications of this treatment include metabolic acidosis and nephrocalcinosis. The furosemide promotes hypercalciuria by inhibiting renal tubular reabsorption of calcium, and the acetazolamide promotes precipitation of calcium salts in the renal tubules by inducing alkalization of urine. The beneficial effect of acetazolamide in prevention of post-hemorrhagic hydrocephalus has not been established. On the contrary, a large, multicenter, randomized trial has shown a greater need for ventriculo-peritoneal shunt and increased neurodevelopmental disability among preterm infants treated with acetazolamide and furosemide as compared with those treated with sequential lumbar punctures. Thus, carbonic anhydrase inhibitor treatment as a means for prevention of post-hemorrhagic hydrocephalus following PIVH cannot be recommended.

The CSF following PIVH is low in plasminogen activity and has high concentrations of plasminogen activator inhibitor, conditions that are conducive to clot formation. Additionally, the CSF following PIVH has high concentrations of transforming growth factor-beta (TGF-beta), the key mediator of deposition of extracellular matrix proteins within the ventricular system, especially along the basal cisterns. The fibrosis induced by TGF-beta can result in chronic obstruction and progressive hydrocephalus. Intraventricular fibrinolytic therapy, as a means to dissolve the clot, restore CSF circulation, and prevent TGF-beta-induced chronic fibrosis, is sound in its rationale. Moreover, by way of its direct action at the site of the clot, the intraventricular approach for administration of a fibrinolytic agent is reasonable. The fibrinolytic agents used in clinical trials have included urokinase, streptokinase, and tissue plasminogen activator (TPA). Most recently, a small, nonrandomized, preliminary trial using historic controls has shown the feasibility of a closed system of ventricular irrigation with TPA. In this trial, human recombinant TPA was injected in a dose of 0.5 mg/kg body weight via a reservoir or anterior ventricular catheter into the cerebral ventricle and left for 8 hours before irrigation for 72 hours with a fluid containing electrolytes and antibiotics. Although the results are promising, the therapeutic benefit is small and the risk is unacceptably high. The treatment is highly invasive, labor-intensive, and expensive, and it carries the risks of iatrogenic injury, serious infection, bleeding, and fluid-electrolyte abnormalities. Thus, in the absence of
supportive data from properly controlled, multicenter trials, intraventricular fibrinolytic therapy as a means for prevention of post-hemorrhagic hydrocephalus following PIVH cannot be recommended.

The rationale behind the use of an osmotic agent is based on the inverse relation between serum osmolarity and CSF formation. A 1% increase in serum osmolarity results in a 15% decrease in CSF production. The osmotic agents used in clinical trials have included isosorbide and glycerol. The dosage of either of these agents has been 8.0 g/kg/d in 4 divided doses. The total duration of treatment has been 3 months. The complications of treatment with an osmotic agent include fluid-electrolyte abnormalities, alterations in glucose homeostasis, and diarrhea and vomiting. Much of the experience with the use of the osmotic agent has involved small clinical trials of treatment of infantile hydrocephalus. The treatment has been used mostly as a temporizing measure pending the placement of a ventriculo-peritoneal shunt. The experience with the use of the osmotic agent as a means for prevention of post-hemorrhagic hydrocephalus in preterm infants is limited.

References:


Ventriculomegaly Trial Group. Randomised trial of early tapping in neonatal posthemorrhagic ventricular dilatation. *Arch Dis Child.* 1990;65:3-10


Content Specifications:

Understand the proposed mechanisms, clinical features, and diagnosis of periventricular-intraventricular hemorrhage

Understand the treatment and long-term consequences of periventricular-intraventricular hemorrhage

Understand the treatment of hydrocephalus
Figure 2: Coronal (panel A) and sagittal (panel B) views on cranial ultrasonography show ventricular dilatation.
Figure 4: Coronal (panel A) and sagittal (panel B) views on cranial ultrasonography show grade II periventricular-intraventricular hemorrhage.
A 26-weeks'-gestation premature infant is receiving mechanical ventilation for respiratory distress syndrome in your NICU. The infant likely will be subjected to multiple noxious interventions over the ensuing days. Pursuant to the recommendations of the American Academy of Pediatrics, a pain score using the Premature Infant Pain Profile (PIPP) is recorded along with vital signs. You are considering a continuous intravenous infusion of morphine for pain prevention.

Of the following, the MOST likely outcomes from continuous prophylactic morphine infusion versus episodic pain treatment are:

1. pain scores reduced moderately and no effect on incidences of death, severe intraventricular hemorrhage (IVH), or periventricular leukomalacia (PVL)
2. pain scores reduced moderately plus reduced incidences of severe IVH and PVL
3. pain scores reduced substantially and no effect on incidences of death, severe IVH, or PVL
4. pain scores reduced substantially plus reduced mortality
5. pain scores reduced substantially plus reduced incidences of severe IVH and PVL

You selected 3, the correct answer is 1.

The American Academy of Pediatrics issued a joint statement with the Canadian Paediatric Society entitled "Prevention and Management of Pain and Stress in the Neonate," recommending to a) evaluate and reduce the stress and pain experienced by neonates, b) use environmental as well as pharmacological methods to reduce pain and stress, c) use analgesics with known pharmacokinetics and dynamics in the neonate, and d) develop and implement pain management policies in neonatal units. Preliminary information from small studies indicated that continuous prophylactic morphine infusions might reduce mortality, intraventricular hemorrhage (IVH), and periventricular leukomalacia (PVL) in infants such as the one in this vignette. A large, multicenter, randomized trial, the NEOPAIN Trial, was carried out to evaluate these early findings.

The NEOPAIN trial enrolled 898 preterm infants between 23 weeks' gestation and 32 weeks' gestation who were intubated prior to age 72 hours and had been ventilated for less than 8 hours before enrollment. Infants were randomized to morphine or placebo infusions. They received a loading dose (100 mcg/kg infused over 1 hour for the morphine group) followed by a continuous infusion of drug or placebo. The infusion was continued for up to 14 days. This trial demonstrated a modest reduction in the pain score (8 for the morphine group, 8.77 for controls, p=0.0034). There was no statistical difference between groups for mortality or in the incidences of severe IVH (grades III and IV) or PVL.

The NEOPAIN Trial suggests that a protocol-based approach for pain control among all ventilated preterm neonates might not be appropriate because of the marked variability of the population. Instead, a more targeted use of powerful analgesics to prevent severe pain is recommended. Long-term effects of routine continuous morphine analgesia would be important to know but have not been assessed so far.

References:

American Academy of Pediatrics Committee on Fetus and Newborn, Committee on Drugs, Section on Anesthesiology, Section on Surgery, Canadian Paediatric Society Fetus and Newborn


**Content Specification:**

Know the importance, recognition, and management of neonatal pain.
You have been asked to attend the term delivery following an uncomplicated prenatal course because the fetal heart rate (FHR) monitor tracing began to show late decelerations of 10-12 beats per minute in association with the contractions. The fetal heart rate between contractions is 146 beats per minute and the beat-to-beat variability is 5 to 10 beats per minute. The obstetrician has raised the possibility of cesarean delivery to avert fetal neurologic damage and has introduced you to the mother. The mother asks you if there is a chance that her child will not have cerebral palsy.

Of the following, the false-positive rate of this FHR tracing in predicting cerebral palsy is CLOSEST to:

1. 19%
2. 39%
3. 59%
4. 79%
5. 99%

You selected 4, the correct answer is 5.

Fetal heart rate (FHR) monitoring is nearly universal. Randomized, controlled studies have not shown consistent benefit of FHR monitoring in terms of reducing infant mortality or the long-term risk of cerebral palsy among women who have no identified antepartum risk factors. In addition, the increase in cesarean delivery has been attributed in part to routine FHR monitoring. For the infant described in the vignette whose FHR pattern is late decelerations with normal baseline variability (reflex late decelerations), the false-positive rate of FHR monitoring for predicting long-term cerebral palsy is closest to 99%.

The following FHR patterns are consistent with hypoxia and indicative of current or impending fetal asphyxia severe enough to place the fetus at risk for neurologic (or other organ) damage and/or death:

- Late decelerations with absent variability
- Variable decelerations with absent variability
- Sustained bradycardia with absent variability

FHR interpretation is plagued with problems that currently are being investigated. Among these are: 1) interobserver reliability in pattern identification, 2) validity of association(s) between specific FHR patterns and adverse neonatal outcomes, and 3) existence of a causal relationship between specific FHR patterns and neonatal outcome. The causal relationship must be linked to the ability to prevent damage by therapeutic intervention. For example, a meta-analysis of studies of FHR monitoring showed a reduction in neonatal seizures (relative risk, 0.5) among monitored neonates, but there was no association with long-term outcome.

Persistent late decelerations with normal FHR variability (called reflex late decelerations), such as seen in this vignette, may be tolerated by the infant. However, the mother should be evaluated (and treated if needed) for abnormal blood pressure (especially hypotension), strength of uterine contractions, hypovolemia, or supine hypotension. Deterioration to nonreflex late decelerations is manifested by deepening of the decelerations and reduction or loss of baseline variability.
variability with continued late decelerations. Unless fetal well-being can be assessed by fetal scalp sampling, expedient (usually operative) delivery is recommended.

References

Freeman RK. Problems with intrapartum fetal heart rate monitoring interpretation and patient management. *Obstet Gynecol.* 2002;100:813-826


Content Specification

Understand the significance, interpretation, and management of late fetal heart rate decelerations in labor
A term male infant was born vaginally with the help of outlet forceps to a 29-year-old primiparous woman with no history of complications during pregnancy. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. After appearing stable for a time, the infant received an injection of vitamin K and routine eye prophylaxis, consisting of 0.5% erythromycin ointment. Physical examinations at birth and before discharge 36 hours after birth showed no abnormalities except for excessive tearing from both eyes. Further examination showed reactive round pupils, normal eye movement, pale conjunctivae, clear media, and normal red reflexes bilaterally, with some resistance to bright light.

Of the following, the MOST likely explanation for the ophthalmic findings in this infant is:

- conjunctivitis
- corneal trauma
- dacryocystitis
- glaucoma
- irritation from eye prophylaxis

You selected 1, the correct answer is 1.

Glaucoma is a condition associated with abnormally high intraocular pressure, which can damage the optic nerve and cause permanent blindness if not treated. In the normal eye, aqueous fluid constantly is produced by the ciliary body and drained through the trabecular meshwork at the junction of the iris and the cornea. The relative rates of formation and drainage of the aqueous humor determine the intraocular pressure.

Congenital glaucoma may occur because of a malformation of the eye's drainage system, or it may be secondary to another eye condition. Congenital glaucoma affects boys in 65% of cases, and 70% of cases involve both eyes.

The classic symptoms of congenital glaucoma are epiphora (tearing), photophobia, and blepharospasm (twitching of the eyelids). Two of these symptoms are found in the infant in this vignette. Before age 3, eye tissues stretch more easily. If the eye pressure is elevated, the eye becomes enlarged (buphthalmos), which can manifest as megacornea. A corneal diameter of 12 mm or more at birth, when the normal limit is 10.5 mm, suggests glaucoma. Congenital glaucoma may be an isolated disease, or it may be associated with other conditions, such as aniridia, rubella syndrome, Lowe syndrome, Hallermann-Streiff syndrome, Axenfeld or Reiger syndrome, and Sturge-Weber syndrome. Suspicion of congenital glaucoma should trigger a consultation with an ophthalmologist. The definitive treatment is surgical, although medications might be prescribed to try to reduce intraocular pressure while surgery is being arranged.

Conjunctivitis can cause tearing and some photophobia, as described in the infant in this vignette. However, the conjunctivae are inflamed, not pale, and the discharge is often cellular, not watery. Matting of the eyelids often is seen.

Dacryocystitis usually manifests as a purulent exudate in the medial canthal area along with a swelling and induration of the lacrimal sac. Photophobia is not described with this condition. Dacryocystitis often involves only one eye.

The eye prophylaxis associated with the highest incidence of irritation is silver nitrate.
Erythromycin ointment is preferred in many institutions to prevent the chemical conjunctivitis caused by silver nitrate. It is, therefore, an unlikely cause of the symptoms in the infant in this vignette.

Finally, corneal abrasions can occur with a traumatic delivery. Outlet forceps procedures are designed to reduce birth trauma, but misapplication of forceps over the eye can be traumatic. The bilateral nature of the condition in the vignette as well as the lack of any description of skin abrasions makes trauma an unlikely cause.

References:


Content Specifications:

Recognize the signs of congenital glaucoma

Recognize the conditions associated with congenital glaucoma
A term newborn experiences generalized tonic-clonic seizures 1 hour after birth. The vaginal delivery was unremarkable, and Apgar scores were 9 at both 1 and 5 minutes. The pregnancy was notable for the mother reporting that the "baby had hiccups." Except for the ongoing seizures, physical examination results are normal, and the baby boy is afebrile. Despite full dosing of intravenous fosphenytoin and phenobarbital, the seizures continue.

Of the following, the MOST likely cause of the child's seizures is

1. Aicardi syndrome
2. benign familial neonatal seizures
3. hypoxic-ischemic encephalopathy
4. nonketotic hyperglycinemia
5. pyridoxine dependency

You selected 5, the correct answer is 5.

Neonatal seizures are defined as seizures that occur during the first month after birth (principally during the first few days). Neonatal seizures can manifest, in order of decreasing incidence, as generalized tonic (primarily preterm infants), multifocal clonic (primarily term infants), focal clonic (term more often than preterm infants), or myoclonic (both term and preterm infants). Myoclonic seizures may presage infantile spasms. More frequent than any of these seizure types are subtle seizures, that is, behaviors and movements that may not be appreciated as seizures (eg, horizontal eye deviation, color change, apnea, drooling, sucking, lip smacking, and swimming or pedaling movements). Once neonatal seizures are identified, determining their cause is key to treating the underlying condition and, in some instances, to halting the seizures.

The infant described in the vignette has typical findings for autosomal recessive pyridoxine dependency. Fewer than 100 cases have been reported. Seizures related to this condition commence in utero (often mistaken as fetal hiccups). After birth, the seizures continue as generalized clonic seizures refractory to fosphenytoin and phenobarbital. Pyridoxine is a coenzyme for glutamic acid decarboxylase that converts glutamic acid to the inhibitory transmitter gamma amino butyric acid. For infants suspected of having pyridoxine-dependent seizures, 100 mg of pyridoxine should be administered intravenously during simultaneous electroencephalography to determine whether the electrical tracing normalizes. Affected individuals require lifelong treatment with pyridoxine. Untreated patients usually die with seizures, and although early treatment may be life-saving, most survivors have mental retardation. Whether earlier treatment leads to better intellectual function is controversial.

Aicardi syndrome is a form of cerebral dysgenesis in a females characterized by agenesis of the corpus callosum and coloboma of the iris. Deterioration of higher brain functions follows a period of normal development. Severe dementia, autism, loss of purposeful use of the hands, jerky truncal ataxia, seizures and acquired microcephaly may follow. Due to its exclusive appearance in females, a dominant defect on the X chromosome leading to lethality in males and affected females is suspected.

Benign familial neonatal convulsions (BFNC) is an autosomal dominant disorder characterized by 10 to 20 seizures per day commencing around the third postnatal day that usually are self-resolving. This child's age at seizure onset and refractoriness to anticonvulsants are not typical of benign familial neonatal seizures. BFNC has been related to loci on 20Q in most families and
on 8Q in another. Resultant mutations in potassium channel proteins have been identified in most families and one family has abnormalities in the acetylcholine alpha-4 receptor unit. Frequent seizures and certainly status epilepticus should be treated. Due to the resolution of BFNC in the first few weeks of life, Phenobarbital is the drug of choice. Fosphenytion may be appropriate for control of status, but not for longer term treatment. Valproic acid is not suggested. In spite of the potassium channel abnormality, the seizures resolve early in infancy. Long-term follow-up reveals normal development, although and 11% risk for later seizures is noted.

The timing of the postnatal seizures and the likelihood of ongoing seizures in utero (the "hiccups") over time are not likely features of hypoxic-ischemic encephalopathy. Of note, some cases of pyridoxine dependency have been confused with birth asphyxia in the neonatal period.

Nonketotic hyperglycinemia manifests seizures days or weeks after birth, often in an infant who is obtunded or exhibits development delay.

When confronted with neonatal seizures, the clinician must be familiar with the wide range of possible causes: hypoxia-ischemia, trauma, hemorrhage, infection (eg, congenital infections with Toxoplasma gondii, rubella, cytomegalovirus, or herpesvirus), cerebral dysgenesis, and metabolic disorders (eg, hypercalcemia in DiGeorge syndrome, urea cycle defect, propionic acidemia, methylmalonic acidemia, maple syrup urine disease, or nonketotic hyperglycinemia). Delineation of the cause requires the combination of careful history, complete physical examination, testing, and response to interventions. Neonatal seizures do not necessarily predict epilepsy (ie, an ongoing seizure disorder). Although neonatal seizures are the best predictor of future neurologic damage, most infants who have these seizures do well. There is little evidence that transient seizures damage the newborn cortex. Neonatal seizures have virtually no relationship to later epilepsy unless the child has suffered sufficient damage to the brain to manifest later evidence of cerebral palsy. More than 50% of children who have neonatal seizures do not develop epilepsy.

References:

Gospe SM Jr. Pyridoxine-dependent seizures: findings from recent studies pose new questions. Pediatr Neurol. 2002;26:181-185. Abstract available online, article available online for subscription or fee only.


Content specifications:

Understand the spectrum of clinical seizures in the newborn infant.

Understand the differential diagnosis and evaluation of neonatal seizures.

Understand the management and prognosis of neonatal seizures.
A 7-day-old term female infant remains in the neonatal intensive care unit because of episodes of hyperpnea alternating with spells of apnea of up to 25 seconds. Physical examination reveals a healthy child who has nystagmus of both eyes that is unassociated with the respiratory variations.

Of the following, the test that is MOST likely to establish the correct diagnosis is

- electroencephalography
- magnetic resonance imaging of the brain
- MECP2 gene testing for Rett syndrome
- molecular genetic testing for spinal muscular atrophy
- urine toxicology screen

You selected 1, the correct answer is 2.

Apnea is defined as not breathing or cessation of airflow in and out of the lungs. If airflow ceases because respiratory effort has stopped, the condition is termed central apnea, referring to the absence of drive from respiratory centers in the central nervous system. When airflow ceases because of occlusion of the upper airway, the condition is known as obstructive apnea. Hyperpnea is deeper and more rapid respirations than normal, and tachypnea is simply rapid breathing.

Of these breathing patterns in an infant, central apnea may be the most ominous or life-threatening. The differential diagnosis includes prematurity, increased intracranial pressure, shunt malfunction, Chiari malformation, myelodysplasia, meningoencephalitis, ischemia, trauma, achondroplasia, the rare congenital central hypoventilation syndrome (Ondine curse) (ie, intact voluntary but not automatic control of breathing), and Joubert syndrome.

Joubert syndrome is an autosomal recessive disorder that is characterized by agenesis of the cerebellar vermis and sometimes other brain anomalies such as brainstem hypoplasia. Episodic apnea alternating with hyperpnea may appear shortly after birth, as in the child described in the vignette. Eye movement disorders, including nystagmus, disruption of rapid eye movements (ie, hypometric saccades), and oculomotor apraxia, may occur, as might retinal dystrophy. Magnetic resonance imaging of the brain establishes the diagnosis.

If the apnea and nystagmus occurred simultaneously, electroencephalography would be useful to exclude a subtle seizure. Such is not the case in the vignette.

MECP2 gene testing is appropriate for an older child who exhibits hand wringing, loss of development, and later episodic hyperpnea, which are suggestive of Rett syndrome.

Genetic testing for spinal muscular atrophy is indicated for a baby who has profound hypotonia and areflexia. A urine toxicology screen can aid in excluding intoxication in any child who has respiratory and eye movement abnormalities, but the child probably would not appear otherwise healthy.

References:


**Content specification:**

Understand the pathophysiology of apnea of prematurity.
A male newborn was delivered by emergent cesarean section for fetal distress following spontaneous placental abruption. At birth, the infant weighed 580 g, and the estimated gestational age was 23 weeks. The Apgar score was 1 at 1 minute and improved to 6 at 5 minutes following resuscitation that included oxygen administration, positive pressure ventilation, and volume expansion. The infant's initial clinical course was characterized by respiratory distress, which was managed with surfactant administration and mechanical ventilation, and persistent hypotension, which required infusion of vaspressors. Cranial ultrasonography at 4 weeks of age shows bilateral cystic lesions in the periventricular cerebral white matter (Figure 1 and Figure 2).

Of the following, the MOST likely mediator of injury resulting in the cerebral lesion in this infant is

1. carbon dioxide
2. insulin-like growth factor-1
3. nitric oxide
4. oxygen free radicals
5. tumor necrosis factor-alpha

You selected 4, the correct answer is 1.

The infant described in the vignette has cranial ultrasonographic evidence of cystic periventricular leukomalacia (PVL). Volpe has described two principal components of PVL: focal and diffuse (Figure 3). The focal component, located deep in the cerebral periventricular white matter, is characterized by localized necrosis of all cellular elements, with subsequent cyst formation. The diffuse component, located more superficially and extensively in the cerebral white matter, is characterized by diffuse apoptosis of oligodendroglial precursor cells. Focal PVL can be diagnosed with cranial ultrasonography; diffusion-weighted magnetic resonance imaging is required to diagnose diffuse PVL. The primary clinical sequela of focal PVL is spastic diplegia; diffuse PVL often results in cognitive and behavioral deficits. The principal neuropathologic sequela of either focal or diffuse PVL is loss of cerebral white matter from deficiency of myelin and consequent ventriculomegaly.

The pathogenesis of PVL generally involves ischemic-hypoxemic injury to cerebral white matter. The two major contributors to the ischemia-hypoxemia are immaturity of the brain and impairment of cerebral blood flow. The vascular supply of an immature brain is characterized by an incomplete development of penetrating cerebral arteries, which renders the cerebral tissue susceptible to ischemic-hypoxemic injury. Moreover, the immature precursors of oligodendroglial cells, in contrast to mature oligodendrocytes, are intrinsically vulnerable to ischemic-hypoxic injury as well as to injury during subsequent reperfusion and reoxygenation. Whereas the cerebral blood flow in healthy term neonates is maintained within a narrow range, despite fluctuations in systemic blood pressure, autoregulation of cerebral blood flow is impaired in preterm neonates, especially sick and extremely immature infants such as the baby in the vignette. A pressure-passive cerebral circulation in preterm neonates makes them vulnerable to ischemia when systemic blood pressure falls and to hemorrhage when systemic blood pressure rises.

Oxygen free radicals are the principal mediators of tissue injury during reperfusion and reoxygenation of previously ischemic-hypoxic tissue. These highly reactive compounds have an uneven number of electrons in the outermost orbital that can react with various cellular components and cause irreversible injury in the form of lipid peroxidation, membrane lysis, and...
cell necrosis. The primary oxygen free radicals involved in the pathogenesis of PVL are superoxide anion, hydrogen peroxide, and hydroxyl radical. The latter, the most toxic form of oxygen free radical, is produced in the presence of iron, which may be deposited at the site of local injury following hemorrhage that may accompany PVL. The deficiency of antioxidant enzymes, such as superoxide dismutase, glutathione peroxidase, and catalase, in immature precursors of oligodendroglial cells and other neuronal cells of cerebral white matter makes them vulnerable to oxidant injury.

The Pco2 in arteriolar blood influences cerebral blood flow. A high Pco2 (hypercarbia) induces vasodilation by increasing perivascular hydrogen ion concentration and increases the cerebral blood flow. An increase in the availability of oxygen as well as the substrate resulting from such cerebral vasodilation protects against ischemic-hypoxemic injury to the neuronal cells. In contrast, a low Pco2 (hypocarbia) induces vasoconstriction and decreases the cerebral blood flow. It is plausible, therefore, that sustained hypocarbia can result in poor perfusion of the brain and consequent ischemic-hypoxemic injury to neuronal cells. However, unless the Pco2 is regulated poorly during mechanical ventilation, resulting in sustained hypocarbia, carbon dioxide is an unlikely mediator of injury in PVL.

The role of growth factors, such as insulin-like growth factor (IGF)-1, in the mediation of neuronal injury in PVL is unclear. In neuronal cultures, IGF-1 and other growth factors, such as nerve growth factor and brain-derived neurotrophic factor, can prevent apoptosis and prolong neuronal survival. Such an effect may protect against the injury induced by apoptosis of oligodendroglial precursor cells characteristic of diffuse PVL. However, under certain conditions, including exposure to oxygen free radicals, IGF-1 and brain-derived neurotrophic factor can promote neuronal cell necrosis. Such an effect may accentuate the injury induced by oxygen free radicals in focal PVL. Thus, the net effect of IGF-1 in the mediation of neuronal injury in PVL is uncertain.

NO is produced in selected neurons of the brain, and the pathway for its synthesis involves the conversion of L-arginine to citrulline by the catalytic cytosolic enzyme nitric oxide synthase (NOS). At least three forms of NOS are recognized: a constitutive neuronal form (nNOS), a constitutive endothelial form (eNOS), and an inducible form (iNOS) found in astrocytes and microglia. Activation of eNOS results in NO-induced vasodilation and preservation of cerebral perfusion, which may be neuroprotective. Conversely, activation of iNOS results in generation of peroxynitrite, which may be neurotoxic. Activation of nNOS varies between the generation of neuroprotective nitrosonium ion and neurotoxic peroxynitrite. Thus, the net effect of NO in the mediation of neuronal injury in PVL is uncertain.

Several clinical, epidemiologic, neuropathologic, and experimental studies have suggested an association between maternal/placental/fetal infection and PVL. The development of PVL in infection is believed to be mediated by inflammatory cytokines acting either directly on oligodendroglial and other neuronal cells or indirectly through oxygen free radicals. The major cytokines involved in the pathogenesis of PVL appear to be interleukin (IL)-1-beta, IL-6, and interferon-gamma, all of which are neurotoxic. The role of tumor necrosis factor (TNF)-alpha, on the other hand, is unclear. In neuronal cultures, TNF-alpha shows little or no toxicity to oligodendroglial cells and, therefore, may not be the cytokine involved in the pathogenesis of PVL. However, under certain conditions, such as exposure to interferon-gamma, TNF-alpha may potentiate cytokine-mediated neurotoxicity to oligodendroglial and other neuronal cells. Thus, the net effect of TNF-alpha in the mediation of neuronal injury in PVL varies, depending on the milieu of other inflammatory cytokines.

References:


Volpe JJ. Hypoxic-ischemic encephalopathy: biochemical and physiological aspects. In:


Content Specification(s):

Understand the risk factors of intraparenchymal cysts/periventricular leukomalacia, and intraparenchymal echodensities
Understand the evolution of intraparenchymal cysts/periventricular leukomalacia, and intraparenchymal echodensities
Understand the outcome of intraparenchymal cysts/periventricular leukomalacia, and intraparenchymal echodensities
Figure 1. Coronal view on cranial ultrasonography.

Bilateral cystic lesions in periventricular cerebral white matter
Figure 2. Sagittal view on cranial ultrasonography.

Bilateral cystic lesions in periventricular cerebral white matter
Figure 3. Components of periventricular leukomalacia.
You are teaching medical students how to perform a neurologic examination in a newborn. The discussion focuses on the evolution of primitive reflexes through gestational development and infancy.

Of the following, the EARLIEST primitive reflex to appear during human gestation is the

1. crossed extension reflex
2. Moro reflex
3. palmar grasp reflex
4. rooting reflex
5. tonic neck reflex

You selected 3, the correct answer is 3.

Primitive neonatal reflexes, also called primary integrated reflexes, are transitory developmental phenomena that appear according to a predictable timetable during gestation and disappear during infancy. The most frequently elicited reflexes are: Moro reflex; palmar and plantar grasp reflex; placing and stepping reflex; rooting, sucking, and swallowing reflex; tonic neck reflex; and crossed extension reflex. Others include Galant's trunk incuration reflex, finger extension reflex, and head traction reflex. These highly stereotypical patterns of automatic movement are elicited by specific sensory stimuli and controlled by subcortical neuronal pathways. Some of the reflexes can be elicited as early as during the 25th week of gestation; most are fully present at birth in term neonates. These reflexes become difficult to elicit after the first half of infancy when cortical inhibition emerges and voluntary muscle activity replaces the reflex movements. Delayed appearance of the reflexes during gestation and persistence of the reflexes beyond the anticipated age for their disappearance are indicators of potential central nervous system dysfunction.

The palmar grasp reflex is one of the earliest primitive neonatal reflexes to appear during human gestation. The reflex is elicited by stroking with a finger the palmar surface of the infant's hand, which results in flexion of the fingers in a grasping motion. This reflex can be elicited, albeit weakly, as early as at 26 weeks of gestational age, is stronger at 32 weeks, and is strong enough to allow the examiner to lift the infant from the bed at 37 weeks. The palmar grasp reflex begins to fade at 2 months of age and disappears by 4 months with the development of a voluntary grasp.

To elicit the crossed extension reflex, one leg is held firmly in extension and the sole of the foot is rubbed. The reflex is observed in the opposite (free) leg in three successive phases: initial flexion (withdrawal), subsequent extension and fanning of the toes, and, in its fully developed form, adduction of the free leg toward the stimulated side as if to push away the stimulus. This reflex is absent at 26 weeks of gestational age, can be elicited in its partial form (only flexion) at 30 weeks, and is complete at 34 weeks. The crossed extension reflex disappears by about 2 months of age.

The Moro reflex can be elicited by startling the infant. The most effective and reproducible method for startling is to create a sensation of falling by sudden dropping of the head in relation to the trunk. With the infant held in supine position, the head is allowed to fall a few centimeters, rapidly but gently, in the examiner's hands. The reflex is observed in two successive phases. The infant's first response is a spreading motion in which the arms are abducted and extended with hands opened. The spreading motion is followed by a clutching motion in which the arms are adducted and flexed over the trunk with fists closed, often
accompanied by an audible cry. The Moro reflex is absent at 26 weeks of gestational age, can be elicited in its partial form (only spreading motion) at 30 weeks, is complete but variable (spreading with or without clutching motion) at 34 weeks, and is fully developed at 38 weeks. The reflex begins to fade at 2 months of age and disappears by 4 months.

In addition to being an index of gestational maturation, the Moro reflex can be useful in other clinical settings. An absent or depressed Moro reflex often accompanies severe illness, especially kernicterus and general depression of the central nervous system or a disorder of motor function. An exaggerated Moro reflex may be a manifestation of narcotic withdrawal or moderately severe hypoxic-ischemic encephalopathy. An asymmetric Moro reflex is seen with brachial plexus palsy and with trauma to the clavicle, humerus, or shoulder joint.

The rooting reflex is elicited by stroking with a finger the upper or lower lip or either corner of the infant’s mouth, which results in the infant turning the head, searching for the finger, and attempting to suck. Sucking tends to reinforce the rooting; a recent feeding tends to suppress it. The rooting reflex tests the integrity of the sensory pathways of the trigeminal nerve and of the motor pathways of the trigeminal, facial, and hypoglossal nerves. This reflex is absent at 26 weeks of gestational age, can be elicited with long patency at 30 weeks, and is fully developed at 34 weeks. The reflex disappears by 4 months of age.

To elicit the tonic neck reflex, the infant is placed in a supine position with the head in the midline, and the head is turned slowly to one side. This maneuver results in extension of the arm on the side to which the head is turned and flexion of the arm on the opposite side. The lower limbs respond similarly, but less strikingly. Ultimately, the infant assumes a “fencing” posture. The tonic neck reflex is one of the latest primitive neonatal reflexes to appear during human gestation. It appears at 35 weeks of gestational age, is most prominent at 2 months after birth, and disappears by 6 months of age.

References:


Content Specifications:

Know the normal integrated (primitive) reflexes that are present in the newborn infant, such as Moro, tonic neck, rooting, and grasping

Know the normal pattern of development of primitive (primary or integrated) reflexes in premature and term infants and through infancy (e.g. grasp, asymmetric tonic neck reflex, tonic labyrinthine)
A term infant presents 10 days after birth with noisy breathing, rhinorrhea, and difficulty with feeding. His birth history is significant for a forceps-assisted vaginal delivery with Apgar scores of 7 and 9 at 1 and 5 minutes, respectively. His mother's rapid plasma reagin was nonreactive, and her cervical swab for Chlamydia was negative. Physical examination of the infant reveals an afibrile patient with clear conjunctiva, watery nasal discharge and mild hypertelorism. Fluid obtained from the nares tests positive for Beta-2 transferrin.

Of the following, the MOST appropriate next step would be to:

1. attempt to pass a 6 French catheter through each naris
2. obtain head computed tomography and magnetic resonance imaging
3. start a trial of a topical vasoconstrictor to each naris
4. start a trial of dexamethasone ophthalmic drops to each naris
5. test the nasal discharge for the presence of glucose

You selected 5, the correct answer is 2.

Neonates are nasal breathers up to several months of age. As a result, anomalies or processes that cause nasal obstruction can present with significant respiratory distress, particularly if bilateral. Symptoms may be evident at birth with obstruction of airflow, minimal rhinorrhea, or a mucopurulent discharge secondary to mucostasis. Such symptoms may indicate a life-threatening disease or a transient, self-limiting process. In fact, some septal deformity may be evident on physical examination of up to 70% of newborns. Most infants with symptoms of pathologic significance present with stertor and grunting respirations, exacerbated by oral feeding. Maintenance of an adequate airway should precede any diagnostic evaluation.

Nasal obstruction may occur due to increased nasal secretions as a response of the nasal mucosa to a variety of stimuli, including infection. Anatomic blockage of the nasopharynx may cause obstruction with or without a nasal discharge.

The infant in the vignette presents with a mild nasal obstruction, exacerbated by feeding. The presence in the nasal fluid of Beta-2 transferrin, a protein produced by neuraminidase activity in the brain and uniquely found in cerebrospinal fluid (CSF), suggests a CSF leak, and the most appropriate next step would be to evaluate for the presence of an intranasal encephalocele by imaging with computed tomography (CT) to delineate a bony defect and magnetic resonance imaging (MRI) to depict the contents of a herniated mass.

An encephalocele is a rare congenital anomaly of the central nervous system in which intracranial contents, containing meninges, CSF, and neural tissue, protrude through a defect in the skull. The incidence of encephaloceles ranges from 1 in 3,000 live births in Southeast Asia, to 1 in 10,000 live births in North America.

Basal encephaloceles, comprising 5% of all encephaloceles, result from a defect in the floor of the anterior fossa and appear in the nasal cavity, nasopharynx, or posterior aspect of the orbit (Figure 1). Associated findings include hypertelorism, cleft lip and palate, and optic and cerebral anomalies. Though the lesion may present in later childhood with recurrent meningitis, in infancy, symptoms typically relate to obstruction of the nasopharyngeal airspace and may be complicated by spontaneous or trauma-induced CSF rhinorrhea.

Glucose is present in CSF, but its finding in nasal secretions is nonspecific as lesser amounts may be found in the nasal secretions from infectious rhinitis or lacrimal secretions. More
specific for CSF is the presence of Beta-2 transferrin. Intranasal examination often reveals a bluish compressible mass, differentiated from a nasal polyp by its pulsating and transilluminating nature, and midline position.

Passage of a catheter through the nasopharynx could cause neural tissue injury or increase the risk for meningitis, and it would not be indicated in the presence of CSF rhinorrhea. The timing of repair of a basal encephalocele varies, with respiratory distress, CSF leak, and risk of meningitis warranting early surgery. The long-term prognosis varies with the location of the lesion and the presence of associated anomalies.

Other nasal anatomic abnormalities causing nasal obstruction in the neonate include choanal atresia, piriform aperture stenosis, congenital cysts, and traumatic nasal septal deformities. Bilateral choanal atresia presents with immediate respiratory distress, while unilateral lesions often present with mucoid rhinorrhea. Traumatic septal deformities may occur in utero as a result of fetal head presentation, or during vaginal delivery, with or without forceps. Diagnosis is suspected with failure to pass a 6 French catheter through the nasopharynx. Choanal stenosis, or narrowing to less than 6mm, also may present with obstruction and difficulty in passing a catheter. Axial CT is the study of choice to delineate the atresia.

Infectious causes of neonatal rhinitis include *Chlamydia trachomatis* and congenital syphilis. Although inclusion conjunctivitis is the commonest manifestation of perinatally acquired *Chlamydia* from colonized mothers, the organism's predilection for columnar epithelium can cause widespread infection of the respiratory tract. While nasopharyngeal infection can occur in the absence of overt conjunctivitis, chlamydial rhinitis should be suspected in the newborn older than 1 week who develops a mucopurulent nasal discharge preceded by conjunctivitis. Current erythromycin ophthalmic prophylaxis at birth does not eliminate nasopharyngeal carriage of *Chlamydia*, and oral erythromycin for 14 days remains the treatment of choice for nasopharyngeal eradication.

Congenital syphilis results from intrauterine transmission of the spirochete, occurring in up to 70% of untreated infected mothers. Symptoms usually appear in the first week after birth, and in as many as 50%, include a thin watery nasal discharge that becomes mucopurulent and sometimes bloody. Without treatment, ulceration of the nasal cartilage with ensuing chondritis and necrosis occurs, leading to the characteristic saddle-nose deformity. Marked nasal obstruction may result from the rhinorrhea, leading to the noisy breathing or “snuffles.” Additional findings include a flattened nasal dorsum, frontal bossing, anemia, hepatosplenomegaly and a rash involving the palms and soles, usually appearing one to two weeks after the rhinitis. Diagnostic tests include serologic titers, CSF analysis, and long bone radiography. Penicillin remains the treatment of choice.

Neonatal rhinitis, characterized by mucoid rhinorrhea and nasal mucosal edema in the afebrile newborn, may result in stertor, poor feeding, sleep disturbance, and respiratory distress. Symptoms typically develop around 3 to 6 weeks after birth and resolve by age 6 months. Diagnosis is made by exclusion of infection or anatomic obstruction and a prompt response to nasal dexamethasone, usually within the first week of treatment. Gentle bulb suctioning and nasal saline drops provide some benefit, while prolonged use of topical vasoconstrictors can lead to rhinitis medicamentosa.

References:


Hospital for Sick Children, Toronto. Figure 1: Intranasal basal encephalocele. Geneva Foundation for Medical Education and Research Web site. Available online. Accessed September 9, 2005

Nandapalan V, Watson ID, Swift AC. Beta-2-transferrin and cerebrospinal fluid rhinorrhea. Clin
Content specifications:

Know the etiology, differential diagnosis and management of nasal discharge in a newborn infant

Understand the clinical and radiographic findings of myelomeningocele and encephalocele
Intranasal basal encephalocele