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Briefly Legal: Tachycardia Mistakenly Attributed to Caffeine Instead of Late-Onset Group B Streptococcus

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The patient is an 18-year-old primigravida with a prenatal course complicated by the use of cocaine. She presented to the hospital in threatened preterm labor at 28 4/7 weeks with unknown Group B Streptococcus (GBS) status. On admission, she had uterine contractions and a questionable rupture of membranes with a 6 cm dilated cervix. Over three days, she was given tocolytics, a full course of steroids, and penicillin G q 4 h until delivery. Despite these efforts, three days after admission, she delivered vaginally.

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At birth, the infant was a vigorous, appropriately grown male who weighed 1350 grams (AGA) and received Apgar scores of 9 and 9 at 1 and 5 minutes of life. Except for moderate respiratory distress, the physical examination was normal. A complete blood count (CBC) was unremarkable. Ampicillin and gentamycin were administered for 72 hours but were discontinued when the blood culture was negative. A chest radiograph was consistent with respiratory distress syndrome (RDS). The infant received surfactant replacement once. He transitioned to nasal continuous positive pressure (NCPAP) within the first few days and was placed on a standard dose of caffeine, initially intravenously and then orally, to reduce the frequency of potential apneic episodes. A percutaneous central line was placed shortly after birth, and parenteral nutrition was provided. At ten days, trophic feeds with breast milk began and were gradually increased. At seven days of age, a cranial ultrasound at seven days was normal. Following caffeine, the infant's baseline heart rates were consistently about 160 bpm, about 10–15 bpm higher than his pre-caffeine baseline.

For the first three weeks, the baby's course was stable with the continuation of the caffeine. On day 20, the infant developed increased work of breathing with intermittent high heart rates averaging 180 bpm, with many reaching or exceeding 200 bpm. Blood pressure and the physical exam, however, remained normal. Although these heart rates represented an increase over the rates seen during the first week of caffeine administration, the further elevation of the heart rate was, nevertheless, attributed to the ongoing caffeine administration. The infant did not receive an evaluation for these increased heart rates.

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On the cusp of day 22, the baby became lethargic, mottled, and had multiple episodes of apnea, desaturation, and profound hypotension. A CBC, blood culture, and arterial blood gas were drawn. The blood gas showed a pH of 6.82, a $pC0_2$ of 183 mmHg, a $p0_2$ of 48 mmHg, and a base excess of -13.2. The baby was intubated and placed on a high-frequency oscillatory ventilator with 100% inspired oxygen. Vancomycin and cefotaxime were started. Multiple boluses of normal saline and pressors were administered for the assumed diagnosis of septic shock. Within 24 hours, the blood culture was positive for Group B Streptococcus (GBS). The Mother's breast milk was not tested for GBS. On therapy, the

baby's condition gradually stabilized; a lumbar puncture done on day 23 was unremarkable. A repeat cranial ultrasound a month after birth (8 days after the episode of septic shock) now showed periventricular leukomalacia. The magnetic resonance imaging (MRI) done at the time of discharge at three months showed massive, diffuse encephalomalacia.

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On follow-up, the child has cerebral palsy and severe neurodevelopmental impairment. The hospital and neonatologist were sued because of a lack of recognition and evaluation of the neonate's tachycardia.

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Plaintiff allegations:

- The nurses and neonatologists failed to timely recognize, interpret and respond to the infant's tachycardia and subsequent respiratory difficulties.
- A CBC, C-reactive protein, blood, urine, cerebral spinal fluid cultures, blood gases, and a complete physical evaluation should have been performed when increased work of breathing and the new higher levels of heart rate developed.
- Failure to properly and timely respond to the baby's condition resulted in profound hypotension and acidosis in the face of infection that caused brain damage.
- A proper and timely response to the changes in the baby's condition would have prevented the serious, permanent neurological consequences.
- If the further rise in heart rate (tachycardia significantly above what had become baseline secondary to the caffeine) had been appreciated and a proper evaluation been performed in a timely manner on days 20–21, the baby would not have developed septic shock from the GBS.

Defense position:

- It was clinically acceptable that nurses and physicians assumed that the tachycardia was secondary to caffeine and maintained that the rest of the physical examination was documented as normal.
- The adverse outcome was secondary to prematurity
- Premature infants are more susceptible to infection.

Discussion

"Group B Streptococcus (GBS) colonizes the vagina and vaginal/rectal areas of 10%–30% of pregnant women. GBS is a significant cause of neonatal and infant infection, with high mortality and morbidity rates. Late-onset neonatal GBS disease (LOGBS) occurs 7–89 days after birth. The incubation period in LOGBS is unknown."

General:

Group B Streptococcus (GBS), or *Streptococcus agalactiae*, colonizes the vagina and vaginal/rectal areas of 10%–30% of pregnant women. GBS is a significant cause of neonatal and infant infection, with high mortality and morbidity rates. Late-onset neonatal GBS disease (LOGBS) occurs 7–89 days after birth. The incubation period in LOGBS is unknown.

"Transmission routes are poorly understood in LOGBS...Colonization acquired during birth can be confirmed up to one year of age...Vertical transmission, however, cannot account for all cases of LOGBS since intrapartum antibiotic prophylaxis (IAP), known to prevent early colonization at birth, had no effects on incidence rates of GBS. IAP may delay LOGBS or reduce its severity, probably by preventing early neonatal colonization at birth and shifting the mode of acquisition of GBS from vertical to horizontal. IAP does not eradicate colonization in the mother, who may remain a postnatal source of GBS..."

Transmission and Risk Factors

Transmission routes are poorly understood in LOGBS but can result from neonatal colonization acquired during passage through the birth canal. Colonization acquired during birth can be confirmed up to one year of age. In a sentinel study, 48% of infants were colonized at birth with the same GBS serotype that subsequently caused LOGBS. Vertical transmission, however, cannot account for all cases of LOGBS since intrapartum antibiotic prophylaxis (IAP), known to prevent early colonization at birth, had no effects on incidence rates of GBS. IAP may delay LOGBS or reduce its severity, probably by preventing early neonatal colonization at birth and shifting the mode of acquisition of GBS from vertical to horizontal. IAP does not eradicate colonization in the mother, who may remain a postnatal source of GBS for the newborn and subsequent pregnancies. Although still under debate, GBS-contaminated breast milk, with or without mastitis, has been associated with heavy neonatal colonization and LOGBS. However, most breastfed infants do not develop LOGBS, as up to 3.5% of breastfeeding mothers carry GBS in their milk. In approximately 1/3 of cases, LOGBS is acquired from non-maternal sources (caregivers and healthcare workers). Such nosocomial transmission of GBS from non-maternal sources is more common in preterm than term infants, undoubtedly secondary to their compromised immune systems and prolonged hospital stays. Approximately 40% of all LOGBS now affect preterm infants under 37 weeks gestation. Preterm infants have a case fatality rate twice that of full-term infants, 7.8% v. 3.4%. Hospital clusters of GBS have been associated with crowding, high patient-to-nurse ratio, and inadequate disinfection practices.

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Presentation:

Typically, LOGBS begins at 3–4 weeks of age. Some presenting signs (apnea, tachycardia, poor feeding) are common in younger preterm infants and overlap with other disorders. LOGBS must be considered in any in-hospital neonate with such clinical issues. A single case of LOGBS identified should be considered secondary to potential nosocomial transmission, and both retrospective and prospective surveillance should be enhanced to identify any possible cluster. Approximately 30% of LOGBS involve meningitis, but other sites such as bone, soft tissue, urinary tract, or lungs may also produce focal infections.

Early recognition of clinical signs, rapid evaluation, and prompt initiation of treatment are crucial to optimize outcomes. Newer approaches to help with early recognition of infection in the NICU include evaluating beat-to-beat HR monitoring. While this is appealing and could add another dimension for a more proactive approach, there is an ongoing need to emphasize dedicated attention to clinical/vital signs changes, as illustrated in the above case.

Prevention:

Since LOGBS is primarily attributed to nosocomial or horizontal pathogen acquisition from the hospital or community environments, impeccable technique is critical in handling indwelling or invasive catheters, in contact with care providers and/or other environmental sources and surfaces. Preventive measures include hand hygiene, strict adherence to infection control protocols, and implementation of antimicrobial programs that promote collaboration between the prescribing clinicians, infection disease specialists, and pharmacists.

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A promising strategy to reduce antibiotic use and to prevent both early- and late-onset GBS infections is the vaccination of pregnant women in the second or third trimester. The vaccination would confer passive immunity to the newborn for up to 3 months of life through the transplacental transfer of IgG antibodies. Vaccination strategy may be less effective in protecting very preterm neonates from LOGBS because the transplacental transfer of antibodies mainly occurs after 34 weeks gestation.

Treatment:

In addition to hemodynamic stabilization and other supportive interventions, the appropriate antibiotic choice is essential. Ampicillin and gentamicin are recommended. High doses of Ampicillin plus cefotaxime should be used in case of suspected meningitis.

Ten–14 days of intravenous antibiotics are suggested for sepsis without a focus or uncomplicated by meningitis. Current guidelines recommend 3 to 4 weeks to treat septic arthritis or osteomyelitis. Routine administration of polyvalent intravenous immunoglobulin (IVIG) is not recommended. For late-onset GBS infants 8–28 days of age, if the infant is not critically ill and has no evidence of meningitis, Ampicillin plus either gentamicin or cefotaxime is adequate. If meningitis is suspected, Ampicillin plus cefotaxime,

not gentamicin, should be used. For infants 29–90 days of age, ceftriaxone is recommended. If evidence of meningitis or critical illness exists, vancomycin should be added to expand empiric coverage.

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Summary:

Preterm infants are at particularly high risk for life-long morbidities and death. Since the clinical presentation of late-onset GBS is varied and nonspecific, the clinician must be vigilant for abnormalities or changes in clinical conditions. Assuming the tachycardia was secondary to caffeine, although the high heart rates exceeded the levels during earlier caffeine administration, caused a delay in evaluation and intervention at the early stage of late-onset GBS. Prompt attention to clinical signals emanating from the baby is critical to timely intervention and preventing serious consequences.

Suggested Reading:

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