A Prolonged Treatment Associated With Absent Septum Pellucidum in Neonatal Abstinence Syndrome: A Case Report

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Neonatal abstinence syndrome (NAS) involves a widely variable treatment course among affected individuals. Prognostic indicators that would help predict length of hospital stay and individualize treatment would be valuable to newborns, parents, and hospital staff, including advanced practice registered nurses. We describe a newborn with a prolonged NAS treatment course necessitating high doses of opioids and phenobarbital, found to have an isolated absent septum pellucidum (ASP). We hypothesize a mechanism for an association between an ASP and a difficult NAS treatment course. Should this be substantiated by other cases, it could provide a valuable prognosticator and indicate alternate treatment pathways. J Pediatr Health Care. (2023) *XX*, 1−4

KEY WORDS

Neonatal abstinence syndrome, septum pellucidum, opioid, NICU, case report

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INTRODUCTION

Neonatal abstinence syndrome (NAS) can occur in 60% to 80% of newborns exposed to drugs of dependence in utero (Grisham et al., 2019). The onset of NAS can range from 1 to 4 days of life, depending on the extent and timing of drug exposure (MacMillan, 2019). Infants with NAS frequently require neonatal intensive care unit (NICU) admission and generally have a long hospital course, but the length of stay varies widely (Grossman & Berkwitt, 2019). NAS symptoms can involve multiple organ systems, including neurological (irritability, tremors, hypertonicity, high-pitched or excessive cry, seizures), gastrointestinal (poor feeding, vomiting, diarrhea, excessive sucking), and autonomic (fever, sweating, tachypnea; Grisham et al., 2019; MacMillan, 2019). Children with a history of NAS are also at higher risk for developmental and language delay, behavioral problems and executive function issues (MacMillan, 2019). Although the pathophysiology of NAS is unknown, hypotheses include increased norepinephrine and hypothalamic-pituitary-adrenocortical activation causing increased stress and reactivity, acetylcholine and glutamate action on gastrointestinal receptors, and decreased dopamine and serotonin which interferes with pleasure and sleep, respectively (MacMillan, 2019).

In assessing and managing NAS, the Eat, Sleep, Console (ESC) approach is often used for its ease of use and focus on functionality: being able to take more than 1 oz/feed (yes/no), sleep undisturbed for more than 1 hr (yes/no), and whether the infant can be consoled within 10 min giving preference to nonpharmacological interventions (yes/no plus a score of one for mild support required, two for moderate support required, and three for inability to console within 10 min; Grisham et al., 2019). When pharmacological interventions are indicated, the first-line agent is usually an opioid agonist such as morphine or methadone, and if the NAS symptoms are hard to control, a secondary agent is often selected, such as phenobarbital or clonidine (MacMillan, 2019). Although benzodiazepines act on similar receptors as phenobarbital, these are not efficacious for NAS and thus are not commonly used (Osborn, Jeffery, & Cole, 2010).

Of note, there are sometimes institutional differences in NAS protocols—at our institution, we use ESC and monitor for 5 days if there is a known exposure; if an infant is asymptomatic, they can be discharged home, whereas if they are symptomatic, they will undergo nonpharmacological intervention, followed by pharmacological intervention if necessary. Urine and meconium testing is performed to help guide treatment, though a positive test will not necessarily mandate treatment in the absence of symptoms (Singh, 2019). Other institutions use scales such as the Finnegan Neonatal Abstinence Scoring System (Finnegan et al., 1975) and use urine and meconium testing to determine the length of observation (e.g., 3 days for short-acting substances such as hydrocodone and 5−7 days for a long-acting substance such as methadone; Brigham and Women's, 2015).

A large challenge of NAS for advanced practice registered nurses, particularly certified nurse practitioners caring for neonates, lies in the inability to predict the length of stay for infants and individualize management plans. An objective marker that helps stratify patients into different care plans would be valuable. Here, we present a case of a NAS infant with brain abnormalities noted on imaging; these abnormalities may, with further study, serve as such a marker.

CASE PRESENTATION

This report was drafted in accordance with the CAre REport Guidelines (Rison, Kidd, & Koch, 2013).

A male infant was born at 39 weeks 4 days gestation via primary Cesarean section to a 24-year-old primigravida mother. Prenatal laboratories were notable for the following: blood type A positive; rubella immune; and hepatitis B, human immunodeficiency virus, syphilis, gonorrhea and chlamydia serologies negative. Maternal medical history was significant for hepatitis C, seasonal allergies, anxiety, depression, posttraumatic stress disorder, tobacco use, marijuana use, and heroin and cocaine abuse, and she was currently on methadone maintenance.

The pregnancy was complicated by late establishment of prenatal care, intrauterine growth restriction, and substance use during pregnancy. The mother's last cocaine use was 6 months before delivery, and she had reported regular heroin use throughout her pregnancy, with adjustments in her methadone dose. Urine toxicology 4 months before delivery was positive for marijuana, methadone and opiates, and repeat urine toxicology on the day of delivery was positive for opiates. In addition, prenatal ultrasound showed fetal liver calcifications and mild intracranial ventriculomegaly, though subsequent fetal brain magnetic resonance imaging was unremarkable.

Labor was induced at 39 weeks and 4 days because of anhydramnios and intrauterine growth restriction. Delivery was converted to Cesarean section because of a nonreassuring fetal heart tracing. The NICU team was called for a high-risk delivery, but the baby was alert and vigorous, with an Apgar score of 9, 9, and 9 at 1, 5, and 10 min, respectively. He was brought to the newborn nursery for routine care. Because the infant was small for gestational age, he was monitored for hypoglycemia and tested for cytomegalovirus. He was placed on the ESC protocol (Grossman et al., 2018) because of maternal opiate abuse and concern for NAS for a 5-day observation. He required multiple glucose gels because of hypoglycemia, but his blood glucose normalized by day of life two. Cytomegalovirus was not detected, and bilirubin and newborn screen were within normal limits.

On his fifth day of life, he began to show increasing signs of withdrawal, including sneezing, tremors, increased tone, and inconsolability. He was taken into emergency custody by the state because of maternal drug use and was admitted to the NICU on that day to manage NAS. Infant meconium was positive for opiates, and he was started on the institutional NAS protocol with morphine, 0.05 mg/kg every 3 hr as needed (Jansson, Velez, & Harrow, 2009; Singh, 2019). After receiving six doses of morphine within 24 hr, he was placed on a scheduled dose of morphine (0.48 mg/kg/day divided every 3 hr) and clonidine (8 μg/kg/day divided every 6 hr). Because of continued positive scores on the ESC protocol as outlined above, he received escalating doses of morphine to 0.96 mg/kg/day and clonidine, 12 μg/kg/day.

On his 12th day of life, because of continued positive scores on ESC, clonidine was weaned by half for 24 hr, then discontinued (Leikin et al., 2009; Singh, 2019), and phenobarbital was started at a dose of 5 mg/kg/day. By his 35th day of life, his phenobarbital had increased to 8 mg/kg/day divided every 12 hr. Because of continued NAS symptoms and inability to wean morphine, as well as marked tremulousness and hypertonia on examination, a head ultrasound was performed to identify other potential causes of neuroinstability and revealed an absent septum pellucidum (ASP) with intact corpus callosum (the meaning and relevance of this finding to NAS is discussed further in the following section). A subsequent magnetic resonance imaging confirmed ASP without associated defects, and an ophthalmoscopic examination revealed no ocular abnormality. An ultrasound of the liver was performed because of prenatal liver calcifications, which were not present at the time of examination. He was slowly weaned off morphine at a rate of 0.02 mg/day

after 24 hr of negative ESC scores, with progress impeded by frequent hypertonicity and inconsolability that necessitated delaying weans. He received his last dose of morphine on his 63rd day of life. He was discharged to foster care on day 65 of life on phenobarbital, 8 mg/kg/day divided every 12 hr. Follow-up plans for neurology and developmental medicine were scheduled. An early intervention referral was made, and a weaning schedule off phenobarbital was planned over a month.

DISCUSSION

NAS has increased in recent years (Grossman & Berkwitt, 2019), consistent with the prevalence of opioid abuse (Cox & Naegle, 2019). Treatment length varies widely, with one study reporting a 1−122 day variance (Seligman et al., 2008). Given this variation, it would be useful to have prognostic indicators for the length of treatment to set both parental and hospital expectations. Factors currently associated with a longer treatment course include later gestational age, concomitant maternal benzodiazepine use (Seligman et al., 2008), and maternal methadone use instead of buprenorphine use (Grossman et al., 2017). There is growing evidence that genetic and epigenetic factors also play a significant role in NAS severity (Wachman & Farrer, 2019). It is important to note that nonpharmacologic intervention and rooming-in with parents can shorten the length of stay (MacMillan et al., 2018; MacMillan, 2019), although sadly, comorbid medical conditions and emergency custody of newborns by state entities can necessitate separation.

For this patient, an ASP may have contributed to his extended stay. ASP is associated with several midline defects, including the absence of the corpus callosum, pituitary abnormalities, and septo-optic dysplasia (Krause-Brucker & Gardner, 1980; Pugash et al., 2013; Sundarakumar et al., 2015; Williams et al., 1993), and in the most serious case holoprosencephaly (Barkovich & Norman, 1989). Our patient had none of these associated abnormalities, and an isolated ASP is normally associated with a benign outcome (Vawter-Lee et al., 2018; Winter et al., 2010), although it is worth noting that the odds ratio of an ASP in mood and psychotic disorders has been found to be significantly elevated at 2.1 (Landin-Romero et al., 2016). Regardless, some minor brain anomalies may occur, such as displacement of the fornix because of the lack of tethering effect of the septum (Barkovich & Norman, 1989).

An important consideration in ASP is the effect on the presence and connection of the septal nuclei in the septum verum inferior to the septum pellucidum (Barkovich & Norman, 1989). These nuclei contain afferents from areas such as the periaqueductal gray (which is heavily involved in pain), locus coeruleus, ventral tegmental area, and raphe nuclei, as well as efferents to the thalamus, hypothalamus, hippocampus, and forebrain (Cavazos et al., 1997). Lesions to the septal area have been associated with hyperreactivity in various animal species, inducing what has been termed a "septal rage" that has lasted variable periods but does not appear to be permanent (it should be noted, however, that perioperative conditions also played a role in the induction of this hyperreactivity; Fried, 1973). There has also been evidence for sensory hyperreactivity (Caplan, 1973), which could contribute to more difficulty consoling a newborn. Perhaps more apropos is a study in rats that demonstrated decreased sensitization to morphine with septal lesions compared with those without (Liu et al., 2012). Although the long-term effects on susceptibility to addiction are unclear, such an effect may contribute to the need for high quantities of morphine, as was seen in our patient.

It is not clear that the septal nuclei themselves were damaged in our patient with an isolated ASP. However, as the septum pellucidum is known to carry nerve fibers and vasculature (Sarwar, 1989), connections to and from the septal nuclei may be disrupted, creating a hyperreactive state that may or may not be less responsive to agents such as morphine. Should this be supported by further evidence, it may warrant routine head imaging (such as an ultrasound, with subsequent magnetic resonance imaging if abnormal) in those infants less responsive to typical NAS treatment and altered NAS management in those with identified ASP. In addition to setting expectations for a longer hospital stay, treatment modifications could include choosing a weaning agent other than morphine (such as methadone or buprenorphine [Disher et al., 2019]), or a lower threshold for adjuvant treatment. Perhaps more importantly for providers, including advanced practice registered nurses, nonpharmacological intervention could be given greater priority, including minimizing parent-infant separation and prioritizing rooming-in or the presence of a babysitter to provide bonding and comfort for emergency custody by state agencies. Regardless, it will be important to follow these patients longitudinally for both neurodevelopmental and psychological/emotional outcomes.

Unfortunately, there are many limitations to testing the causality of an ASP with the length of NAS treatment. NAS necessarily involves a confluence of physical, psychological, and social factors that all adversely affect a newborn. In addition, the exact prevalence of ASP is uncertain, particularly in neonates who did not receive head imaging. However, a larger retrospective observational study, either within a hospital system or multisite, examining the length of stay and ESC scores in children with an ASP compared with those with an intact septum may shed further light on the effects of this phenomenon.

In conclusion, we have reported on an infant with a severe NAS that was refractory to first-line treatment and required additional pharmacological intervention. Imaging revealed an ASP, which may be related to the increased severity of illness by its effect on the septal nuclei and its connections. Should this be substantiated, it may provide valuable clinical information for advanced practice registered nurses, particularly nurse practitioners, to tailor the management of this increasingly common illness.

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