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Neonatal Abstinence Syndrome (NAS) in Appalachia: Changing Trends, Clinical Presentation and Management of NAS

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Review Article

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Abstract

Neonatal abstinence syndrome is a significant and rapidly growing public health concern in Appalachia. In 2017, 1090 cases of NAS were reported to the State of Tennessee surveillance program. The incidence of NAS in Tennessee since early 2000s has increased 10-fold, while the national average over the same time period has only increased 3-fold, with the highest rate of increase between 2000-2012. Currently, buprenorphine is a predominant drug of opioid exposure in our region. In this review article, authors describe the incidence of NAS, changing trends, clinical presentation, management protocols and long-term outcomes of infants exposed to buprenorphine. We reviewed the literature, in terms of clinical presentation, changing trends in drug use in pregnancy and choice of drugs available for the management of NAS.

Keywords: Neonatal Abstinence Syndrome; Polymerase Chain Reaction; Symptoms; Psychotropic; Gastrointestinal

Abbreviations: NAS: Neonatal Abstinence Syndrome; SIDS: Sudden Infant Death Syndrome; EEG: Electroencephalogram; NICU: Neonatal Intensive Care Unit; PCR: Polymerase Chain Reaction; PSW: Positive Slow Wave Response; MDI: Mental Development Index.

Introduction

Neonatal Abstinence Syndrome (NAS) is a clinical presentation in newborn infants who exhibit signs and symptoms of withdrawal from substances they were exposed to in utero. Sudden discontinuation of substances taken in pregnancy leads to a constellation of symptoms in newborn infants. It is a generalized disorder with multi system involvement. Symptoms typically start within the first 5 days of life and affects 75-90% of exposed infant [1].

The diagnosis is made clinically by signs and symptoms of withdrawal, with measure of withdrawal severity assessed by the modified Finnegan scoring system. The bulk of withdrawal is related to opiate exposure. Opiates are lipophilic molecules that can cross the placenta as well as the blood brain barrier. Potential risk factors for increased severity of NAS are male gender, polysubstance use, benzodiazepine use, concomitant use of antidepressants, antipsychotic medications, and anti-anxiety medications. Use of psychotropic medications for control of anxiety, depression, and bipolar disorders has increased over the last decade. SSRI, tricyclic anti-depressants, and benzodiazepine exposure make the presentation and management of NAS more complex [2,3]. Of the opiates, methadone was the most common drug of exposure up until 2009. Currently buprenorphine use in pregnancy is the most common drug leading to neonatal abstinence syndrome in Northeast Tennessee and Southwest Virginia. Buprenorphine is a partial μ-opioid agonist, with 25-40x the analgesic effects of Morphine. It was approved in 2002 as a schedule III-controlled substance for the treatment of opioid dependence. Buprenorphine is utilized

for maternal opiate dependence during pregnancy; however, neither methadone nor buprenorphine is approved for use in pregnancy. Buprenorphine is categorized by the FDA as a class C pregnancy drug.

Diagnosis and Clinical Presentation

A diagnosis of NAS can be confirmed with the following criteria: clinical presentation of signs and symptoms of withdrawal with NAS scores over ten, history of maternal use of opioids or laboratory confirmation of maternal narcotic use that may include toxicology testing or severity of illness requiring prolonged hospital stay [4]. There are many scoring systems, however most hospitals follow a modified Finnegan scoring system for calculating NAS scores. Unfortunately, it is not a perfect system and results can depend on nurse training and experience. In our institution, two reliable and certified nurse's score the infant and compare results, which helps to decrease subjectivity. Modified Finnegan scoring scale is a measure of 21 potential signs of symptoms of withdrawal, including dysregulation of the central nervous system, autonomic and gastrointestinal systems. These include tremors, irritability, jitteriness, seizures, excessive crying, sneezing, sweating, skin mottling, diarrhea, and vomiting [5].

The predominant symptoms are neurological including: irritability, hypertonicity, agitation, sleeplessness, uncontrollable crying, and high-pitched cry. Infants may also have an exaggerated Moro reflex or myoclonic jerks. Interestingly, the dose of maternal opiates does not directly correlate with the severity of withdrawal in the neonate [6]. Preterm infants have been documented as having less severe symptoms of withdrawal; this is attributed to decrease in cumulative exposure, immature liver and kidney functions, decreased fatty tissue, and decreased trans-placental passage of the drugs, and decreased receptor development and sensitivity [7]. Tachypnea and nasal flaring with associated nasal stuffiness may mimic transient tachypnea of newborn or respiratory distress syndrome. Hyperthermia may be misdiagnosed as possible sepsis. Gastrointestinal symptoms of emesis and diarrhea could lead to dehydration and electrolyte imbalance. NAS is generally not fatal; however, some infants may have unusual presentations with apneas, respiratory distress, or seizures. If they are not identified or if they get discharged too early, they are at potential risk of SIDS.

SIDS(Sudden Infant Death Syndrome)

Maguire DJ, et al. [1] discussed that an increased risk of SIDS could be correlated with Buprenorphine exposure, although almost all of the moms in the study also smoked tobacco, so the effect of Buprenorphine exposure alone is difficult to extrapolate [1]. Cohen and associates reported a study where autopsy was done on 138 infants who died before the day 28 of life. 32 infants died of sudden death.8 37.5% of these had exposure to methadone or other drugs of use with symptoms of withdrawal. However, history of smoking, prematurity and inappropriate sleeping environment may have contributed to the increase in incidence of SIDS among these infants. Additional studies are needed at this time to determine the correlation begin opiate-exposure in utero and risk of SIDS.

Incidence

The incidence of NAS in the United States increased nearly five-fold between 2000 and 2012 from a rate of 1.2 per 1000 hospital birth per year in 2002 to 5.8 per 1000 hospital births in 2012. A total of 21,732 infants were diagnosed with NAS in that year [5] this is equivalent to one infant born with NAS every 25 minutes. As a result of the opioid epidemic, in 2013 Tennessee became the first state in the nation to mandate NAS as a reportable disease. The incidence of NAS in TN since early 2000s has increased 10-fold, while the national average over the same time period has only increased 3-fold, with the highest rate of increase between 2000-2012 [6]. In 2017 alone, 1090 cases were reported to the state surveillance portal. This represents 1.35% of all live births in the state, which is an increase of 15.4% since 2013 [7]. The highest rates within the state are in the NE region of TN, with 66% of cases being in Northern and Northeastern Tennessee [8] (Figure 1).

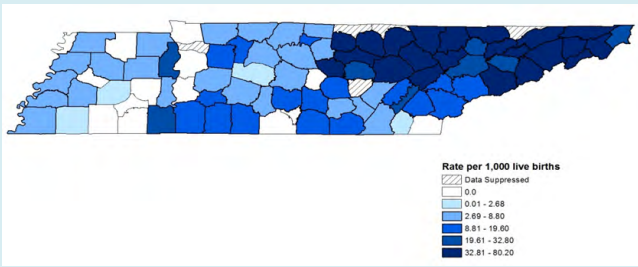

Figure 1: Rate of NAS Cases in Tennessee by County, 2017 [9].

NAS has become an epidemic in the Northeast Tennessee region of Appalachia. There are many counties within the Appalachia region with NAS rates as high as 10x the national average, with rates over 60/1,000 live births [9]. In addition, the hospitalization rates for infants diagnosed with NAS have increased 15-fold from 2000-2012. From 2001-2009, 2.5% of our hospital's NICU admissions were related to NAS. From 2015-2017, almost 1/3 of NICU patients had a primary or secondary diagnosis of NAS. The average length of stay for infants with NAS is 19 days (range 5-54 days). The cost of NICU care for such infant in 2009 was already over $40,000.

Pathophysiology

Opioid receptors are located throughout the body in various tissues including brain, peripheral neural tissues and gastrointestinal tract. There is a propensity and affinity of μ receptors in newborn brain similar to that of adults. Opioid medications attach to neuronal cells and inhibit transmission of acetylcholine, serotonin and catecholamines. Withdrawal from opioids causes increased production of norepinephrine, a chemical predominantly responsible for most of the signs of neonatal abstinence syndrome. Decreased serotonin levels leads to sleep deprivation and sleep fragmentation. Opioid deficits are followed by increased production of acetylcholine, which presents with diarrhea, sneezing, excessive yawning, sweating and emesis. These symptoms may lead to electrolyte imbalance and dehydration.

Management of NAS

Treatment of NAS consists of both pharmacological and non-pharmacological measures. The American academy of pediatrics recommends early initiation of non-pharmacological therapy followed by pharmacological therapy after reaching a set threshold, encouraging breast-feeding if no concomitant cocaine or amphetamine use and ensure long-term follow-up [5]. There is no consensus about the use of adjunctive therapy for NAS. Traditional pharmacological replacement for heroin withdrawal in the past has been tincture of opium, paregoric, phenobarbital and chlorpromazine. There is still no standard for pharmacological treatment of NAS although morphine replacement appears to be the most commonly prescribed medication for NAS. The goal for effective treatment of NAS include appropriate and frequent feeding, attaining good weight gain, prevention of seizures and other comorbidities, improved parental and family interaction, reduced incidence of sudden infant death syndrome, reduced infant mortality and providing early intervention and developmental screening after discharge from the hospital.

The crux of the management of NAS is a non-pharmacological therapy. These infants should be handled gently and maintained on a minimum stimulation protocol (clustering clinician's hands-on time and placement in a dark and quiet environment), swaddled and cuddled frequently and given frequent feedings. These infants may have an increased caloric requirement. Frequent use of pacifiers, sugar drops, massage therapy and kangaroo care is helpful. In our NICU we seek the help of parents, grandparents, volunteers and cuddlers. Due to such a high prevalence in our region and importance of non-pharmacological care, we have established a special NICU wing where the parents are able to room in with their babies. We focus on providing multi-disciplinary care to the infant and support for the family. This gives an opportunity to supervise the parental skills to manage NAS and to provide social support to the families. There is a growing body of literature that supports breast-feeding while the infants are on methadone or morphine therapy for NAS [10]. Breast-feeding with NAS is associated with improved parental bonding and is associated with shorter stay in the neonatal ICU. In our study, conducted at Johnson City Medical Center, the formula fed infants were significantly more likely to require opiate replacement than the breast-fed infants. The relapse rate of NAS after discontinuation of opiate replacement was higher in formula fed babies. The length of stay was significantly longer in formula fed infants compared to breast fed infants regardless of gestational age (10.6 days vs. 13.8 days) [10]. However, breastfeeding may not be recommended with continued maternal exposure to cocaine, amphetamines or other street drugs.

When there is not enough improvement with supportive care alone, and NAS scores remain elevated, medical therapy is initiated. Our current therapeutic drug of choice is morphine. We start oral morphine at 0.08 milligram/kilograms per dose q.3 hours. The dose is increased gradually to a maximum of 0.15 milligrams/kilogram per dose if symptoms do not improve. Morphine is typically initiated with two subsequent scores over ten. When the NAS score is eight or less, morphine is gradually tapered every day or every other day by 10-15%. If an infant has increasing NAS scores after termination of therapy, we initiate a rescue dose every three hours. Typically, the rescue dose is 10% higher than the last dose used at the termination of therapy. For infants that do not respond to morphine treatment, the second drug choice is methadone at 0.1 milligram per kg divided twice a day. Morphine is discontinued prior to starting methadone therapy. The maximum dose of methadone is 0.2 milligram per kg. Clonidine, an alpha-adrenergic receptor agonist, is used concomitantly in difficult to manage NAS infants. The initial dose is 1 microgram per kg per dose q 8 hours. In our experience phenobarbital has been ineffective in the management of NAS. We prefer not to use phenobarbital as an adjunctive therapy. Currently, we do not use buprenorphine for management of NAS, although recent studies have shown promising results with sublingual buprenorphine therapy. Further studies are required before it becomes an acceptable choice of medication for the management of NAS. Opioid antagonist are absolutely contraindicated and could potentially precipitate seizures.

Seizures have been reported in infants with neonatal abstinence syndrome. Exact etiology for withdrawal seizures is not known. Seizures can be seen in infants in the initial phase of presentation of NAS prior to starting medical therapy, during medical therapy, during weaning from medications or after termination of the medication. Because of high risk of

associated comorbidities and infections, a significant number of these infants may require workup that includes a short or long EEG, neuro imaging, and anti-seizure medications. In our practice, seizures without EEG association are observed clinically and generally no anti-seizure medications are given. The treatment with morphine or methadone may be indicated for routine management of NAS. Seizures could be subtle seizures, myoclonus, tonic posturing or tonic-clonic seizures. A lumbar puncture for CSF analysis is a common procedure done in the workup of generalized seizures. Herpes infection in neonates can present with seizures. Prior to confirmation of negative herpes by polymerase chain reaction (PCR), some of the infants may require acyclovir intravenously. Few of our infants with NAS and seizures in the NICU have had abnormal EEG. They required a combination of anti-seizure medications including phenobarbital, fosphenytoin, and levetiracetam. NAS seizures without EEG association have been managed with routine treatment of neonatal abstinence syndrome.

Changing Trends of NAS

A recent study by Hall E, et al. [11] evaluated 360 infants, treated with either traditional replacement or sublingual buprenorphine and evaluated the outcomes of duration of treatment and length of stay. Infants treated with sublingual buprenorphine had statistically significant decreased duration of treatment by three days and decreased by length of hospital stay by 2.8 days [11]. Kraft and associates studied buprenorphine for management of infants with NAS. 5.3 microgram per kg per dose of buprenorphine was used q 8 hours sublingually. The dose was increased by 25% until symptoms were controlled. The medication was weaned 10% every day as tolerated, and medication was stopped after reaching 10% of initial dose. Phenobarbital was added when buprenorphine was 60 microgram/kg per day. Buprenorphine therapy was associated with decreased length of stay (32 vs. 42 days in morphine group), shorter duration of treatment for NAS (23 vs. 38 days), and slightly higher need of phenobarbital [12].

Drug enforcement agency as well as Federal agents have raided several pain medicine clinics and medical practices in Tennessee, Florida, Maryland, as well as other states. Over 100 prescribers have been reprimanded for inappropriate prescriptions. In 2018, we are noticing a drop in NICU admissions with NAS. This could be multifactorial. Several newborn nurseries and physician practices are currently managing their NAS patients without a referral to the neonatal ICU. Some practices are using methadone as an outpatient therapy for NAS management. We assume that the overall number of buprenorphine prescriptions have decreased in our region. This has coincided with an increase in maternal use of amphetamines, cocaine, and synthetic marijuana. This change in maternal drug exposure is leading to lower number of infants identified with withdrawal symptoms. Even though these infants are not always getting admitted to the neonatal ICU, they remain at risk for long-term effects from intrauterine drug exposure.

Long Term Effects

Much is known in regard to the short-term effects in the neonatal period of how opiate withdrawal affects infants. Unfortunately, there is less known on how intrauterine drug exposure, specifically opiates, can affect these children in the future. Mechanisms for how opiate exposure in utero can affect the developing brain include alterations of neuronal apoptosis, dendritic morphogenesis and homeostasis of neurotransmitters [13]. There are currently no guidelines on obtaining routine neuroimaging in this population, although some institutions recommend head ultrasound or a magnetic resonant imaging of the head in infants with prenatal exposure to cocaine or amphetamines due to their vasoactive nature and potential for ischemic changes.

Clinical/Medical Outcomes

Longer-term clinical effects from opiate exposure in-utero include increased incidence of acute otitis media, potential vision changes and sleep disturbances [1]. Increased otitis media has been seen in infants born to mothers with methadone use [14]. Children who experience recurrent otitis media can subsequently develop language delay or hearing deficit. Studies have shown that this population has an increased prevalence of strabismus as well as. These problems persist at age five and are associated with long-term changes such as reduced visual acuity [15]. These changes in normal eye development can also affect long-term development including difficulty with hand-eye coordination and decreased visual-spatial organization ability [16]. These infants should also be screened for relative microcephaly [17].

School Performance

In school aged children, general pediatricians should be screening for school absence, failure and behavioural problems [16]. Children diagnosed with NAS as infants had poorer school performance demonstrated by lower mean test scores in third grade. Of note, the decline became more profound with increasing grade level [13]. This is significant because success in school as a child is a predictor for adult success. In one study, children with a previous diagnosis of NAS were tested on five different domains (reading, writing, numeracy, spelling and grammar/punctuation) and compared with age-matched peers. The study demonstrated that the children with a diagnosis of NAS performed poorer

on every domain and in every grade. By the 7th grade, 37.7% of NAS children were not meeting the minimum standard set by the region (compared to 14.5% of their age-matched peers). Results demonstrate overall poorer performance on standardized tests for kids with NAS, starting as early as age eight, with worsening function as they entered high school [14].

In a study done by Sunderlin WV, et al. [16] Buprenorphine exposed preschoolers ages 5-6 performed standardized neurodevelopment tests, including the WPPSI-R as well as MSCA exam. WPPSI-R tested two major areas: Performance and Verbal (Information, Comprehension, Arithmetic, Vocabulary, Similarities, Sentences). Performance was assessed with Object assembly, Geometric design, Block design, Mazes, Picture completion, Animal pegs. Verbal assessment evaluated General cognitive index, Verbal, Perceptual performance, Motor, Quantitative and Memory. Testing indicated decreased performance overall on both Performance and Verbal measures. Overall difficulties with executive functioning, planning, controlling impulses and adaptability was demonstrated. In addition, MSCA testing demonstrated decreased scoring in verbal and memory. This same group of opiate exposed children had lower scores for the full-scale IQ than average [16].

Effects on Development

Developmental screening should include assessing for delays of the child's motor function or cognitive function. Hunt concluded that infants exposed to opiates in utero had significantly lower scores on the Mental Development Index (MDI) at both 12 and 18 months [18]. EEG changes have been seen in opiate-exposed infants, demonstrating positive slow wave response (PSW), which acts as an indicator of working memory updating [19]. Motor delays, including inability to sit independently or crawl, were seen in 37.5% of opiate-exposed infants at the age of 9 months [20]. Other impairments include poor hand-eye coordination, visual-spatial ability and organization/planning [16].

Behavioural Changes

Buprenorphine exposure in utero has been associated with increased hyperactivity, impulsivity and problems with attention in 5-6 year old [16]. Questionnaires (Brown ADD and SDQ) were performed by both parents and teachers of the pre-school students. Interestingly, the parental results indicated no problems, but teacher evaluation indicated that the kids were both hyperactive and inattentive [16]. There has also been concern about the risk of drug abuse for in-utero drug exposed kids. At the time, the risk appears to be unknown [21].

Environmental Effects

Some of the problems may be attributed to environmental effects of growing up in a home with on-going substance abuse or other socioeconomic factors. One study demonstrated that placement of children into foster homes improved their intellectual and learning abilities, although their overall decreased performance on intelligence testing persisted [22]. However the rate of attention deficits was increased among both adopted and non-adopted children.16 Interestingly, children adopted into homes with a non-addicted caregiver were noted to have normal verbal IQ and learning scores, although all exposed children (both adopted and those who stayed with addicted parents) had reduced performance IQ.22 Drug-abusing parents reported significantly more physically abusive as well as neglectful behaviours [23]. Studies also indicate that these children have a three-fold increase in risk of child abuse if they continue to be raised by a drug-abusing caregiver [1]. This may be exacerbated by the fact that upon discharge, many infants with NAS may have persistent withdrawal manifesting as mild irritability, excessive cry and poor sleep patterns.

Why don't we Know More?

Despite the importance of these long-term outcomes of this unique population, it is unfortunately a difficult population to obtain data on. This is due to the inherent nature of confounding factors in a drug-using population, including poverty, polysubstance abuse, parental mental health, and other co-existing high-risk behaviours. Uebel H, et al. [24] demonstrated that NAS was associated with an increased risk of health, social and psychological problems even into the teenage years [24]. However, it is difficult to determine whether these outcomes are secondary to the drug exposure in utero or the surrounding related socioeconomic/environmental factors [13]. In addition, there is usually an inconsistent caregiver, chronic stress, family instability, and mistrust of healthcare and out of home placement for these kids. It appears that the coinciding environmental risks magnify the weaknesses caused by opiate exposure [1].

Conclusion

NAS continues to be a challenge for diagnosis, treatment and a follow-up in the neonatal period. Opiate withdrawal is relatively easy to diagnose and manifests earlier, but cocaine and amphetamine withdrawal can be subtle. Children diagnosed with Neonatal Abstinence Syndrome should be identified early and a multi-disciplinary team of physicians, nurses, physical therapists, social workers, and neurologists can provide effective and appropriate management of NAS in the hospital and after discharge from

the hospital. In the state of Tennessee, these infants are enrolled in an early intervention program. Follow-up after discharge should include neurodevelopmental assessments, psycho-behavioral assessments, ophthalmologic screening, nutritional/growth assessments and assessment of family support [25]. Discussing these potential risks with families of children diagnosed with NAS in the initial phase of management of NAS may encourage parents to become involved with early intervention programs to ensure that these children are being appropriately monitored. It is important to ensure open communication in a safe and non-judgmental environment; this may improve relationships with clinicians and empower parents to play an important role in the screening and treatment process.

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