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Infant autonomic functioning and neonatal abstinence syndrome

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ABSTRACT

Background: Neonatal abstinence syndrome (NAS) expression is widely variable among affected infants and the reasons for this variability are largely unknown; mechanisms that predispose infants to NAS expression are not understood. It has been postulated that the regulatory problems of prenatally drug exposed infants are manifested in dysfunctional vagal regulation of autonomic processes. The current study examines whether cardiac vagal tone, an indicator of parasympathetic neuroregulation, provides a marker for autonomic dysregulation subsequently expressed as NAS in prenatally opioid-exposed newborns.
Methods: Heart period (HP) and cardiac vagal tone (*V*) were derived from electrocardiogram data collected from 64 methadone-exposed infants on postnatal days 1 and 3. The postpartum NAS course was assessed serially.
Results: Infants with lower *V* on day 1 had significantly higher NAS symptomatology on day 3. Boys had more severe NAS symptoms than girls through the first 4 days of life and, among infants receiving pharmacologic treatment for NAS, boys required longer treatment course and hospitalizations. Greater poly-drug exposure, detected through toxicology screening throughout pregnancy, and cocaine use in particular, were associated with lower *V* and shorter HP (faster heart rate) in newborns. Multiple regression models accounted for 25–35% of the variance in NAS symptoms and duration of hospitalization in methadone-exposed infants. Significant predictors included infant sex, SSRI/SNRI use, and cigarette smoking.
Conclusions: Results support the hypothesis of a biologic vulnerability of autonomic regulatory functioning in methadone-exposed infants and greater male infant vulnerability to maternal methadone use.

1. Introduction

Internationally, the diversion and abuse of narcotic-containing pharmaceuticals, which constitutes a serious health risk, has increased. This has lead to the tripling in the global consumption of methadone over the past decade, with countries in North America and Europe reporting the highest levels of use (International Narcotics Control Board, 2008). Opioid use during pregnancy continues to be a major public health problem in the US, and there is evidence that use of opioid drugs, especially misuse of opioid prescription drugs by women of childbearing age, is increasing (SAMSHA, 2008). Opioid dependent pregnant women comprise a special population due to the multiple considerations of the mother, the pregnancy, and the fetus. Management of opioid dependence with methadone has been used for decades in this population, and its use offers significant health benefits to the mother–infant dyad (Kaltenbach et al., 1998). However, a major consequence of maternal opioid/methadone use is a constellation of withdrawal symptoms in the newborn known as neonatal abstinence syndrome (NAS), which occurs in between 48 and 94% of exposed newborns (Osborn et al., 2005).

Infants with NAS typically express dysfunction of respiratory, gastrointestinal, and/or nervous system regulation. Symptoms generally commence within 48–72 h of birth and include, but are not limited to hypertonicity and tremors, irritability, hyperthermia, tachypnea, vomiting and poor feeding (American Academy of Pediatrics, Committee on Drugs, 1998). NAS is generally scored and treated empirically, that is, treatment is typically based on the number and severity of symptoms. The Finnegan Scale Scoring System (Finnegan et al., 1975), or a variant of this scale, is often used to assess NAS in affected newborns and (Sarkar and Donn, 2006), in clinical settings, often provides the basis for a treatment algorithm.

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Standard treatment involves the use of non-pharmacotherapeutic interventions, in combination with the use of an opiate replacement drug such as morphine when symptoms become more severe.

NAS expression is widely variable among individual infants, and while almost all opioid-exposed infants express some withdrawal symptoms, only a subset of infants manifest severe enough symptomatology to require pharmacotherapy; the reasons for this variability are largely unknown (Jansson et al., 2007) and myriad factors are likely to affect expression (Seligman et al., 2008; Burns and Mattick, 2007). The relationship between maternal methadone dose and NAS severity has been disputed, with most studies finding that the degree of methadone exposure during pregnancy is unrelated to NAS expression (McCarthy et al., 2005; Berghella et al., 2003; Mack et al., 1991; Jansson et al., 2007). Currently, there is no specific identifiable maternal or infant factor linked conclusively to the severity of NAS displayed by the newborn. The pathophysiology of this disorder, costly to the infants affected, their families, the health care system and society, remains unknown.

Drug-exposed infants exhibit significant impairment in their ability to regulate internal homeostatic processes and to organize behavioral and physiologic responses (Bard et al., 2000). It has been postulated that the regulatory problems of prenatally drug exposed infants are manifested in dysfunctional vagal regulation of autonomic processes (Porges and Greenspan, 1991). The autonomic nervous system is a crucial regulator of neural homeostasis and physiological adaptability, by dynamically controlling the body's responses to external and internal stimuli (Porges, 2007). A well-established indicator of autonomic function in developmental research is the degree of spontaneous variability in heart rate (Bernston et al., 1997). Since heart rate variability is subject to both autonomic and non-autonomic influences, efforts to isolate the parasympathetic input have relied on quantifying the magnitude of the respiratory sinus arrhythmia which is mediated by the vagus. Measures of vagal tone have been applied to examination of neonatal adaptability to extra uterine life in both full-term and preterm infants; results indicate that lower vagal tone is associated with greater perinatal risk (DiPietro et al., 1994; Doussard-Roosevelt et al., 1997). Studies of the effects of prenatal drug exposure on vagal tone in infants have been limited to cocaine exposure. A dose-dependent effect of cocaine on respiratory sinus arrhythmia has been reported (Schuetze and Eiden, 2006). Prenatal methadone exposure is associated with disruption to autonomic functioning in the developing fetus expressed as decreased fetal heart rate variability (Ramirez-Cacho et al., 2006; Navaneethakrishnan et al., 2006; Jansson et al., 2005) and with disruption to maternal autonomic functioning and subsequent NAS expression in the infant (Jansson et al., 2007).

Male sex provides a vulnerability to developmental deficits throughout infancy and childhood (Nagy et al., 2001). Sex differences in neurobehavior among healthy, term infants have been described, with male infants displaying poorer levels of functioning on the Brazelton neonatal behavioral assessment scale (Lundqvist and Sabel, 2000). Male infant vulnerability to affective regulatory (Weinberg et al., 1999), developmental (Nagy et al., 2001) and health (Morse et al., 2006; McGregor et al., 1992) dysfunction has long been established. Male infants have been found to be more susceptible to behavioral deficits secondary to teratogenic drug exposures (Riese, 1989) and more vulnerable to maternal depressive symptoms (Weinberg et al., 2006) than female infants, suggesting differential vulnerability of the developing nervous system. Female infants demonstrate greater activation of the autonomic nervous system than males during the challenge of adaptation to extra uterine life (Bernardes et al., 2009). In animal models, prenatal morphine exposure induces long-term alternations in adult rat brain and behaviors in both males and females, but these alterations differ between sexes (Vathy, 2002). Greater sensitivity to methadone in the neonatal brain of male offspring has been shown in rats (Hou et al., 2004). Among methadone-exposed infants, boys are predisposed to more severe NAS expression as neonates (Jansson et al., 2007) and increased vulnerability to adverse environmental conditions as infants (Johnson and Rosen, 1982).

We have previously shown that among methadone-maintained women who were otherwise drug free in the last trimester of pregnancy, maternal autonomic nervous system functioning is correlated with newborn NAS severity. Specifically, offspring of women who reacted to methadone administration with greater change in vagal tone, regardless of whether methadone had a suppressive or augmenting effect, had more severe NAS expression (Jansson et al., 2007). This association was stronger for boys than girls. The current study was designed to further examine the relationships among prenatal methadone exposure, infant sex, and NAS expression by evaluating vagal tone in opioid-exposed offspring. We predicted that opioid-exposed infants with lower vagal tone will have greater difficulties with functional regulation during the early neonatal period, which will be expressed in terms of more severe NAS course than infants with higher vagal tone, and that male infants prenatally exposed to methadone will have more severe NAS expression.

2. Methods

2.1. Participants

Participants were infants of women enrolled in comprehensive, multidisciplinary treatment at the Center for Addiction and Pregnancy in Baltimore, Maryland. The program, described fully elsewhere (Jansson et al., 1996), provides an array of services, including substance abuse treatment, psychiatric consultation, obstetric care and methadone maintenance when warranted to pregnant women with drug dependency living in Maryland. Participants were opioid-dependent women meeting federal criteria for methadone maintenance, delivering a singleton infant at term and free of significant pregnancy or pre-existing medical conditions. Participants were enrolled for study participation upon the birth of their infant. Alcohol dependent women were ineligible. Eligible program participants were approached for enrollment following consecutive deliveries between December 2006 and August 2008. Of the 66 women offered enrollment, one declined, resulting in 65 subjects. All women provided written informed consent for the participation of their infants and the study was approved by the governing Institutional Review Board.

Maternal participants were mature (M age = 29.1 years, sd = 5.95), mostly unmarried (86.2%) and had less than a high school education (M years of education = 11.13; sd = 1.42). Subjects were principally Caucasian (72.3%) and African-American (24.6%). Most (70.8%) delivered vaginally. Maternal medical, substance use, and drug treatment history was obtained via self-report from participants and maternal chart review upon the infant's birth. At the time of delivery, 21 women (32.3%) were maintained on psychotropic medications, primarily for depression. Of these, 13 were maintained on selective serotonin or serotonin–norepinephrine reuptake inhibitor (SSRI/SNRI) medications (duloxetine, citalopram, fluoxetine, sertraline and escitalopram). Almost all (96.9%) smoked cigarettes (M cigarettes daily = 11.1, sd = 6.1). Cocaine was the single most frequently reported drug used in addition to heroin during pregnancy, with reported use by 36 (56.3%) participants at any point during gestation. Maternal urine toxicology was obtained at the time of delivery and was available for all but one participant; 84.6% were negative for illicit substances. Of the 9 positive samples, detected substances included heroin (5), non-prescribed benzodiazepines (2), cocaine (1) and another opioid (1). Maternal drug abuse history and methadone treatment parameters are presented in Table 1. Twenty-eight women (43.1%) were methadone-maintained for all three trimesters, 27 (41.5%) were methadone-maintained for the 2nd and 3rd trimesters and 10 (15.4%) for the 3rd trimester only.

Infants were hospitalized for a minimum of four full days for observation for signs/symptoms of NAS per standard operating procedure of the birth hospital. Infants not requiring NAS treatment were discharged on hospital day 5. All infants received NAS scoring every 3–4 h for their entire hospitalization beginning at birth, using a modification of the Finnegan Neonatal Scoring System (Finnegan et al., 1975) which provides a weighted ranking of symptoms to assess NAS severity. Scoring was done by the clinical nursing staff which is highly experienced in the treatment of drug-exposed neonates. Opiate replacement treatment (i.e., morphine sulfate) was provided based on a symptom-based algorithm that has been previously described (Jansson et al., 2009). Pharmacotherapy for the treatment of NAS began when two consecutively obtained scores were greater than 8. Increasing doses of mediation