

# Abnormal Presentation of Hypoxic Ischemic Encephalopathy Attributed to Polysubstance Exposure

Authors' Contribution:  
Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
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**Conflict of interest:** None declared

**Patient:** Male, newborn  
**Final Diagnosis:** Hypoxic ischemic encephalopathy  
**Symptoms:** Arthrogyposis • bitemporal wasting • graf type IIa dysplasia • NAS symptoms  
**Medication:** —  
**Clinical Procedure:** —  
**Specialty:** Pediatrics and Neonatology

**Objective:** Congenital defects/diseases

**Background:** With the increasing prevalence of substance use in pregnancy, the rates of neonatal abstinence syndrome (NAS) are dramatically increasing. There is little information on the use of multiple substances in adults, even less so of polysubstance abuse during pregnancy and the consequences for the fetus as well as the mother.





**Case Report:** A newborn male born at 35 weeks presented post-delivery with hips bilaterally dislocated and hyperflexed. The patient's legs fully extended and their shoulders were bilaterally mid-flexed with arms fully extended. This neonate was also reported to have bilateral hearing and vision loss as well as NAS symptoms of high-pitched crying and respiratory distress. During pregnancy the mother in this case study admitted to using buprenorphine, benzodiazepines, gabapentin, and heroin. The consequences of using this combination has not been well studied in pregnancy.

**Conclusions:** The presented case had severe complications, likely due to maternal polysubstance use and poor prenatal care in pregnancy. Clonidine was used to control the NAS symptoms, ranitidine was used to treat the gastroesophageal reflux, and glycopyrronium bromide was used for the neonate's excessive secretions. After delivery, the patient was placed on a nasal noninvasive cannula for respiratory distress and was transferred to a different hospital for treatment of the more serious comorbid conditions.

**MeSH Keywords:** Hypoxia, Brain • Maternal-Fetal Exchange • Neonatal Abstinence Syndrome

**Abbreviations:** NAS – neonatal abstinence syndrome; HIE – hypoxic ischemic encephalopathy

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/918091>

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## Background

Many children in the catchment area of our institution have been born with neonatal abstinence syndrome (NAS) or other complications due to their exposure *in utero* to illicit substances, particularly opioids. The following case is that of a neonate who presented with significant *in utero* exposure to multiple neuroactive substances that are known to be teratogenic [1]. Hypoxic ischemic encephalopathy (HIE) has been demonstrated in adults after prolonged non-medical use of neuroactive substances [2], but this has not yet been reported as a consequence of prenatal exposure to the same substances. It is difficult to determine whether any one of the problems described in this case were due to exposure to one drug or a combination of drugs, poor prenatal care, or an unexplored genetic abnormality. Any of these scenarios could result in a severe hypoxic event that could potentially lead to HIE. Gabapentin exposure has been linked to low birth weight, preterm birth, neonatal jaundice, bradycardia, respiratory distress, and diarrhea [3]. The use of buprenorphine is the current standard of care for medication-assisted treatment in pregnancy; however, a fetus exposed to buprenorphine will have the typical presentation of NAS hypersensitivity: low-grade fevers, tremors, and poor sleep [4]. Neonates who had prolonged exposure to benzodiazepines *in utero* can have hypotonia, poor suck reflexes, impaired metabolic functions, and slower development for the first year of life [5]. This is one of the more severe cases that has presented to our institution with NAS symptoms and other complications potentially due to drug exposure *in utero*.

## Case Report

The mother was a 27-year-old non-Hispanic white female who had little or no prenatal care along with significant substance abuse during pregnancy. She denied alcohol consumption but admitted to the use of buprenorphine, benzodiazepines, gabapentin, and heroin. Urine drug screens revealed buprenorphine, benzodiazepines, gabapentin, heroin, and other opioids. Maternal labs revealed an A positive blood type that was positive for hepatitis C and negative for HIV and syphilis. The mother had no significant medical history, no personal history of hypertension, thyroid disorders, or diabetes mellitus, and no known family history of any members with a similar condition. The mother reported smoking ½ pack per day throughout her pregnancy. There was no significant obstetrical history other than she has had a preterm premature rupture of membranes (PPROM) during a previous pregnancy. The mother was referred to our institution for an abnormal fetal ultrasound, due to a suspicion for cystic structure of the brain.

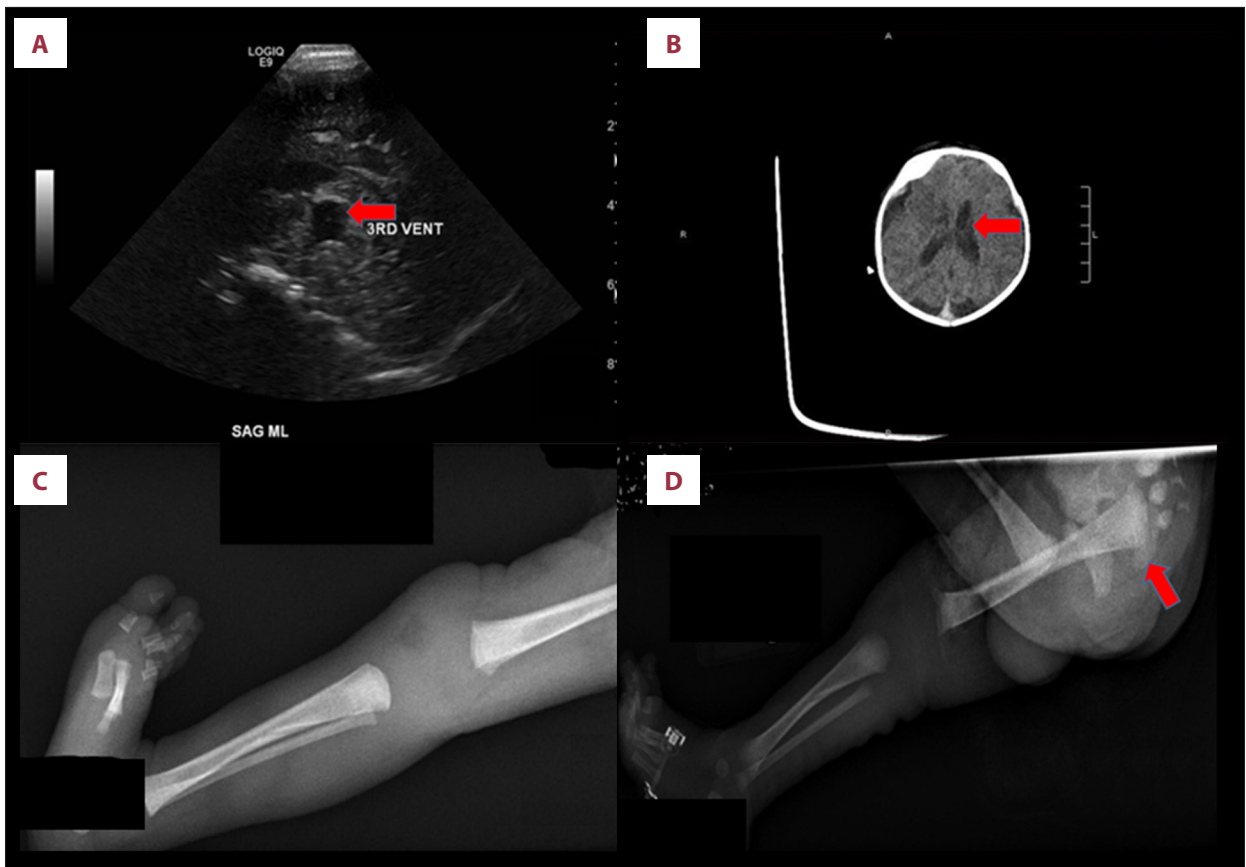
A male infant was born by cesarean at 35 weeks' gestation to a 27-year-old gravida 3, para 2 white female. The neonate was

small for gestational age, the birth weight was 1920 grams, birth length was 45 cm, head circumference was 31 cm, and the 1- and 5-minute Apgar scores were 7 and 9, respectively. After delivery, the vital signs, including temperature, heart rate, and respiratory rate, were all initially normal. After delivery, the neonate developed respiratory distress and was placed on a nasal cannula. Physical exam revealed bilaterally dislocated and hyperflexed hips with fully extended legs and bilaterally mid-flexed shoulders with fully extended arms. The patient was diagnosed with arthrogryposis (Figure 1C), a congenital condition in which the joints become permanently fixed in either the flexed or extended position [6]. The patient was referred for ophthalmic and hearing screening for concerns of blindness and deafness, and exams showed blindness bilaterally and significant-to-severe bilateral hearing loss. All lab values were within normal ranges. The creatine phosphokinase was within normal range, with a negative microarray. Whole exome and whole genome tests were performed and both tests were negative. It was noted that the placenta had a large umbilical cord.

The neonate was transferred to a larger regional hospital to receive treatment and evaluation of neuromuscular nerve abnormalities. The patient was diagnosed with profound hypotonia, a decrease in muscle mass including bitemporal wasting. Also, bilateral ptosis, the ability to move his face appropriately, was lacking, and the formal diagnosis was severe HIE. HIE is a condition resulting from diminished cerebral blood flow and oxygen in the brain; this can cause poor suck reflexes, weak or poor muscle tone, and seizures [7].

Radiologic findings showed that this cystic structure was a dilated third ventricle (Figure 1A), and it was also found that the fetus had an abnormality in the ventrolateral thalamus and globus pallidus (Figure 1B). Further physical exam findings included low-set ears, high palate, micrognathia, 2 noted anal tags, and bilateral genu recurvatum, which is an abnormality of the knee joint in which the legs are hyperextended [8]. It was also observed that the patient had an abnormal high-pitched cry, abnormal facial movements, and seizures, which can be associated with NAS.

This neonate was monitored for NAS due to the extensive exposure to substances *in utero*. The patient exhibited the hallmark NAS high-pitched cry as well as a poor suck reflex, no gag reflex, no root reflex, a weak grasp, and having excessive secretions. After several days, the patient developed some respiratory distress and was placed on a nasal cannula and later switched to a continuous positive airway pressure (CPAP) device. The neonate was fed donor milk, eventually developing a feeding intolerance and persistence vomiting. A nasogastric tube was placed to manage this.



**Figure 1.** (A) Sagittal ultrasound of head, with the red arrow showing the dilated third ventricle. (B) CT scan without contrast of head, with the red arrow showing enlarged bilateral ventricles. (C) X-ray image of the hyperflexed right lower extremity, consistent with arthrogryposis. (D) X-ray image of the hyperflexed lower left extremity. The red arrow indicates the left acetabular immaturity, showing this patient's Graf type IIa dysplasia.

The neonate was started on albuterol, ipratropium bromide, and dornase alfa nebulizers on day of life (DOL) 11 for respiratory distress. Vancomycin 26.5 mg was used to treat the developing sepsis on DOL 11. Ampicillin began on DOL 1 to combat infection, and phenobarbital was administered on DOL 11 and 12 for seizures. A one-time dose of methadone was given on DOL 11 for withdrawal symptoms. The patient received an echocardiogram for a heart murmur, which was negative. An upper gastrointestinal tract radiography revealed gastroesophageal reflux. Magnetic resonance imaging (MRI) revealed several abnormalities, including immaturity of the left acetabulum consistent with a Graf type IIa dysplasia (Figure 1D). An electromyography (EMG) showed hypotonia, decreased muscle mass, and diminished conduction and amplitudes in the left tibial and peroneal motor nerves. A renal ultrasound revealed mild hydronephrosis. A peripheral inserted central catheter (PICC) line was placed for better IV access. The patient was placed on clonidine starting DOL 12 for neonatal abstinence syndrome treatment to lessen the withdrawal symptoms, as well as ranitidine for reflux and glycopyrronium bromide for the secretions. Once the neonate's conditions stabilized, the mother and neonate were transferred

to a different hospital for a surgical consult for treatment of the more serious conditions. The stay at the different hospital revealed no abnormalities in the exome or genome.

## Discussion

The case described shows the dangers of a child being exposed to substances *in utero*, as well as the lack of prenatal care, preventing the diagnosis of this infant's comorbid conditions. Poor prenatal care reduces the likelihood of detecting any problems the fetus may have, and can cause problems shortly after birth and in managing any chronic maternal condition [9]. In this case, the mother had no significant medical history other than illicit substance use and addiction. The diminished prenatal care along with the multiple substance use led to this patient begin born with many problems. Use of prescribed and the illegal substances can have an effect *in utero* and cause serious consequences after birth. The lack of information about reported polysubstance abuse cases makes it difficult to discern which symptoms were caused by which

drug he was exposed to or whether it was due to the combination of them all.

Some of the known risk factors for HIE are maternal uterine rupture, placenta previa or abruptio placenta, cord prolapse, maternal hypotension, shoulder dystonia, and breech presentation [7]. Any of these events can cause a decrease in cerebral blood flow and decrease of oxygen getting to the brain, which can lead to HIE. The development of HIE may be attributed to the mother's heroin use, as heroin commonly causes hypotension [10]. Genu recurvatum has long been linked to the exposure to teratogenic agents in pregnancy, malposition during delivery, infection, oligohydramnios, and a traumatic event *in utero* [11]. As mentioned earlier, the mother in this study admitted to limited prenatal care, substance abuse, smoking during pregnancy, and hepatitis C infection. The obstetrical history was unremarkable with the exception of PPRM, and her medical history was unremarkable as she has no history of hypertension, hypotension, diabetes, or thyroid deficiencies. The neonate's hearing and vision loss can be attributed to the nerve abnormalities; however, the cause of the abnormality could not be determined. Because she does not fit any of the known risk factors for her son developing HIE and genu recurvatum, these conditions may be attributed to the intrauterine exposure to cigarettes and multiple substances and the maternal complications from substance abuse. The patient's NAS symptoms may have been overshadowed by his other conditions; however, they were addressed with clonidine and his reflux was treated with ranitidine. It was noted that the

patient had poor suck and poor grasp reflex. The poor suck reflex could be due to exposure to benzodiazepines, as that is a common complication of maternal use in pregnancy. The low birth weight, respiratory distress, and preterm delivery could be attributed to the gabapentin exposure. Due to the lack of literature on intrauterine heroin exposure, there is no way to differentiate which symptoms could be attributed to exposure to this drug or the interactions of it and the other substances. Any one of these substances could complicate the pharmacologic reaction of another one, and this compounding of substances can have worse or new effects on the fetus than any one substance would have. However, due to the lack of research on these substances being used concurrently, the level of effect is not known.

## Conclusions

HIE has not been previously associated with *in utero* substance exposure. However, with the increase in polysubstance exposure and the hypoxic effects often associated with higher-dosage substance use, this may be an early indication of hypoxia-related symptomatology in exposed neonates. This case is a stark reminder that more research into polysubstance exposure is needed to address this new, troubling chapter in NAS.

## Conflict of interest

None.

## References:

1. Furray A: Substance use during pregnancy. *F1000Res*, 2016; 13: 5
2. Virmani A, Ali SF, Binienda ZK: Neuroprotective strategies in drug abuse-evoked encephalopathy. *Ann NY Acad Sci*, 2010; 1199: 52–68
3. Fujii H, Goel A, Bernard N et al: Pregnancy outcomes following gabapentin use: Results of a prospective comparative cohort study. *Neurology*, 2013; 80(17): 1565–70
4. Jones HE, Fischer G, Heil SH et al: Maternal Opioid Treatment: Human Experimental Research (MOTHER) – approach, issues and lessons learned. *Addiction*, 2012; 107(Suppl. 1): 28–35
5. McElhatton PR: The effects of benzodiazepine use during pregnancy and lactation. *Reprod Toxicol*, 1994; 8(6): 461–75
6. Møller-Madsen B: Arthrogryposis multiplex congenital – an update. *J Child Orthop*, 2015; 9(6): 425–26
7. Allen KA, Brandon DH: Hypoxic ischemic encephalopathy: Pathophysiology and experimental treatments. *Newborn Infant Nurs Rev*, 2011; 11(3): 125–33
8. Loudon JK, Goist HL, Loudon KL: Genu recurvatum syndrome. *J Orthop Sports Phys Ther*, 1998; 27(5): 361–67
9. National Institute of Child Health and Human Development. What is prenatal care and why is it important? Available from: <https://www.nichd.nih.gov/health/topics/pregnancy/conditioninfo/prenatal-care>
10. Paranthaman SK, Khan F: Acute cardiomyopathy with recurrent pulmonary edema and hypotension following heroin overdose. *Chest*, 1976; 69(1): 117–19
11. Charif P, Reichelderfer TE: Genu recurvatum congenitum in the newborn: Its incidence, course, treatment, prognosis. *Clin Pediatr (Phila)*, 1965; 4(10): 587–94