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Case Report

Pathologies in a preterm infant exposed to methamphetamine in utero: Case report and literature review ☆,☆☆

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ABSTRACT

Methamphetamine (M-AMP) use among women of childbearing age is a growing global concern Herein we present an unusual clinical presentation in a preterm infant born to a mother who used M-AMP during pregnancy. A 26-year-old woman, with no prenatal care, presented to the emergency department with aggressive behavior and visible skin wounds led to suspicion of substance abuse. Urine analysis confirmed high levels of amphetamines (2000 ng/mL). The infant was delivered by cesarean section at 30 + 5/7 weeks, with a birth weight of 1580 grams. The infant, admitted to the NICU due to respiratory distress and prematurity, initially required nasal CPAP and exhibited transient tachypnea. Enteral feeding was initiated at 24 hours of life but was halted due to feeding intolerance. Once the baby's symptoms subsided, enteral feeding was gradually reintroduced and slowly increased. The infant successfully transitioned to full enteral feeding by the 15th postnatal day. Cranial ultrasound revealed hyperechoic areas in the right parietal lobe, and subsequent MRI showed millimetric T1 hyperintense areas, indicative of parenchymal microischemia. Preterm infants exposed to methamphetamine in utero may not show typical withdrawal symptoms.

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Diagnostic challenges arise from prematurity, with significant impacts on brain development and potential neurocognitive deficits.

Introduction

Methamphetamine (M-AMP) is one of the illegal stimulant substances and has become a significant issue, especially among women of childbearing age, with its increasing use worldwide [1,2]. Methamphetamine causes an increase in dopamine in the brain, leading to heightened alertness, euphoria, and increased self-confidence in users, making it a potent sympathomimetic agent [2]. Although the proportion of M-AMP users among substance abusers is low, the anorectic effect and its slow metabolism, resulting in high blood levels for an extended period (8-24 hours), have increased its use during pregnancy [1]. Continuous M-AMP use throughout pregnancy is associated with preterm birth, low birth weight (LBW), intrauterine growth restriction (IUGR), congenital anomalies, and drug toxicities in the exposed newborns. All these effects contribute to neonatal morbidity and mortality [3–5]. Babies born to mothers exposed to harmful substances (including M-AMP, opioids, heroin, and alcohol) have a significantly increased risk of long-term neurological dysfunction [3].

In this report, we aim to present the unusual clinical presentation and findings related to intracranial pathologies in a preterm infant born to a mother who used M-AMP during pregnancy.

Case presentation

A 26-year-old pregnant woman, G4P2A1, without any prenatal care throughout her pregnancy and not legally married, presented to our emergency department due to preterm labor. During her presentation, her aggressive behavior, tachycardia, and visible skin wounds led to the suspicion of substance abuse. Consequently, obstetricians conducted a urine screening for illegal substances before delivery. The analysis of the urine sample revealed an amphetamine level of 2000 ng/mL, which was above the reference range (0-500 ng/mL). The levels of other substances tested, including benzodiazepine, cannabinoid, ecstasy, cocaine, buprenorphine, heroin metabolite, and synthetic cannabinoid, were found to be below the reference values. Additionally, prenatal viral infection screenings for AntiHIV, AntiHCV, HbsAg, TORCH, and syphilis antibodies from the mother were negative. Due to the threat of preterm birth, antenatal steroids were administered to the mother. Further anamnesis revealed that the mother used stimulant substances, and cigarettes throughout her pregnancy.

Our case was delivered by cesarean section at 30 weeks and 5 days of gestation due to a history of previous cesarean sections. The female infant's birth weight was 1580 grams (67th percentile), length was 43 cm (91st percentile), and head circumference was 28 cm (60th percentile). The Apgar scores were 7 at the 1st minute and 8 at the 5th minute postbirth. The prematurely born baby was admitted to the neonatal intensive care unit (NICU) and nasal CPAP was started due to respiratory distress that began from the first minutes of life. The chest X-ray was consistent with transient tachypnea of the newborn (TTN). The cord blood gas values were pH: 7.14, pCO2: 62, BE: −7, lac: 4.8, and HCO3: 15.7. The tests taken from the patient postbirth showed wbc: 8300 10^3/uL, plt: 144,000 10^3/uL, Hgb: 18.6 g/dL, Hct: 52%, and C-reactive protein: 4.4 mg/dL. An umbilical venous catheter was inserted into the patient, and blood culture was taken. Empirical antibiotic therapy and total parenteral nutrition were started. On the 24th postnatal hour, the patient's need for respiratory support decreased, and monitoring continued in room air. During the neurological examination, the baby exhibited hypotonia and diminished reflexes, which gradually resolved over time. In addition to close monitoring of vital signs, our hypotonic patient was assessed with the Finnegan Neonatal Abstinence Scale (FNAS) every 3-4 hours. The patient's initial score was 3, which decreased to 1 on the second day and was assessed as zero after the 48th postnatal hour. However, the monitoring was continued, with intervals extended up to 5 days.

At the 24th postnatal hour, since breast milk could not be obtained, minimal enteral feeding (20 ml/kg/day) with formula was initiated. However, the baby could not tolerate minimal enteral feeding and developed feeding intolerance, manifested by increased gastric residuals, vomiting, and progressively increasing abdominal distension. As a result, feeding was stopped at the 96th postnatal hour, and orogastric drainage was started. Upon examination, clinical, laboratory, and radiological evaluations did not indicate necrotizing enterocolitis (NEC) (Fig. 1). The abdominal ultrasound was normal. Within 48 hours of ceasing feeding, the baby's symptoms relatively subsided, and minimal feeding was restarted. However, the amount of feeding could only be increased very slowly.

On the 7th postnatal day, the acute phase reactants were negative, and no growth was detected in the cultures taken, so the patient's antibiotic therapy was discontinued. Hearing and eye screenings showed no pathology, and the echocardiogram was normal. Due to prematurity, routine cranial ultrasound imaging at the 72nd postnatal hour revealed "hyperechoic asymmetric areas in the parenchyma of the right parietal lobe." Consequently, a noncontrast cranial MRI was performed, which was reported as "millimetric T1 hyperintense appearances in the anterior cingulate gyrus level midline and left corona radiata line frontal-parietal white matter areas (ischemic foci)" (Fig. 2). The findings from our case are summarized and compared with the available literature at Table 1.

The baby, whose feeding could only be increased very slowly, was able to transition to full enteral feeding on the 15th postnatal day. Oral feeding trials began on the 20th post-

Table 1 – Comparison of clinical and imaging findings in a preterm infant exposed to methamphetamine in utero vs. literature reported outcomes.

Study	Findings in current case	Findings in literature
Preterm birth	Baby delivered preterm at 30 + 5/7 wk	Prenatal M-AMP exposure increases the risk of preterm birth, low birth weight, and IUGR [16,17]
Neonatal abstinence syndrome (NAS)	Initial FNAS score of 3, decreased to zero by 48 h	Preterm infants have a lower incidence of NAS compared with term infants and it is unclear whether prenatal M-AMP exposure causes NAS in the neonate [36,37,39]
Feeding tolerance	Initial feeding intolerance with abdominal distension, resolved after cessation of feeding, and resumed slowly	The gastrointestinal effects of M-AMP are not well understood [29] No data on gastrointestinal specific effects
Abdominal radiograph	Dilated loops are observed in all abdominal quadrants	No data on gastrointestinal specific effects
Cranial imaging	Cranial ultrasound at 72 h showed hyperechoic areas in the right parietal lobe. MRI showed millimetric T1 hyperintensity in the anterior cingulate gyrus and left corona radiata	Cranial MRI studies have shown decreased brain volume and altered brain structures in M-AMP-exposed infants, including reduced volumes in the striatum, hippocampus, and frontal cortices [20,22,23]
Infant's clinical outcome	Feeding tolerance improved and successfully transitioned to full enteral feeding by day 15. Normal weight gain. Echocardiography was normal	Infants exposed to M-AMP may experience feeding difficulties, growth restriction, and delayed milestones, though long-term clinical outcomes depend on the severity of exposure [16,17,25,39]
Neurodevelopmental outcomes	No available long-term neurodevelopmental findings in this case, with normal hearing screening and no retinopathy on the eye examination	Long-term studies report developmental delays, cognitive deficits, and increased risk for neurological and behavioral disorders in children exposed to M-AMP [22,23,29]
Social handicap	The baby, was placed in a childcare institution through social services	Higher referral incidence to child protective service in infants with prenatal M-AMP use [47]

FNAS, Finnegan neonatal abstinence scale; IUGR, intrauterine growth restriction; M-AMP, methamphetamine; MRI, magnetic resonance imaging;
NAS, neonatal abstinence syndrome.

natal day, and within 72 hours, the baby was fully orally fed. During subsequent clinical follow-up, the baby's weight gain increased, and there were no additional problems. The eye examination revealed no retinopathy. The baby, who was in good clinical condition and feeding entirely by sucking, was discharged to be placed in a childcare institution through social services as the mother did not take the baby.

Discussion and literature review

Substance use during pregnancy carries significant short- and long-term risks for both the mother and the child. Regarding the prenatal exposure to M-AMP, the clinical and radiological findings of our case and the long-term consequences such as increased susceptibility to neurodevelopmental disorders, behavioral issues, and possible potential complications in later stages of life are illustrated in Fig. 3. Both panels collectively underscore the significant impact of prenatal M-AMP exposure on the overall health and well-being of the offspring.

While opioids are the most commonly used substances in this context, substances that can affect the pregnant user and the newborn, causing withdrawal symptoms (neonatal abstinence syndrome, NAS) depending on the substance used, can be grouped into 4 main categories [6]. These are legal and over-the-counter substances (cigarettes, alcohol, etc.), the inappropriate use of prescription drugs (opioids/painkillers, sedatives/hypnotics, stimulants, psychotic medications), illegal drugs (cocaine, amphetamines, heroin, hallucinogens, cannabis in some regions), and medications used to treat maternal substance dependence (methadone, buprenorphine, buprenorphine-naloxone). However, it is observed that many pregnant women use multiple substances [7].

Methamphetamine enhances the release of monoamine neurotransmitters such as serotonin, dopamine, and norepinephrine through various mechanisms [8,9]. At the cellular level, methamphetamine-induced neurotoxicity and degenerative effects are linked to oxidative stress, mitochondrial dam-

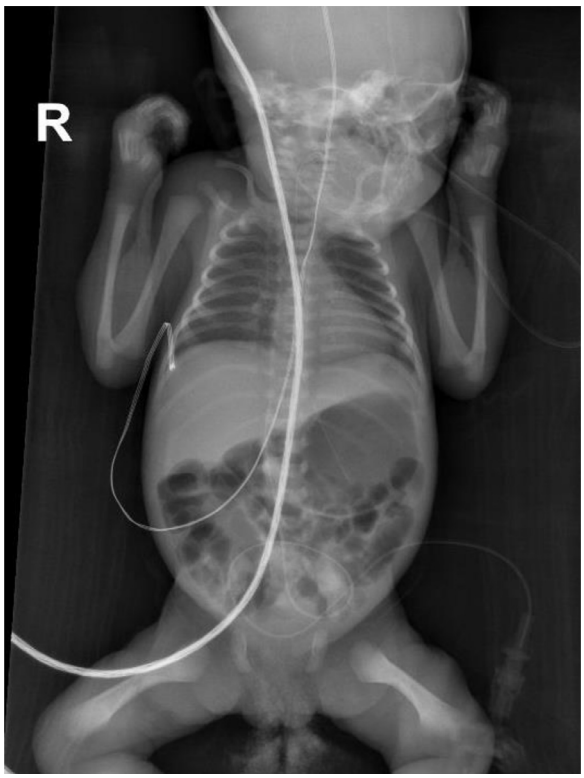

Fig. 1 – X-Ray in supine position, dilated loops are observed in all abdominal quadrants, but there is no rectal gas. There are suspicious granular appearances in both lower quadrant bowel loops. Pneumatosis intestinalis or portal venous gas is not observed.

age, and cell cycle dysregulation [10]. Exposure to M-AMP ultimately inhibits the proliferation, differentiation, maturation, and survival of primarily neural stem cells [10,11].

Methamphetamine is classified among substances that cause NAS, but its primary effects are seen through pregnancy complications such as preterm birth, IUGR, and gestational hypertension. Serotonin and norepinephrine, which are released in high amounts in the placenta, play a crucial role in the homeostasis of amniotic fluid and fetal circulation, and they significantly impact the vasoconstrictive control mechanisms of the placental vascular bed. This situation can contribute to the development of preeclampsia, IUGR, placental abruption, and preterm birth [12]. The vasoconstrictive effect of M-AMP on the placental bed causes a decrease in fetal blood flow, leading to fetal hypoxia, IUGR, and other comorbidities, including brain dysfunction in the developing fetal brain [13–15].

Gorman et al., retrospectively analyzed paired maternal and infant data in California and demonstrated that among pregnant women who used M-AMP, there was an increased risk of preeclampsia, gestational hypertension, placental abruption, intrauterine fetal death, preterm birth, and an increased risk of infant mortality [16]. Wright et al. [17], after excluding social confounding factors that increase the risk of prematurity and IUGR, found in their prospective studies investigating the effects of M-AMP on pregnancy outcomes, that women who continued to use M-AMP throughout their pregnancies had an increased risk of preterm birth and delivering infants with IUGR. Similarly, our case involved a premature infant with LBW, and the mother had used M-AMP throughout her pregnancy, which resulted in early delivery.

Amphetamines have vasoconstrictive effects, leading to reduced nutrient supply, particularly to the developing brain and intestines of the fetus [14]. In-utero exposure to M-AMP causes abnormal cerebral hemodynamics and alters neurotransmitter activity in the brain, which negatively impacts brain morphogenesis, leading to decreased brain volume and reduced subcortical thickness. Additionally, this exposure disrupts cellular metabolism and network connectivity, resulting in abnormal neuronal development and subsequent neurocognitive deficits [5,18–20]. Intracranial hemorrhage has also been reported in these infants [18].

Structurally, the effects resulting from these mechanisms may present with findings that cannot be adequately diagnosed using ultrasound. Therefore, MRI is recommended for assessing the cranial effects of substance use during pregnancy [21]. In the United States, Chang et al. conducted cranial MRI imaging studies to investigate the long-term effects of prenatal M-AMP exposure on brain structure and cognitive function. They found that patients exposed to M-AMP before birth had decreased volumes in the bilateral putamen, globus pallidus, hippocampus, and caudate nucleus. Additionally, these results were associated with delays in attention and verbal memory in the long term [20]. Sowell et al. [22], also reported reductions in the volumes of the thalamus, anterior prefrontal cortex, and parieto-occipital cortex, as well as volume decreases in the anterior and posterior cingulate, ventral and medial temporal, and perisylvian cortices. Additionally, studies have shown that children with M-AMP exposure exhibit volume loss in the striatum and hippocampus, along with white matter abnormalities in the frontal regions [23]. Volume reductions were found to be more severe in the striatum, a dopamine-rich brain area known to be particularly vulnerable to the neurotoxic effects of M-AMP. These changes are thought to indicate potential disturbances in neuronal and glial development, which may negatively affect the cognitive and behavioral development of these children [23]. Studies showing long-term outcomes indicate that prenatal exposure to M-AMP is associated with increased neurological and behavioral disorders, deficiencies in cognitive functions and problem-solving skills, anxiety, depression, short-term memory issues, and delays in language development [4,24,25].

While most research has focused on older children, only a limited number of studies have addressed the brain structure of newborn infants [25]. So, there is a lack of data on pathological findings in imaging conducted during the neonatal period. Importantly, Warton et al. [26] demonstrated that prenatal M-AMP exposure leads to changes in the corticostriatal white matter and neural networks in newborns. In our case, the cranial MRI showed millimetric T1 hyperintensities in the midline at the level of the anterior cingulate gyrus and in the frontoparietal white matter at the level of the left corona radiata. These findings were interpreted as micro ischemic foci in the subacute phase, likely resulting from the vasoconstrictive effects of M-AMP on the developing fetal brain.

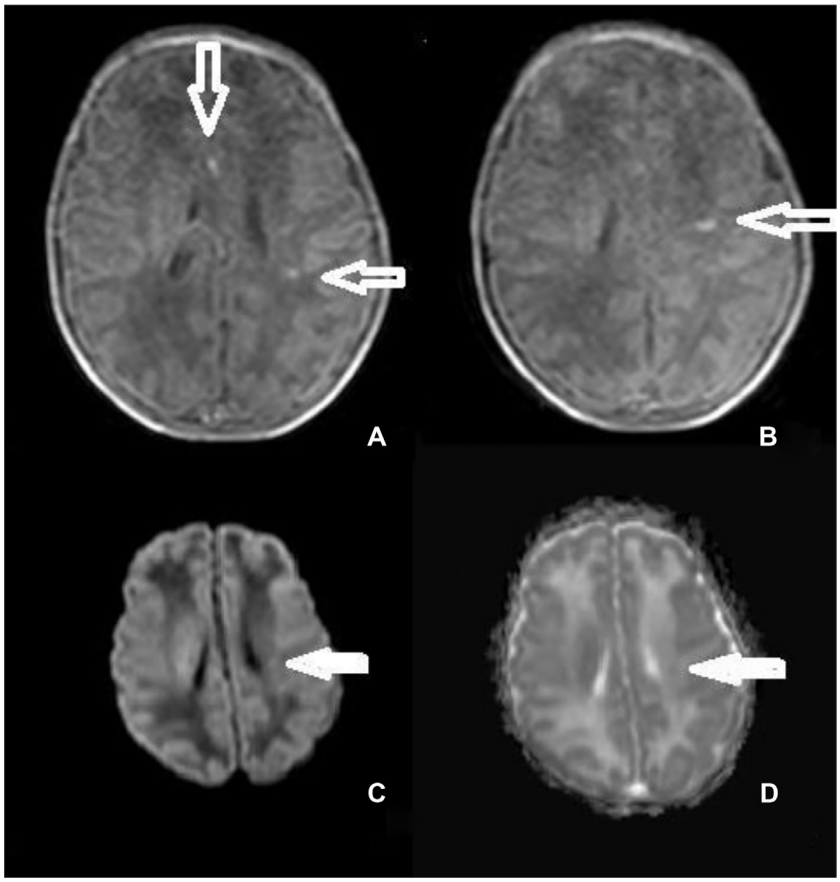

Fig. 2 – (A and B) MRI images showing millimetric T1 hyperintensities at the midline level of the anterior cingulate gyrus and in the frontoparietal white matter at the level of the left corona radiata (arrows). (C and D) In the diffusion-weighted sequence, minimal hyperintensity is noted in one of the lesions (C), with mild hypointensity on the ADC map (D) (solid arrows). These findings were interpreted as microischemic foci in the subacute phase.

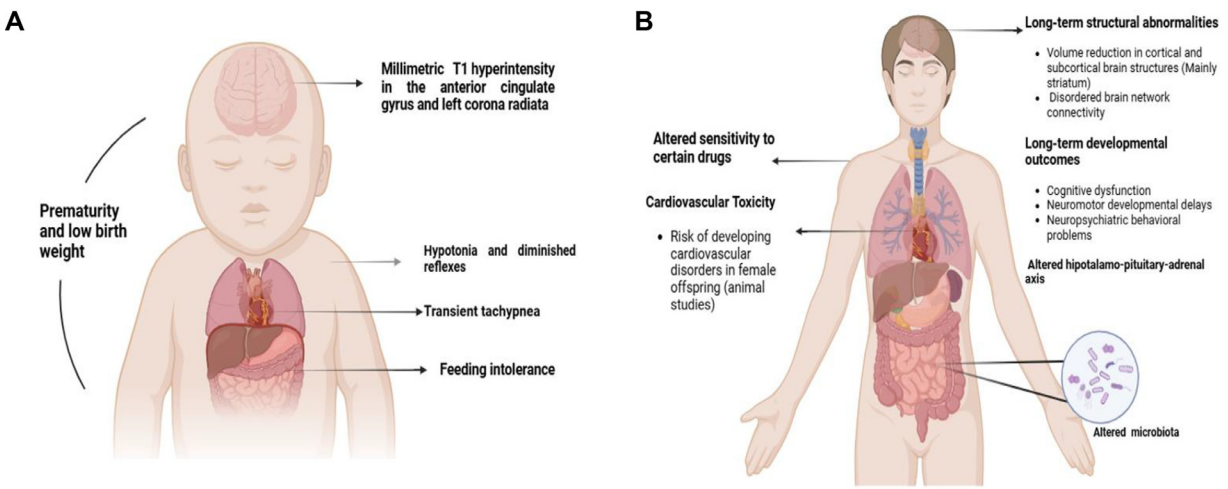

Fig. 3 – Adverse health outcomes of offspring resulting from M-AMP exposure during pregnancy.
(A) The clinical and radiological findings observed in our case. (B) Long-term consequences, such as increased risk of neurodevelopmental disorders, behavioral issues, and other possible health complications in later stages of life.

It is believed that the peripheral effects are primarily due to the rapid and sustained release of norepinephrine following M-AMP use, which results in systemic arterial vasoconstriction [14]. In addition to the well-documented cerebrovascular effects of amphetamines, several cardiovascular pathologies, including myocardial ischemia, hypertension, arrhythmias, and rhabdomyolysis, have been observed in adult patients. These conditions may be predicted due to the drug's vasoconstrictive cardiovascular effects [27]. However, ongoing studies in rats have provided some evidence suggesting that the impact of M-AMP use during pregnancy may differ between males and females, particularly increasing the risk of developing cardiovascular disorders later in life, with a higher likelihood in female offspring [24,28].

However, the gastrointestinal effects of M-AMP are not well understood even in the adult population [29]. The resulting release of norepinephrine following M-AMP use may lead to systemic arterial vasoconstriction in the splanchnic region, with results reported only in a few adult case reports [30,31]. This effect may result in acute intestinal ischemia, paralytic ileus, and increased intestinal permeability [30,31]. According to recent literature, oxidative stress increases damage to enteric neurons, which exacerbates M-AMP-induced intestinal inflammatory injury by altering the gut microbiota and triggering inflammatory responses. This process leads to increased gastrointestinal dysfunction [31,32]. Moreover, the effects of dopamine and norepinephrine on the enteric nervous system can result in reduced bowel contractility and intestinal smooth muscle tone, contributing to dysmotility in the gut [31–33].

A recent animal trial studying the effects of multiple high-dose M-AMP administration on enteric dopaminergic neurons and intestinal motility in rats showed significant effects of M-AMP on intestinal motility [34]. In the literature, no studies have been found that evaluate the effects of prenatal M-AMP on the gastrointestinal system of newborns. We did not observe any NEC-related pathology in radiological, laboratory, or clinical findings, but our case experienced prolonged feeding intolerance and had difficulty increasing feedings. We speculated that feeding intolerance might be due to M-AMP-induced vasoconstriction. Neonatologists should maintain a high index of suspicion for intestinal dysmotility or hypoperfusion when dealing with infants of M-AMP user mothers. Prompt diagnosis can possibly prevent complications and save bowel resection.

Infants exposed to M-AMP should be closely monitored for NAS postbirth. Neonatal abstinence syndrome is the manifestation of withdrawal symptoms in a newborn following chronic in utero exposure to opioids and similar drugs once the exposure is abruptly ceased after birth [35]. Symptoms of NAS due to withdrawal can present as central nervous system dysregulation, gastrointestinal disturbances, autonomic dysregulation, and respiratory abnormalities [36,37].

Opioid withdrawal symptoms typically appear within the first 48 hours after birth and are primarily characterized by prolonged neurological findings, including poor sucking. LaGasse et al. [38], reported that preterm infants with prenatal M-AMP exposure do not exhibit typical NAS signs. Instead, these infants display difficulties in muscle tone control, delays in responding to stimuli, or general motor skill deficiencies, manifesting as poorer quality of movement, increased physiological stress, and CNS stress. It is believed that the lower frequency and severity of withdrawal syndrome in preterm infants are due to shorter exposure duration, reduced drug clearance due to immaturity, and decreased receptor levels [37,39] Neurobehavioral assessments indicate differences between infants exposed to opioids and those exposed to M-AMP; infants exposed to M-AMP show lower arousal and less excitability [38,40].

Numerous scoring systems have been developed to diagnose NAS and decide on nonpharmacological or pharmacological interventions for infants born to substance-using mothers. Among these, the FNAS is the most commonly used, particularly for morphine treatment [41]. However, the use of this scoring system has been met with skepticism by some clinicians due to issues related to its subjectivity, length, and reliability. Rather than focusing on characterizing all withdrawal signs, a new assessment tool, the Eat, Sleep, Console (ESC) approach, emphasizes the functionality of the infant during routine clinical assessments. This approach prioritizes nonpharmacologic interventions before resorting to pharmacologic treatment [42].

Nearly all scales developed to assess NAS symptoms are used for late preterm and term infants. Unfortunately, there is no standardized scoring system specifically designed for preterm infants [39]. In a study by Allocco et al. [43], comparing NAS symptoms in preterm and term infants exposed to methadone using the FNAS, it was demonstrated that the clinical manifestations of NAS differ between preterm and term infants. Additionally, preterm infants exposed to M-AMP may display different neurobehavioral characteristics such as lower arousal, decreased excitability, and increased stress responses, rather than the classic NAS symptoms [37].

Assessment tools typically evaluate neurological dysfunction and response to pain; however, the immature functional responses, immature pathways for pain perception and response, poor self-regulation, and higher stress levels in preterm infants compared to term infants, as well as decreased tone and reflexes even in healthy preterm, limit the complete utility of these scales [39,44]. Therefore, when using these scoring systems in premature infants, it is essential to carefully discern whether symptoms such as tone abnormalities, poor feeding, and regurgitation are due to prematurity and associated comorbidities or if they reflect withdrawal symptoms.

Due to the absence of a scale specifically designed for preterm infants, our case was monitored every 3-4 hours for 5 days using the FNAS system, along with close monitoring of vital signs. However, we found that the FNAS subcategories were not optimal for evaluating our preterm patient. The respiratory distress due to transient tachypnea in the first 24 hours rapidly improved with NCPAP, and subsequent observations primarily focused on feeding problems. Although clinical signs such as crying and irritability appeared to be short-lived, the prolonged feeding intolerance in our infant was a clear indicator of the extent of the impact. Studies have shown that preterm infants display lower arousal, increased stress responses, decreased excitability, and differences in movement quality rather than classic NAS symptoms [36,37]. This highlights the need for careful assessment and tailored ap-

proaches for monitoring and managing NAS in preterm infants.

Due to the lack of sufficient tools for the diagnosis and monitoring of withdrawal symptoms in preterm infants, tracking vital signs, exposure levels (hair analysis), maternal hair metabolites, or, more recently, genetic susceptibility has been evaluated. However, there is still no practical, inexpensive, easy, and validated method for use in clinical practice [45].

It is crucial to evaluate mothers with a history of substance use, especially in cases of preterm labor. Biological materials such as blood, saliva, sweat, and urine can be used for toxicological analysis to assess substance use. The significant advantage of urine toxicology is that the substance used can be found in high concentrations in the urine, and collecting urine samples for toxicology is relatively easier [46]. In our case, a urine toxicology sample taken from the mother before delivery, with a history of preterm birth and suspected substance use, showed high levels of amphetamine.

For NAS, the recommended first-line treatment options are nonpharmacologic interventions such as low stimulation environments, on-demand feeding, parental presence, swaddling, calming, and cuddling. The American Academy of Pediatrics recommends the use of an assessment tool for withdrawal signs and pharmacologic management only when nonpharmacologic management efforts are unsuccessful [37].

Substance use in pregnant women and their infants carries not only the direct adverse effects of the substance but also additional risks such as nutritional deficiencies in the mother-infant pair, problems related to inadequate infant care, and difficulties in mother-infant bonding [3]. Additionally, the sociological impact on public health should not be overlooked, including factors like the mothers' marital status, higher risk of other sexually transmitted diseases, and the potential rejection of the infant postdelivery [39]. All infants who develop neonatal abstinence syndrome, regardless of the need for pharmacotherapy, should be closely monitored after discharge. Some symptoms, such as feeding problems, may persist for months and require ongoing support [39].

Conclusion

Our case, born prematurely and experiencing cerebral and gastrointestinal disorders, appears to have been significantly affected multisystemically by prenatal M-AMP exposure. The differences in NAS symptomatology among preterm infants, along with the prevalence of concurrent diagnoses that complicate assessments, highlight the need for a modified scoring tool tailored specifically to the preterm NAS population. Additionally, in the neonatal period, gastrointestinal symptoms, along with cerebral pathologies, may become prominent as NAS indicators. Therefore, the potential differences in prenatal M-AMP exposure symptoms compared to opioid exposure symptoms, and the masking of diagnosis due to prematurity, call for additional studies to evaluate these infants even if they do not show signs on imaging or clinical examination. Furthermore, the increasing use of harmful substances leading to premature birth makes the development of an instrument that can accurately assess NAS symptoms in preterm newborns urgent.

Author contributions

Criteria for inclusion in the authors / contributors list: Z.Y. and E.A. designed and coordinated the study. Z.Y. collected clinical data and drafted the manuscript. O.A. conducted the literature review and contributed to the initial draft. E.C. performed the radiological evaluations and contributed to the study from this perspective. T.K.G. carried out the neonatal clinical assessments. E.A. reviewed the manuscript and approved its publication. All authors contributed to the interpretation of the data, writing, and revision of the manuscript. All authors reviewed and approved the final version of the manuscript. A statement that the manuscript has been read and approved by all the authors: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Patient consent

Written and informed consent has been obtained from the patient for the publication of the case presented in this article. The patient/guardian has acknowledged that the information will be published without identifying details, that the article will be accessible in print or digital formats, and that the content may be used for scientific purposes. During the consent process, relevant details were explained to the patient/guardian, and they were provided with the opportunity to review the text.

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