Brain & Development 41 (2019) 191–194

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Case Report

Severe neurologic and hepatic toxicity in a newborn prenatally exposed to methamphetamine. A case report

Eugenia Maranella [a,*], Arianna Mareri [a], Valentina Nardi [a], Cecilia Di Natale [a], Luisa Di Luca [a], Emanuela Conte [a], Veronica Pannone [a], Alessia Catalucci [b], Sandra Di Fabio [a]

[a] *Neonatology and Neonatal Intensive Care Unit, San Salvatore Hospital, L'Aquila, Italy*
[b] *Radiology Unit, University of L'Aquila, Italy*

Received 21 November 2017; received in revised form 8 February 2018; accepted 24 August 2018

Abstract

Objective: In the recent years the increase of methamphetamines (MTA) abusers women has become an emerging problem. Very little data has been published regarding the effects of prenatal MTA exposure. We describe a case of MTA related toxicity in a term newborn which have early onset of neonatal encephalopathy and liver failure.

Case report: A term infant born to a MTA abuser mother developed seizures and severe neurological symptoms shortly after birth. Methamphetamine was detected both in maternal and in neonatal urine. The laboratoristic tests revealed severe hepatic insufficiency, coagulopathy and thrombocytopenia. Due to neonatal encephalopathy the newborn underwent hypothermia. Phenobarbital, fresh frozen plasma, platelet transfusions and vitamin K were administered. Cranial ultrasonography and magnetic resonance imaging (MRI) showed diffuse white matter damage and two ischemic-hemorrhagic cerebral lesions. Gradually the clinical conditions improved, at 1 month MRI showed a stabilization of cerebral lesions with residual diffuse leukomalacia. Physiotherapy and neurological follow up is ongoing to evaluate the long term effects. *Conclusions*: although infrequent, MTA-related toxicity should be suspected in infants with neurologic and hepatic symptoms. Further studies are warranted to confirm our findings in order to identify newborns at high risk of acute MTA toxicity in time to provide them the appropriate support.

Keywords: Methamphetamine; Neonatal encephalopathy; Hepatic toxicity

1. Introduction

In recent years, prenatal methamphetamine (MTA) exposure has become an emerging problem. On a worldwide scale, amphetamines, for both licit and illicit use are the third most common abused drug after alcohol and cannabis [1]. More women than men are first-time users so this implies the possibility of MTA exposure during pregnancy [2]. Very little data has been published regarding the effects of prenatal MTA exposure. We report a case of an infant born to a MTA-abuser mother with neonatal encephalopathy and liver failure.

2. Case presentation

A male infant was born by emergency cesarean section due to CTG deceleration at 39 weeks after an uncomplicated pregnancy. His birth weight was 2400 g (3–10th percentile) and his head circumference was

* Corresponding author.
E-mail address: emaranella@libero.it (E. Maranella).

https://doi.org/10.1016/j.braindev.2018.08.010
0387-7604/

34 cm (25th percentile), the Apgar score were 6 and 9 at 1st and 5th min of life, respectively. The arterial blood gases at birth showed pH 7.11, and BE-14. He was the first child of an healthy G1-P1 30 years-old mother. Maternal history revealed drug abuse up to 6 years previously the conception. No history of drug abuse, smoking or alcohol consumption was referred during the pregnancy.

In the first hours of life he was admitted to NICU due to a progressively worsening respiratory distress syndrome and neurological impairment. Chest-X-ray showed wet lungs, he was started on nCPAP with a progressive resolution of transient tachypnoea after 48 h. Neurological examination revealed a floppy infant with hypotonia and hyporeactivity, weak primitive neonatal reflexes, fisting of the hands and weak symmetrical plantar response. He had moderate hepatomegaly and jaundice, no facial dismorfism and soft open fontanelles. The amplitude integrated electroencephalography (aEEG-Olympic-CFM6000) showed an high-voltage pattern with seizure activity, lasting 40 min, with simultaneous twitching of the arms and apnoea during sleep followed by a moderate abnormal pattern that normalized at 24 h of life (Fig. 1). He underwent therapeutic hypothermia and Phenobarbital administration. Due to the previous maternal history we conducted urine screen test which was positive for MTA in both the mother and the newborn, no others abuse substances were found, even alcohol. Laboratory tests showed: AST 875 UI/L, ALT 295 UI/L, gammaGT 105 UI/L, total serum bilirubin 9.89 mg/dl (n.r.0–2 mg/dl), PT 25.9 s, PTT 42 s, fibrinogen 61 mg/dl and thrombocytopenia (Plt 29.000/mmc). One fresh frozen plasma, two platelet transfusions and vitamin K were administered. NEUROIMAGING: cranial ultrasound showed diffuse white-matter hyperechogenicity and subcortical right temporo-parietal hyperechoic area as hemorrhage (Fig. 2). The MRI at 7 days confirmed an area of subacute cortico-subcortical hematoma (22 × 14 cm) into the right temporal lobe, a second smaller acute hemorrhagic right parietal lesion and a diffused white-matter damage, such as hypoxic-ischemic injury (Fig. 3a). FOLLOW-UP: liver and coagulation tests gradually normalized, the newborn slowly improved, no further clinical-electrical seizures were registered with ongoing phenobarbital therapy.

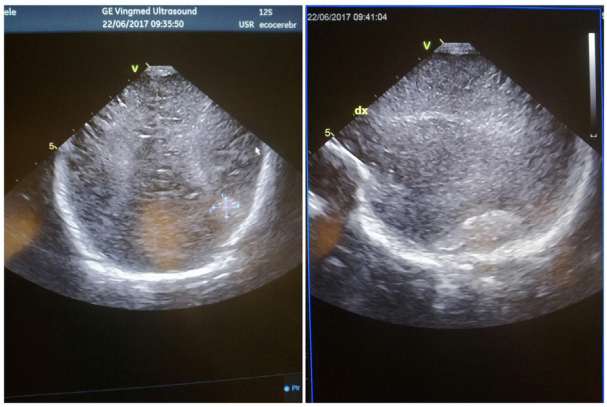

Fig. 2. Cerebral Ultrasonography at 6 h of life: diffuse bilateral white matter hyperecogenicity and an hyperecogen area in the right parietal region (2,1 × 1,4 cm in the coronal scan and 3,4 × 1,1 cm in the sagittal scan).

MTA-related neurologic and hepatic toxicity were suspected. Electrophysiological and neuroimaging follow-up were run. At one month, the MRI showed a stabilization in the ischemic-hemorrhagic lesions and a cavitation in the parieto-occipital white-matter, as cystic

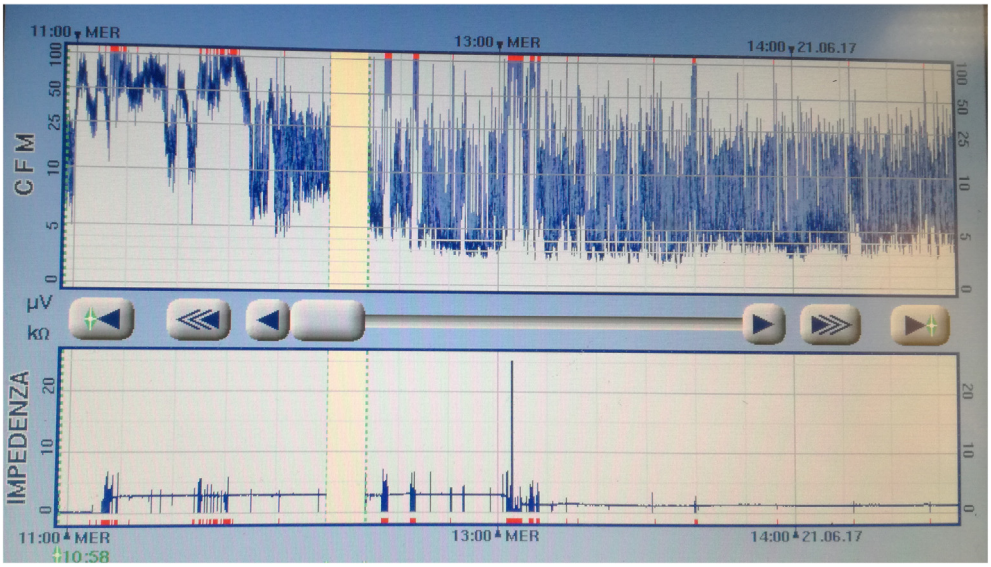

Fig. 1. EEG pattern at admission: high voltage pattern with seizure activity followed by a moderate abnormal pattern.

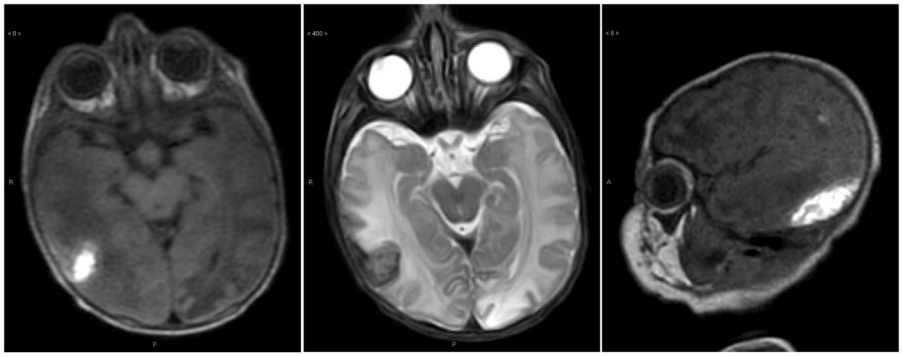

Fig. 3a. MRI at 7 days of life: T1- and T2-weighted axial images and sagittal T1-weighted image showed an extensive area of subacute cortico-subcortical hematoma into the right temporal lobe; sagittal image shows another smaller hemorrhagic right parietal cortical lesion. In addition, axial images show a diffuse parieto-occipital white matter hyperintensity on T2-weighted image and hypointensity on T1, as hypoxic-ischemic injury.

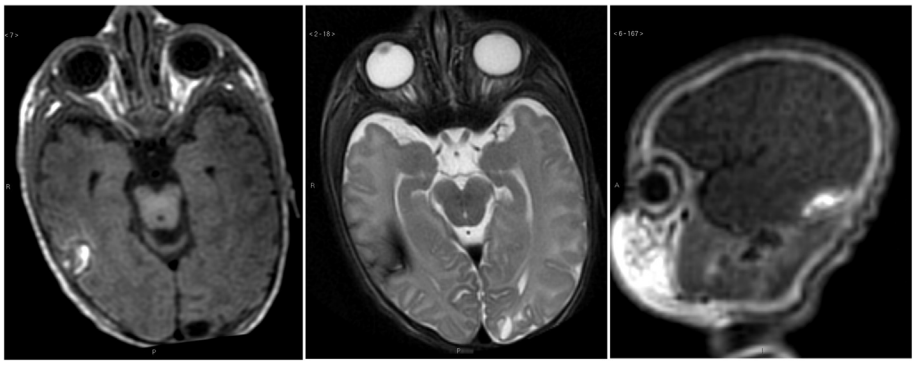

Fig. 3b. MRI at 1 month of life: T1- and T2-weighted axial images and sagittal T1-weighted image show a reduction of hemorragic right parietal and temporal lesions; T2 axial image shows subcortical cavitations in the parieto-occipital white matter, as cystic encephalomalacia.

encephalomalacia (Fig. 3b). Visual evoked potentials registered a slow bilateral response time. At 3 months [weight 5.500 g (10th percentile), CC 39.5 cm (10–25th percentile)], the patient had mild hypertonia and a reduction in spontaneous motor activity on the left side. He was started early on physiotherapy to reduce the risk of long-term disability. Follow-up is ongoing to evaluate the long-term outcome.

3. Discussion

To our knowledge this is the first case of acute neurotoxic and hepatic neonatal injury in a term newborn with prenatal exposure to MTA. Amphetamines users have increased in the last years particularly among young women [1]. Amphetamines cross the placenta and transfer into the breast milk, causing neonatal toxic effects in different organs. Published data regarding neonatal symptoms are lacking.

The most common neonatal sign, as in our patient, is the low birth weight related to intrauterine growth retardation (IUGR) [1,2]. Rare subclinic and self-limited withdrawal symptoms such as drowsiness, poor feeding and lethargy are reported after birth. Only 2–4% of exposed infants requires pharmacological intervention [2,3]. Relation between seizures and MTA are reported in adults and children but not in newborns [1]. The main neurological effects in children concern behavioral problems, emotional reactivity and attention deficit in the infancy [4,5]. In our patient unusually the MTA related toxicity had a rapid onset and it was followed by a quick deterioration leading to life-threatening conditions. After birth he presented severe neurological symptoms mimicking the onset of perinatal asphyxia. Although the good clinical conditions at birth (AS 9 at 5′, pH 7.11, BE-14), the neurological deterioration during the first hours of life and the previous maternal history lead us to differentiate a MTA related toxicity from a typical perinatal asphyxia. We suppose that the vasoconstrictor effect of MTA, as reported in cocaine abuse, induced placental dysfunction, reduced oxygen delivery resulting in a prenatal ischemia. The chronic hypoxia was responsible for IUGR, cerebral damage and CTG decelerations. In addition, the direct neurological effect of MTA, through the modulation of dopamine, serotonin and norepinephrine release may have deteriorated the neurological status [2]. In fetal rat cells cultures, the MTA exposure causes a decrease in the number of neu-

rons and neuronal differentiation. Some studies report a decrease in myelination and in the white-matter maturation [6]. Moreover, as reported in foetal-alcohol syndrome, an abnormal methylation of neuronal DNA, as epigenetic effect, could be involved in the development of the neurological toxicity [7]. In our case, the MRI showed a diffuse leukomalacia and two area of chronic and acute hemorrhages. During pregnancy MTA induced a chronic ischemic damage with secondary hemorrhagic lesions. Moreover, during the neonatal period the coagulopathy due to the liver failure may have exacerbate the bleeding conditions. MTA induce acute hepatocellular failure in adults mediated by oxidative stress and changes in the mitochondrial membrane, no data have been reported in newborns apart from a prolonged but self-limited conjugated jaundice [8]. In our baby the association between the neurological and the hepatic MTA toxicity led to the severe cerebral damage and the neurological impairment.

4. Conclusion

To our knowledge this is the first case of acute neurologic and hepatic toxicity in a newborn exposed to MTA during pregnancy. Attention should be paid to the possible onset of critical conditions in newborns prenatally exposed to MTA. Further studies are warranted to confirm our findings in order to identify newborns at high risk of acute MTA toxicity in time to provide them the appropriate support. Multidisciplinary involvement of pediatricians, neuropsychiatrists and social services is of paramount importance in order to offer the best outcome to these infants.

Funding

No funding source.

References

[1] Oei JL, Kingsbury A, Dhawan A, et al. Amphetamines, the pregnant woman and her children: a review. J Perinatol 2012;32:737–47.
[2] Smith LM, Yonekura ML, Wallace T, et al. Effects of prenatal methamphetamine exposure on fetal growth and drug withdrawal symptoms in infants born at term. J Dev Behav Pediatr 2003;24:17–23.
[3] Thaithumyanon P, Limpongsanurak S, Praisuwanna P, Punnahitanon S. Perinatal effects of amphetamine and heroin use during pregnancy on the mother and infant. J Med Assoc Thai 2005 Nov;88:1506–13.
[4] La Gasse LL, Derauf C, Smith LM, et al. Prenatal methamphetamine exposure and childhood behavior problems at 3 and 5 years of age. Pediatrics 2012;129:681–8.
[5] Kiblawi ZN, Smith LM, Diaz SD, et al. Prenatal methamphetamine exposure and neonatal and infant neurobehavioral outcome: results from the IDEAL study. Substance Abus 2014;35:68–73.
[6] Loak CC, Ernst T, Fujii L, et al. Lower diffusion in white mattern of children with prenatal methamphetamine exposure. Neurology 2009;72:2068–75.
[7] Lussier AA, Weinberg J, Kobor MS. Epigenetics studies of fetal alcohol spectrum disorder: where are we now? Epigenomics 2017;9:291–3.
[8] Dahshan A. Prenatal exposure to methamphetamine presenting as neonatal cholestasis. J Clin Gastroenterol 2009;43:88–90.