

Maternal Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-Like Episodes Syndrome and Neonatal Magnesium Toxicity: A Case Report

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Abstract

Introduction: Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome is a progressive disorder associated with neurologic, cardiac, neuromuscular, hepatic, metabolic and gastrointestinal dysfunction, including potential anesthetic and obstetrical complications. Increased susceptibility to drugs in patient with MELAS syndrome can be due to drug-induced mitochondrial toxicity and/or decreased elimination. We present here a case of severe neonatal magnesium sulfate toxicity in the context of MELAS syndrome.

Case presentation: A 43-year-old, gravida 5, para-5 (4 prior vaginal deliveries and the current cesarean section) woman with asymptomatic MELAS syndrome (carrier of the genetic variant NC_012920.1: m3243A>G in 20% of the mitochondrial DNA) was given intravenous magnesium sulfate for preeclampsia shortly before an emergency cesarean section at 33 weeks. The newborn presented a severe toxic effect characterized by cardio-respiratory arrest. Genetic evaluation revealed that he carried the same maternal mutation, but at a higher rate (80%). There was no other risk factor for cardio-respiratory arrest other than the potential interaction between the maternal/neonatal mitochondrial disease and the medication, thus potentially leading to the risk of overdose.

Conclusion: The cause of the severe toxicity is uncertain, but it may have resulted from magnesium accumulation in the mother and/or the newborn due the presence of the MELAS syndrome in the neonate. A close assessment of potential severe drug toxicity in mothers and neonates with MELAS syndrome is warranted.

Keywords: MELAS syndrome; Mitochondrial diseases; Genetics; Carriers; Magnesium sulfate; Interaction; Neonatal; Pregnancy

Introduction

Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome is one of the most frequent maternally-inherited mitochondrial disorders. The m.3243A>G mutation in the *MT-TL1* gene encoding for the mitochondrial *tRNA^{Leu}* is the most common cause of MELAS syndrome, but other genetic variants have been found to be also associated [1]. During pregnancy, MELAS syndrome or the presence of the m.3243A>G mutation have been found to be associated with cardiomyopathy, gestational diabetes, myopathy and hypertensive complications, such as preeclampsia [2]. They may also promote a higher risk of drug-induced mitochondrial toxicity and/or decreased elimination [3].

Women with a MELAS syndrome and preeclampsia may receive magnesium sulphate for the prevention of eclampsia. Although the administration of maternal magnesium sulfate has been associated with respiratory depression in neonates, it is usually well tolerated and does not require any change in neonatal reanimation techniques. However, in the context of MELAS syndrome, maternal magnesium sulfate can be associated with severe neonatal toxicity. We present here a case of severe neonatal toxicity potentially due to maternal administration of magnesium sulfate in the context of a maternal-neonatal m.3243A>G syndrome.

Case Report

A 43-year-old, gravida 5, para-4 woman discovered her new pregnancy at 19 weeks. Her past medical history was significant for MELAS syndrome diagnosed at the age of 19 years by genetic testing; her mother had also been diagnosed with the disorder. The patient was carrying a heteroplasmic mutation variant (NC_012920.1:m3243A>G) in 20% of the mitochondrial DNA. She was considered as asymptomatic, but she was being followed because of migraines and the presence of cerebral white matter lacunas on magnetic resonance imaging. The former four pregnancies ended at term with vaginal deliveries of normal weight newborns, but all were complicated by gestational hypertension and diabetes. She presented with a suspicion of preeclampsia during her last pregnancy, which was finally confirmed and she received a bolus (4 g) of magnesium sulfate with no toxicity observed. Since the fourth pregnancy, she was considered as having chronic hypertension and treated with amlodipine, valsartan and hydrochlorothiazide. During the current pregnancy, the antihypertensive treatment was stopped as her blood pressure was normal. The patient was diagnosed with placenta praevia that resulted in two hospital admissions due to genital bleeding at 27 and 30 weeks' gestation. At the last hospital stay, she was tocolysed with atosiban and received betamethasone for fetal lung maturation. Fetal weight on ultrasound was 1900 g, 70th percentile. The patient was diagnosed with gestational diabetes and insulin treatment was started at 30 weeks. At 33 weeks' gestation, she was admitted to the delivery room for the reappearance of genital bleeding and severe preeclampsia. The decision

was taken to start prophylactic treatment with intravenous magnesium sulfate to prevent eclampsia (4 g bolus followed by 1 g/h) and to perform an emergency cesarean section. She received only the 4 g bolus of sulfate before she gave birth to a male neonate of 2060 g (P50), Apgar 9/6/9, arterial pH 7.35 and venous pH 7.41. The cesarean section was unremarkable with neither hypotension nor bleeding.

At 2 min of life, the newborn presented apnea, extreme bradycardia (<60 bpm) severe hypotension (impossible to register) and then cardio-respiratory arrest. Resuscitation with mask ventilation with 100% fraction of inspired oxygen (FiO₂) was initiated and external cardiac massage was performed in the absence of the resumption of spontaneous ventilation. After 30 sec, the neonate resumed spontaneous breathing, normal cardiac frequency (161 bpm) and oxygen saturation of 93% under continuous positive airway pressure with 25% FiO₂. The newborn was transferred to the neonatal intensive care unit with the continued use of continuous positive airway pressure and surfactant for prematurity-related wet lung syndrome. On day 1, orotracheal intubation for a pneumothorax with a thoracic drain for exsufflation was needed, but it could be removed at day 4 of life. At the cardiovascular level, there was a non-resolving arterial duct under intravenous nonsteroidal anti-inflammatory therapy requiring surgical closure at one month of life. Genetic evaluation of the newborn was positive for the same maternal mutation, but with a higher heteroplasmy of 80%. The infant was able to go home at two months of life. Severe bronchodysplasia persists and he is followed regularly in the pneumology unit. The neonatologists considered that the most probable cause of the cardio-respiratory arrest was magnesium sulfate, which is rare when taking into account the small amount received by the mother. Regarding the mother, she was kept on magnesium sulfate 1 g/h for 24 h and then put on enalapril and nifedipine due to hypertension (170/100 mmHg). She had no further complications and returned home after 9 days.

Discussion

The m.3243A<G mutation in the *MT-TL1* gene encoding for the mitochondrial tRNA is the most frequent mutation for MELAS syndrome. There are several types of phenotypic expression including maternally-inherited diabetes, deafness, hypertrophic cardiomyopathy, macular dystrophy, myoclonic epilepsy with ragged-red fibers, and chronic progressive external ophthalmoplegia [2]. The penetration of the disorder is inconstant because of the particularity of mitochondrial DNA. First, maternal heredity, meaning that all members from the maternal line are carriers of the mutation and second, the heteroplasmy, which defines the number of mitochondria mutated in each cell (a cell contains 100-1000 mitochondria, each with 1-10 copies of mtDNA).

When all are mutated, there is a homoplasmic mutation. When not all mtDNA copies are affected, the mutation is called heteroplasmic [4].

During pregnancy, women with MELAS syndrome or carrying the m.3243A>G mutation are at high risk of obstetrical complications, such as diabetes and preeclampsia [5]. In their cohort study, De Laat et al. showed a prevalence of 12% for preeclampsia in women carrying the m.3243A>G mutation compared to 3.5% in the general population (a 7-fold higher risk) [2]. The risk for preeclampsia was independent of the heteroplasmy level. This higher prevalence of preeclampsia in carriers of the m.3243A>G mutation can be explained by a fundamental disorder of placental mitochondria, with an abnormality

in the oxidative chain in this tissue characterized by the need to generate more energy than other tissues during pregnancy and leading to the apoptosis of placenta cells [6]. Therefore, the question of the potential maternal and/or neonatal toxicity of magnesium sulfate treatment is important in this population at high risk of preeclampsia. Patients with MELAS syndrome should avoid agents with potential mitochondrial toxicity [1]. Drug-induced mitochondrial respiratory chain dysfunction may result from various mechanisms, such as the direct inhibition of the enzyme complexes, uncoupling of oxidative phosphorylation and impairment of mtDNA replication. Moreover, agents that cause an increase in cellular oxidative stress may also lead to mitochondrial respiratory chain toxicity [3]. Several drug classes have been associated with mitochondrial toxicity, including nucleoside reverse transcriptase inhibitors used in the treatment of human immunodeficiency virus infection, antipsychotic drugs (such as haloperidol), the serotonin reuptake inhibitor sertraline, levodopa, anticonvulsant agents (such as valproic acid and carbamazepine), the lipid-lowering 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, paracetamol and aminoglycosides [3,7]. Among others, clinical manifestations of drug-induced toxicity include liver toxicity, myopathy and peripheral neuropathy [3,7]. A preexisting mitochondrial disease may increase the risk of drug-induced mitochondrial toxicity [3]. In theory, magnesium sulfate should be considered as safe as it is not metabolized and thus not supposed to induce mitochondrial respiratory chain dysfunction.

Two cases of exacerbated magnesium sulfate toxicity in pregnant women with MELAS syndrome have been reported. In both cases, toxicity occurred in the mother. Hosono et al. described the case of a pregnant carrier of the m.3243A>G mutation who developed muscle toxicity after magnesium sulfate treatment in the context of threatened preterm delivery [8]. They suggested that magnesium toxicity in MELAS syndrome could be due to a competition of magnesium with calcium in mitochondrial membranes, which would then interfere with the calcium-dependent enzyme system [8]. Moriarty et al. also described magnesium sulfate inducing toxicity in a pregnant woman carrying the same mutation, despite magnesium therapeutic serum levels. Toxicity was characterized by drowsiness and decreased oxygen saturation. In this case, the authors found no explanation for the mechanism driving towards toxicity [9].

In our case, magnesium sulfate was well tolerated by the mother, but the newborn presented severe toxicity in the form of cardio-respiratory arrest. The mother only received the 4 g bolus dose before the baby was born and was kept on 1 g/hour for a total of 24 h. However, it is well known that magnesium sulfate crosses the placenta and readily distributes into the amniotic fluid and the fetal compartment [10]. Neonatal adverse effects correlate with mean maternal and neonatal magnesium concentrations [11]. Several observational studies showed that neonatal adverse effects were significantly associated with increasing concentrations of magnesium ions in the maternal circulation [12,13]. On the other hand, the doses of magnesium sulfate used in the treatment of preeclampsia or in neuroprotection have been shown to be safe and without any requirement of higher neonatal reanimation needs [14]. Azria et al. described that the concentration of magnesium sulfate in maternal plasmatic serum 30 min after the administration of the bolus is normally under the range of respiratory distress [15]. Therefore, the severity of the adverse event observed in our case is potentially due to another cause. The newborn carried the same familial mutation as his mother, but with a higher heteroplasmy of 80%. Only 5-8% of individuals present symptoms of MELAS before the age of 2 years. The tissues and organs have different thresholds

according to the percentage of heteroplasmy before clinical phenotypes manifest, which explains the multiplicity of symptoms in individuals bearing the same mutation. The threshold of muscle mutation load at which oxidative impairment occurs is approximately 50% [1]. One of our first hypotheses for the cardio-respiratory arrest was the presence of a cardiomyopathy deficiency in this newborn with a high degree of heteroplasmy, but an echocardiography showed normal biventricular systolic function, thus excluding this as a possible cause.

A second hypothesis was the presence of maternal and/or neonatal impaired kidney function and therefore drug accumulation. It is well known that the neonatal kidney function is impaired compared with adults due to immature glomerular filtration and tubular function and reduced kidney perfusion pressure [16]. Moreover, mitochondrial diseases are associated with renal functional impairment, despite normal serum creatinine levels [17]. Magnesium sulfate is exclusively excreted from the body by the kidneys through free glomerular filtration [10]. Altered elimination of magnesium consecutive to renal impairment linked to a MELAS syndrome in the mother and/or the fetus would lead to potential accumulation in both the mother and the fetus and therefore towards an adverse neonatal effect. Although it is difficult to explain the exact mechanisms explaining neonatal and/or maternal toxicity of magnesium sulfate in pregnant women/newborns with MELAS syndrome and/or carrying the m3243A>G mutation, it is important to be aware of this possible association due to the increased risk of preeclampsia in these patients. In the case of administration of magnesium sulfate to pregnant women with MELAS syndrome, a strict surveillance of the mother and the newborn should be performed to promptly diagnose potential severe adverse events.

Conclusion

In pregnant patients with MELAS syndrome or with genetic mutations for mitochondrial diseases, the possibility of drug toxicity for both the mother and the newborn should be kept in mind. Strict follow-up should be performed in order to prevent the occurrence of severe complications. In the case of unintended neonatal drug toxicity in the context of a maternal MELAS syndrome, it is important to test the newborn for the carriage of associated genetic mutations.

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Conflicts Of Interest

The authors declare that they have no any commercial or financial relationship that could be construed as a potential conflict of interest.

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