CASO CLÍNICO/CASE REPORT

Congenital Myasthenic Syndromes and Pregnancy Outcome

Síndrome Miasténica Congénita e Gravidez

Firmina Sambayeta [1,*], Luísa Sousa [1,2], Luís Ribeiro [3], Sara Duarte [1], Carla Silva Pinto [4], João Martins [5], Enerstina Santos [1,6]
1-Department of Neurology / Centro Hospitalar Universitário do Porto, Portugal
2-Centro Hospitalar de Entre o Douro e Vouga, Santa Maria da Feira, Portugal
3-Department of Neurology / Hospital Pedro Hispano - Unidade Local de Saúde de Matosinhos, Matosinhos, Portugal
4-Department of Obstetrics and Gynaecology / Centro Materno-Infantil do Norte, Centro Hospitalar Universitário do Porto, Porto, Portugal
5-Electromyography laboratory, MedicilLisboa, Lisboa, Portugal
6-Unit for Multidisciplinary Research in Biomedicine, Instituto de Ciências Biomédicas Abel Salazar (ICBAS) da Universidade do Porto, Portugal

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Abstract

Congenital myasthenic syndromes (CMS) are genetic conditions characterized by dysfunction of the neuromuscular transmission. There is limited data on pregnancy safety in myasthenia gravis for both mother and child. Retrospective study on pregnant CMS patients who were followed in two tertiary hospitals and their clinical data was analyzed.

Sixteen pregnancies from 9 patients with CMS and history of pregnancy were included: one had *CHAT*, two had *DOK-7* and six had *CHRNE* mutations. Previous reports showed that pregnancy can exacerbate the clinical manifestations of CMS. There are no specific recommendations for the disease during pregnancy. Our work adds sixteen pregnancies of women with CMS, without major complications for the mothers or newborns, except in one woman, with a *CHAT* mutation, who had significant worsening of her symptoms during pregnancy and post-partum period. The follow-up results of these women by a multidisciplinary team resulted in better outcomes.

Resumo

As síndromes miasténicas congénitas (SMC) são doenças genéticas caracterizadas por disfunção da transmissão neuromuscular. Existem dados limitados sobre a segurança da gravidez na miastenia *gravis*, tanto para a mãe como para o filho. Análise retrospetiva de doentes grávidas com um SMC seguidos em dois hospitais terciários. Dezasseis gestações de 9 doentes com SMC foram incluídas: um tinha mutação no gene *CHAT*, dois *DOK-7* e seis no gene *CHRNE*. Estudos anteriores mostraram que a gravidez pode exacerbar as manifestações clínicas do SMC. Não existem recomendações específicas para a doença durante a gravidez. Nosso trabalho, acrescenta dezasseis gestações de mulheres com SMC, sem maiores complicações para as mães ou recém-nascidos, exceto em uma mulher, com mutação *CHAT*, que teve agravamento significativo dos sintomas durante a gravidez e pós-parto. O seguimento dessas mulheres em um centro multidisciplinar ocasionaram uma melhoria nos resultados.

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***Autor Correspondente / Corresponding Author:**
Firmina Sambayeta
Rua Fernandes Costa, 230, 2B, bloco 4,
4100-240, Porto, Portugal
essanju86@hotmail.com

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Introduction

Congenital myasthenic syndromes (CMS) are congenital diseases characterized clinically by an insufficient neuromuscular transmission leading to progressive paresis. There is little data on the safety of pregnancy in CMS. The risk for children, related to genetic transmission or teratogenicity of the treatments, is not known.[1] According to previous reports, pregnancy can exacerbate the clinical manifestations of CMS for mothers. Patients considering pregnancy should be counseled to plan their management during pregnancy, delivery and postpartum, however there are no specific recommendations.[2]

Case Reports

Case 1: A 32-year-old woman, born to non-consanguineous parents, began having difficulties walking at 15 months, with frequent falls and fatigability. On neurologic evaluation she presented with bilateral facial paresis, proximal weakness, myopathic gait and scoliosis. Respiratory function was normal. Electromyography (EMG) showed a 15% decrease of compound muscle action potential (CMAP) amplitude after 3Hz repetitive nerve stimulation (RNS). She was diagnosed with CMS and the genetic test confirmed compound heterozygote mutations c.1124_1127dup and c.1378dup in *DOK-7* gene. She was started on oral salbutamol 4 mg/day, with partial improvement. At the age of 30, she expressed the intention to get pregnant. She had a genetic counseling consultation prior to the pregnancy that occurred one year later. Salbutamol was stopped in the first trimester, with slight worsening of fatigability. Salbutamol 1mg/day was restarted at the 20th week, with improvement. There was another slight worsening period at the 28th week, while maintaining treatment.

The patient had a vacuum-assisted vaginal delivery after 41 weeks. The newborn was a healthy boy with an Apgar score of 9/10 and a weight of 2880 g. In the postpartum period, she showed greater fatigability for 3 weeks that improved once salbutamol was increased to 2 mg/day. Since then, she has remained with minimal symptoms.

Case 2: A 22-year-old woman, born to non-consanguineous parents and without family history of neuromuscular disease. She had the first symptoms early in childhood, with easy fatigability and difficulty climbing stairs. She also reported long-term drooping eyelids, with progressive worsening. On the examination at age 17, she had symmetrical ptosis, bilateral ophthalmoparesis, marked facial diparesis and proximal tetraparesis. RNS showed a pathologic decremental response of CMAP amplitudes. Respiratory function was normal. Anti-acetylcholine receptor and anti-MuSK antibodies were negative. The genetic study for CMS showed compound heterozygosity with c.134C>T and c.1124_1127dup mutations in *DOK-7* gene. She was started on oral salbutamol 2-4 mg/day. An unplanned pregnancy occurred at age 21 years and she received genetic counseling. Salbutamol was stopped during the 1st trimester, with moderate worsening and restarted at the end of the 1st trimester, 6 mg/day, with improvement. She had a vacuum-assisted vaginal delivery after 39 weeks. The newborn was a healthy boy with good vitality, a weight of 2930 g and an Apgar score of 9/10. Postpartum was uneventful. Since then, she returned to the pre-pregnancy clinical status. There were no complications with the newborn, under exclusive breastfeeding for 6 months.

Case 3: A 39-year-old woman, born to first-degree consanguineous parents, along with 6 healthy brothers. The onset of symptoms was in childhood, with global fatigability on minimal efforts. She could not perform full arm elevation. On neurological evaluation, she had ptosis, ophthalmoparesis with diplopia, facial diparesis and proximal asymmetric tetraparesis.

Her first pregnancy was at the age of 25 years, with a normal course. By this time, she was not under specific therapy. A caesarean section was performed at 41 weeks due to lack of fetal descent, under general anesthesia. The newborn had neonatal hypoxia requiring resuscitation, with a good outcome. His weight was 3150 g. At 27 years old, she performed an EMG with RNS that showed a pathologic decremental response of CMAP amplitude in the facial muscles. Anti-acetylcholine receptor and anti-MuSK antibodies were negative. She was initially diagnosed with seronegative MG and started on pyridostigmine 180 mg/day plus prednisolone 60 mg/day without improvement. At this time, the diagnosis of probable CMS was also considered. Fluoxetine 20 mg/day was also given for associated depression.

At the age of 33, genetic testing for CMS was performed that detected two homozygous mutations, c.130dup in *CHRNE* gene. Prednisolone was stopped, and continued pyridostigmine with fluoxetine. The second pregnancy was at the age of 37 years; fluoxetine was stopped prior to the pregnancy. Respiratory function was normal. A caesarean section was performed under epidural anesthesia. The newborn was a healthy child, with an Apgar score of 9/10, weighing 3100 g. In both pregnancies, she experienced tolerable clinical

worsening during the post-partum period, without requiring hospitalization. Currently, the patient remains stable, with fluctuating weakness but being able to perform normal daily life activities.

Case 4: A 31-year-old woman, born to non-consanguineous parents, and with a sister with *CHRNE* mutations. Symptoms started at the age of 2 years, with global muscle weakness and ptosis. On evaluation, she had severe ophthalmoparesis, bilateral ptosis and proximal weakness. Genetic testing confirmed the compound heterozygote: c.1293insG and c.70insG mutations in *CHRNE* gene. She received pyridostigmine 240-360 mg/day, achieving optimal performance in daily activities. The RNS was not provided. Respiratory function tests showed a mild restrictive ventilatory pattern. The pregnancy occurred at the age of 30 years, with prior genetic counseling. She decided to reduce pyridostigmine to 180 mg/day, without clinical deterioration. The delivery was vaginal, vacuum-assisted, after 39 weeks. The newborn was a girl with good vitality, Apgar score 9/10, weighing 3020 g. There were no complications in the postpartum period. The baby was under exclusive breastfeeding until 6 months of age.

Case 5: A 46-year-old woman, born to non-consanguineous parents, presented with general motor weakness, ptosis and dysphonia since age of 3. The neurological evaluation at age 13 showed bilateral ptosis, ophthalmoparesis, diplopia and facial diparesis. Anti-acetylcholine receptor and anti-MuSK antibodies were negative. The RNS revealed a pathologic decremental response of CMAP amplitude and a positive edrophonium test. A diagnosis of seronegative MG was made. A thymectomy was performed and she was started on prednisolone 60 mg/day and pyridostigmine 360 mg/day. There was partial improvement of the cranial symptoms, with sustained limb weakness. Respiratory function tests showed a mild obstructive ventilatory syndrome. The pregnancy occurred at the age of 19 years, with a normal course and she had forceps assisted vaginal delivery, after 39 weeks. The newborn weighed 3000 g and had an Apgar score of 9/10. The patient had slight worsening of muscular weakness in the postpartum period, but remained stable afterwards. At the age 41 years, a clinical worsening occurred under pyridostigmine and prednisolone. Intravenous human immunoglobulin plus azathioprine 150 mg/day were started and improvement of motor symptoms was reported. At the age of 42 a genetic test was performed revealing homozygote mutations, c.130dup in *CHRNE* gene. Accordingly, immunosuppression was stopped and fluoxetine and salbutamol were started with objective clinical improvement.

Case 6: A 40 year old woman, born to a non-consanguineous parents, had two miscarriages in the first trimester (the autopsy of the first fetus was non-conclusive) and a family history of myasthenic symptoms (mother and aunt, in whom the genetic test for CMS is on-going). The symptoms started at the age of 16, with episodes of diplopia and progressive weakness of proximal limbs. She was started on pyridostigmine 180 mg and fluoxetine 20 mg daily. She had no pathologic decremental response of CMAP amplitude in RNS. Anti-acetylcholine receptor and anti-MuSK antibodies were negative. The genetic test showed a heterozygote mutation in *CHAT* gene (-c.707C> T). She had two viable pregnancies, at the age of 32 and 36 years old. In both she experienced significant clinical worsening of fatigue and muscular weakness, during the post-partum period. Both deliveries were performed with caesarean section. The newborns had good vitality and are healthy, until the current date.

Case 7: Three women in a vertical family line (proband, mother and grandmother), without known consanguinity, their ages are 39, 57 and 80 years respectively. They had a previous clinical and electromyographic (uniformly slowed speeds in peripheral nerves around 20 m/s) diagnosis of Charcot-Marie-Tooth-1 with *GARS* mutation (c.178G mutation> A, exon-1). Their first signs/symptoms of neuropathy appeared in the 1st/2nd decade of life. All three women also had complex oculomotor dysfunctions, fluctuating muscular fatigability, and variable severity with onset at the 4th decade. They all had favorable clinical response to pyridostigmine and fluoxetine. Anti-acetylcholine receptor and anti-MuSK antibodies were negative. A genetic panel (74 genes) on the proband detected a known *CHRNE* gene mutation (c.130 duplication, exon-2) confirmed by mendelioma and later confirmed in both the mother and grandmother.

All three women had pregnancies, all before the diagnosis of the myasthenic syndrome. Proband had three pregnancies and two deliveries. The first pregnancy was at the age of 20 years, with a miscarriage of a 26 weeks old fetus. The autopsy was inconclusive. The second pregnancy was at the age of 24 years old with normal course and delivery with forceps, at 41 weeks. The newborn weighted 3400 g and had an Apgar of 10/10. He died at 11 months by accidentally choking with an object. The third pregnancy occurred at 26 years old and the delivery was vaginal at 38 weeks. The newborn weighed 2100 g and had an Apgar of 10/10. He is healthy to date. All babies were under exclusive breastfeeding

Table 1. Clinical characteristics of our patients, their pregnancies and their newborns.

Case	Age of onset and CMS symptoms	Genetic mutation	Age at pregnancy	Symptoms during pregnancy	Delivery	Post-partum	New-born
Case 1	Symptom onset at 15 months Proximal limb muscle weakness Myopathic gait. Scoliosis RNS:15% decrease of CMAP amplitude after 3Hz RNS	Compound heterozygote mutations c.1124_1127dup and c.1378dup in *DOK-7* gene	31 yo	Mild worsening (1st and 3rd trimester)	Full term Vaginal Vacuum-assisted Epidural anaesthesia	Greater worsening in the first three weeks, improved after salbutamol	Apgar score of 9/10
Case 2	Symptom onset in early childhood Fatigability with minimal efforts Ptosis, ophthalmoparesis facial diparesis Proximal limb weakness RNS: pathologic decremental response of CMAP amplitude	Compound heterozygote mutations c.134C>T and c.1124_1127dup in *DOK-7* gene	21 yo	Mild worsening (in the 1st trimester after salbutamol suspension)	Full term Vaginal Vacuum-assisted	No symptoms	Apgar score of 9/10
Case 3	Symptom onset in childhood Easy fatigability. Ptosis, ophthalmoparesis, facial diparesis. Proximal limb weakness RNS: pathologic decremental response of CMAP amplitude	Homozygous mutations, c.130dup in *CHRNE* gene	25 and 37 yo	No relevant symptoms	Caesarean section General anaesthesia Caesarean section Epidural anaesthesia	Mild worsening on the 2nd post-partum period	Apgar score of the 1st newborn not provided (he had neonatal hypoxia requiring resuscitation with good outcome) 2nd newborn Apgar 9/10
Case 4	Symptom onset at age 2 Severe ophthalmoparesis and ptosis Proximal limb weakness Mild restrictive ventilatory pattern EMG was not provided	Compound heterozygote mutations: c.1293insG and c.70insG in the *CHRNE* gene	30 yo	No relevant symptoms	Full term Vaginal Vacuum-assisted	No symptoms	Apgar score of 9/10
Case 5	Symptom onset at age 3 Ophthalmoparesis, ptosis, facial diparesis, dysphonia. Proximal limb weakness Mild obstructive ventilatory syndrome RNS: pathologic decremental response of CMAP amplitude	Homozygote mutations, c.130dup in *CHRNE* gene	19 yo	No relevant symptoms	Full term Vaginal Forceps-assisted	No symptoms	Apgar score of 9/10
Case 6	Symptoms onset at age of 16 Diplopia and progressive weakness of the proximal limbs. RNS: no pathologic response was detected	Heterozygote mutation (-c.707C>T in *CHAT* gene	2 miscarriages in the 1st trimester and two viable pregnancies at the age of 32 and 36 yo	Clinical worsening with fatigue and muscular weakness in both pregnancies	Caesarean section in both deliveries	Important worsening of fatigue and muscular weakness, in both post-partum periods	Information not provided
Case 7	Three women in a vertical family line. All 3 had diplopia due to complex oculomotor misalignments, fluctuating muscular fatigability, onset in the 4th decade, except for the probando whose symptoms began earlier	*CHRNE* gene mutation (c.130 duplication, exon-2 detected	3 women aged 39, 57 and 80 years (the probando had 1 miscarriage in the 2nd trimester, at age of 20) 5 viable pregnancies: Probando at age of 24 and 26 yo Mother at age of 19 and 26 yo Grandmother 24 yo	All viable pregnancies had normal course	1 delivery with forceps 1 with caesarean section 3 vaginal deliveries	No symptoms	2 newborns had an Apgar of 10/10. The Apgar of the others 3 newborns was not provided, but no major complications were reported.

Yo: years old; RNS: repetitive nerve stimulation; CMAP: compound muscle action potential; EMG: electromyography.

until 6 months of age. Proband's mother had two pregnancies. The first at 19 years old with a vaginal delivery of a 3800 g baby girl (proband). The second occurred at 26 years old. The delivery was performed by caesarean section. She was born with 3450 g. Both babies were under exclusive breastfeeding until 6 months of age. The grandmother delivered at the age of 24 years a baby with 2400 g (proband's mother) by vaginal delivery. The baby was exclusively breastfed until 6 months of age. Although the diagnosis of the myasthenic syndrome was made after the pregnancies, a retrospective enquiry about possible relatable symptoms (or their worsening) during and in the months after the pregnancy and all three reported no symptoms.

Discussion

We present the description of 16 pregnancies from 9 patients with congenital myasthenic syndromes. In our cohort all pregnancies were followed-up at a multidisciplinary center and occurred without significant major complications or life-threatening symptoms, as did the deliveries and postpartum period, with the exception of two pregnancies. One woman, with a *CHAT* mutation had a significant worsening of her symptoms in the course of pregnancy and post-partum period, although not requiring hospitalization in an intensive care unit. There were 3 miscarriages in two women (with *CHAT* and *CHRNE* mutations), one of them in the second trimester of pregnancy. The fetal autopsies were non-conclusive in both women and we cannot ascertain if there was a causal relationship with the mother's CMS. Some women suffered transient worsening in the pregnancy and post-partum period, all with good recovery.

There are few reports in the literature on pregnancy in CMS patients. The risks for their children are not known. In fact, so far, the largest cohort of pregnancies in CMS included only 8 patients, with mutations in *CHRNA1* that had mutations in *CHRNA1*, *CHRNE*, *CHRND*, *GFPT1*, *COLQ* and *DOK-7* genes.[3] In this group, symptoms worsened for six patients during at least one of their pregnancies, and one patient required hospitalization in an intensive care unit during the post-partum period. One patient never recovered to the pre-pregnancy clinical condition. Only one caesarean section was performed. The children's outcome was excellent, with the exceptions of a pulmonary artery atresia in the offspring of a mother on pyridostigmine, and a newborn with a severe neonatal CMS. For the mothers, the overall clinical prognosis was good since the vast majority of patients recovered to their pre-pregnancy clinical status six months after delivery. Contrary to the French study, in our cohort most of women could breastfeed for 6 months, without complications. This work adds sixteen pregnancies from 9 mothers with a CMS: three of them resulted in spontaneous abortion (of uncertain cause), but in the remaining 13 a viable pregnancy was achieved without significant complications for the mothers or their newborns. This suggests that, with adequate planning and patient selection, pregnancy and delivery in CMS seems reasonably safe. Follow-up at a center specialized in neuromuscular diseases is very important.[3] ■

Contributorship Statement / Declaração de Contribuição

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

F.S.: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B
L.S.:1C, 2B, 3B
L.R.: 1C, 2B, 3B
S.D.:1C, 2C, 2B
J.M.:1A, 1B, 2B, 3C
C.S.P.: 1B, 3B
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