

Road to conception and successful delivery for a facioscapulohumeral muscular dystrophy patient

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Abstract

Facioscapulohumeral muscular dystrophy is a muscular dystrophy affecting all ages, primarily people in the second decade. The disease is initially presented with face, shoulder girdle, and upper arm involvement, followed by lower extremity muscle weakness. Disease progression is usually slow, although about one-fifth of patients will require a wheelchair to accommodate mobility. Women with this muscular dystrophy could rarely have poor birth outcomes, with facioscapulohumeral muscular dystrophy symptom deterioration post-partum. In this study, we present a case of a woman with a genetically confirmed facioscapulohumeral muscular dystrophy I who underwent cesarean section with epidural anesthesia with favorable outcomes following the procedure. Eight months post cesarean section, the patient reported no facioscapulohumeral muscular dystrophy symptom deterioration. We reviewed the literature with emphasis on large studies concerning facioscapulohumeral muscular dystrophy and birth outcomes and concluded that the hereby presented approach is important for the comprehensive obstetric care and future risk assessment and management in such patients.

Keywords

Facioscapulohumeral muscular dystrophy, pregnancy, cesarean section (C-section), post-partum complications

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Introduction

Facioscapulohumeral muscular dystrophy (FSHD), a condition belonging to the hereditary progressive skeletal muscle dystrophies group, represents the second most common cause of muscular dystrophy in adults with an estimated prevalence of 1–2.4:20,000.^{1,2} FSHD may be either inherited in autosomal dominant pattern or present as a de novo mutation, where no family history has been identified.³ Somatic mosaicism is well reported in about 40% of the de novo cases.⁴ Two genetic variations of FSHD, which are phenotypically indistinguishable, exist. FSHD1 (MIM:158900) represents 95% of all FSHD cases while FSHD2 (MIM:158901) represents the remaining 5%. The genetic basis of FSHD pathogenesis is ectopic expression of the transcription factor DUX4 (double homeobox 4) in skeletal muscle. In FSHD type 1, partial deletion of the D4Z4 repeats on chromosome 4 affects the expression of DUX4, while FSHD type 2 is a result of mutations in the chromatin methylation regulatory proteins, namely, SMCHD1 and DNMT3B.⁵ In FSHD1, one copy of 4q35 has a contracted number of repeats (1–10 repeats), resulting in a more permissive

chromatin structure, as demonstrated by the hypomethylated DNA.⁶ The penetrance and the severity of FSHD are in inverse correlation with the number of D4Z4 repeats on the 4qA haplotype and with the level of methylation. Moreover, the length of the D4Z4 array is in direct correlation with the age of the onset of the disease: the smallest number of the D4Z4 repeats is found more often in patients with early onset of disease.⁵

FSHD can present with variability of symptoms and rates of progression. Usually, the disease presents with asymmetric upper extremity and facial muscle weakness affecting the

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facial muscles, shoulder girdles, and upper arms, followed by weakness of the trunk and distal lower extremities.⁷⁻⁹ Symptoms from shoulders and arms as well as mobility difficulties are associated with poor morbidity outcomes.¹⁰ Extramuscular manifestations of FSHD are infrequent, except for neuromuscular restrictive lung disease which occurs in about 20% of patients and asymptomatic right bundle branch block, which occurs with a high incidence.¹¹⁻¹³ As this type of muscular dystrophy can affect the majority of muscle groups, it may lead to abdominal and truncal muscle weakness, resulting in complications at the second stage of labor, where the baby is pushed through the birth canal.²

There is still limited information about the pregnancy course and birth outcomes in women with hereditary neuromuscular disorders, and especially with FSHD. The clinical management of women with FSHD requires a multidisciplinary approach including obstetrician, neurologist, and anesthesiologist input to minimize the risk of permanent disability after labor. In this report, we present a woman with FSHD who underwent cesarean section with epidural anesthesia and an excellent pregnancy and birth outcome, as well as review of the literature.

Case presentation

A 33-year-old Caucasian nulliparous woman was admitted to our clinic for fertility and genetic counseling. She is presented with known FSHD1 and a *de novo* pattern of mutation (deletion of chromosome 4q35, FSHD allele 1 size of 18 kb), as indicated from proband analysis. The size of D4Z4 allele ranging from 12 to 37 kb was considered abnormal.¹⁴ The patient presented symptoms of the disease at the age of 15. As a teen, she reported difficulty of complete eyelid closure due to facial weakness. The patient reported pronounced facial weakness affecting nutritional as well as social aspects of life, such as drinking through a straw and smiling. At the age of 30, exclusive upper body involvement was reported, resulting in a palsy of wrist extensors and periscapular shoulder weakness. Over the last 3 years, the disease involved proximal lower extremity muscles (quadriceps, hamstring, and glutes). Particularly, there was a noticeable atrophy of the quadriceps, resulting in difficulty walking. In addition, the patient did not report extramuscular complications which could rarely be present in the context of FSHD, including hearing loss, respiratory failure, cardiac arrhythmias, and retinal telangiectasia.^{11,12}

Given the age of onset, severity of disease,¹⁵ and ovarian reserve, we advised the patient to undergo *in vitro* fertilization (IVF) prior to disease progression. Her anti-Müllerian hormone (AMH) level was 0.5 ng/mL, antral follicle count (AFC) 3, and FSH 15 mIU/mL. Since the age of 40, the patient has undergone a total of eight natural cycles, and three embryo transfers (ETs) under sonographic guidance were performed. The first one resulted in miscarriage at the eighth gestation week and the last two embryo transfers were

not successful. The possibilities of using donor eggs as well as adoption were also explored with the patient.

Interestingly, at the age of 42, the patient got naturally pregnant and was admitted to us for follow-up. After careful consideration and discussion, the patient decided not to proceed to any prenatal testing. Her pregnancy was uncomplicated, but her symptoms worsened. The weakness of proximal lower extremity muscles became more severe and the lower limb abduction was minimal. A neurologist examined thoroughly the patient prior to delivery, including the presence or absence of scapular winging; facial, limb, and abdominal muscle weakness; and asymmetry of muscle weakness. Muscle strength was evaluated by using the Manual Muscle Testing (MMT, according to Medical Research Council) and Ricci Clinical Severity Score (CSS) was also assessed.¹⁶ According to the neurologist's input, the patient had a CSS of 4, suggesting severe disease. Elective cesarean section (C-section) with epidural anesthesia was performed at 39 weeks of pregnancy. The weight of the newborn was of normal range (3.100 g). The woman mobilized the same day of the procedure with no remarkable pain. Eight months post-delivery, she confirmed no deterioration of her symptoms at the 1-year follow-up clinic appointment, suggesting no effect of the pregnancy on the progression of the disease, in this case.

Discussion

FSHD is a muscular dystrophy with significant variability of onset age and progression rate. Usually, individuals present with symptoms in the second decade of life and the majority deteriorate slowly over the years. However, a small number of patients may require wheelchair to accommodate mobility after the age of 50.^{10,17} Recent studies indicated that, due to different genetic background, variable phenotypes and penetrance can appear among patients carrying the same molecular signature, making FSHD counseling in these patients quite challenging. Therefore, counseling FSHD patients should include, apart from molecular testing, estimating the precise clinical status of the patient and, whenever possible, of the extended family.¹⁸

Women with FSHD, who are contemplating pregnancy, should be counseled adequately on FSHD genetics, clinical severity variability, and reproductive options. During the pregnancy, a multidisciplinary approach should be pursued to assess optimal delivery approach as well as the type of anesthesia. After childbirth, women should be observed for possible symptom deterioration.

At present, two studies have correlated pregnancy and birth outcomes in women with FSHD. Ciafaloni et al. surveyed 38 women with FSHD reporting 105 gestations and 78 births. The authors observed increased incidence of operative vaginal delivery, due to truncal and abdominal muscle weakness. In addition, a significantly higher rate of low birth weight as well as muscle weakness exacerbation and pain

following birth has been reported.² Six years later, Awater et al. reviewed the obstetric histories of 178 patients with different hereditary neuromuscular disorders. From them, 13 women with FSHD achieved 26 births. Approximately 12% FSHD sufferers recorded deteriorating muscle weakness compared with other hereditary neuromuscular disorders. Nonetheless, no significant pregnancy complications were observed in the FSHD group compared with the general population.¹⁹

In this case report, a risk-benefit analysis was performed, with patient input at every stage, to decide between modes of delivery, namely, C-section or vaginal delivery. Upon patient assessment, significant difficulty in leg abduction and abdominal/truncal muscle weakness was noted. Taking into consideration the skeletal muscle effort required for vaginal delivery and the profound muscle weakness of our patient, C-section was selected as the preferable delivery mode for patient and fetus. Considering anesthetic approach, while the neurologist's advice was against the use of epidural anesthesia, due to leg numbness sequela, the operating team, including the anesthesiologist, decided in favor of epidural anesthesia which was shown to be, in retrospect, without complications. However, it is worth mentioning that our approach with C-section might not benefit patients who are much more mildly affected; there might be different management options.

Ciafaloni et al.² reported a statistically significant amount (24%) of women with deterioration of symptoms after pregnancy that for the most part did not resolve after childbirth. However, in our case, no deterioration of symptoms during pregnancy or after childbirth was reported. The same research group reported increased C-section rate (23.8%) in comparison with average national data (16.9%). Of note, this study may be outdated (2006) and, since then, C-section expertise has increased. Mode of anesthesia is not mentioned in the paper; thus, epidural may be a great option. Taking into consideration the extreme muscle effort required in the second stage of labor, we believe that C-section with epidural anesthesia should be strongly considered in women with lower extremity as well as abdominal muscle involvement. Even if the patient had an uncomplicated vaginal delivery, the abdominal and truncal muscle effort required to push the baby through the birth canal may have deteriorated the patient symptomatology. However, there is not enough evidence to support our hypothesis. As for the low birth weight, the baby was born at a normal weight but generally birth weight is difficult to interpret based on what is yet known about the pathophysiology of FSHD. In the Awater et al. study, associations between low birth weight and FSHD mother were not safely drawn, so it remains unclear whether this finding from Ciafaloni et al. is relevant.

Conclusion

In conclusion, FSHD is a rare muscular disorder affecting all muscle groups, including those required for delivery.

Muscular weakness is of slow progression and individuals diagnosed at a young age frequently require a wheelchair to facilitate mobilization. From a patient perspective, muscle weakness should not be a discouraging factor, if they wish to procreate, given that a multidisciplinary team is in place to facilitate their wishes with focus on patient and neonate safety. The multidisciplinary approach to facilitate optimal outcomes for mother and baby was highlighted in our case. Our approach with C-section and epidural anesthesia showed favorable results and may be used as a guide in severely affected FSHD, pregnant patients, albeit patient outcomes need to be validated in subsequent studies. Given the rarity of the described condition, clinical decision-making may benefit from further relevant case reports.

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Author contributions

T.O., S.K., and K.S.L. contributed to concept, analysis, format, revision, literature search, and manuscript drafting. T.O. and V.N. conducted the operation. S.K. and K.S.L. contributed to editing. T.O. and V.N. gave expert opinion.

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