PERINATAL JOURNAL

Case Report

Perinatal Journal 2012;20(1):35-39

Recurrent lethal multiple pterygium syndrome: prenatal ultrasonographic and postmortem findings

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Abstract

Objective: Multiple pterygium syndrome (MPS) covers a disorders characterized by multiple congenital anomalies typified by pterygia of the neck, elbows, and knees and associated with limited fetal movement and joint contractures. The lethal forms of this condition frequently exhibit multiple fetal abnormalities. We aimed to discuss a recurrent MPS case with the patient' s pedigree, ultrasonographic and postmortem findings.

Case: We are presenting a 29-year-old, gravida 5 para 4 woman with a diagnosis of recurrent MPS whose pregnancy was terminated on her 20th gestational week.

Conclusion: MPS is found to be a rare cause of recurrent midtrimester pregnancy losses in which the inheritance may be autosomal or Xlinked recessive. Genetic counseling and pedigree analysis are the important steps in the evaluation of recurrent MPS subjects. Although researches for the understanding of the underlying mechanisms of this syndrome are promising, obstetric ultrasound is still the gold standard diagnostic technique.

Key words: Lethal multiple pytergium syndrome, LMPS, cutaneous pterygia, joint contractures.

Tekrarlayan letal multipl piterjium sendromu: prenatal ultrasonografik ve postmortem bulguları

Amaç: Multipl piterjium sendromları (MPS), birçok konjenital anomali ile karakterize olup, tipik olarak özellikle boyun, dirsek ve diz eklemlerinde piterjiumların görüldüğü ve eklem kontraktürlerine bağlı fetal hareketlerin kısıtlandığı bozuklukları kapsar. Bu tablonun letal formları sıklıkla multipl fetal anomaliler ile kendini gösterir. Tekrarlayan bir MPS olgusunu; hastanın soyağacı, ultrasonografik ve otopsi bulguları ile tartışmayı hedefledik.

Olgu: 29 yaşında G5 P4, tekrarlayan MPS tanısı ile 20. gebelik haftasında gebeliği sonlandırılan olguyu sunmaktayız.

Sonuç: Tekrarlayan orta trimester gebelik kayıplarının çok nadir bir nedeni olan MPS, otozomal veya X' e bağlı resesif kalıtım gösteren bir hastalıktır. Tekrarlayan MPS olgularının değerlendirilmesinde, genetik konsültasyon ile soyağacı analizlerinin yapılması en önemli basamaklardır. Bu sendromun altında yatan mekanizmaların anlaşılmasına yönelik yapılan araştırmalar ümit vaad edici olsa da, obstetrik ultrasonografi halen tanıda altın standart tekniktir.

Anahtar sözcükler: Letal multipl piterjium sendromu, LMPS, kutanöz pterjium, eklem kontraktürleri.

Introduction

Fetal akinesia deformation sequence (FADS) results from impaired fetal movement and triggered by genetic and environmental factors.[1,2] Multiple pterygium syndrome is a heterogenous disease phenotypically and genetically, and it has two types on prenatal period as lethal and non-lethal (Escobar).[3] Lethal multiple pterygium syndrome (LMPS) is a FADS disorder characterized by multiple pterygia (webbing) and flexion contractures of the neck, elbows and knees, and may be associated with other abnormalities such as, fetal hydrops, cystic hygroma, club foot, intrauterine growth restriction (IUGR), hypoplastic lungs and facial anomalies. It is a rare cause of recurrent midtrimester pregnancy loss.[4] The inheritance may be autosomal or X-linked recessive.[5] Homozygous mutations in the fetal acetylcholine receptor subunits.[1] may cause fetal akinesia leading to LMPS. This brings up

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Received: July 21, 2011; **Accepted:** December 20, 2011

Available online at:
www.perinataljournal.com/20120201004
doi:10.2399/prn.12.0201004
QR (Quick Response) Code:

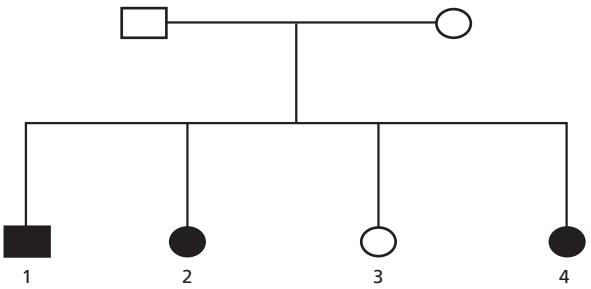
the possibility of prenatal diagnosis by genetic analysis where it is not possible at the moment. Therefore, prenatal diagnosis depends upon the patients' history, pedigree analysis and ultrasound findings. Here, we would like to report a recurrent LMPS case with its second trimester ultrasonographic pictures and postmortem findings.

Case Report

A 29-year-old, gravida 5, para 4 woman was referred to our tertiary center on her 20th week of gestation. The couple was otherwise healthy and non-consanguineous. Her first pregnancy resulted in a fetal demise at 24th gestational week (GW). Autopsy revealed a hydropic male fetus with webbing of the elbows and knees and club foot deformity. She had her second pregnancy two years later. Although amniocentesis revealed a normal karyotype, the pregnancy again resulted in a fetal demise at 20th GW. Autopsy report was similar, moreover kyphoscoliosis was present. Four years later, she had delivered a healthy term female baby on her 3rd pregnancy. Two years later, her 4th pregnancy ended with a fetal demise at the 26th GW. The postmortem findings revealed a female fetus with webbed neck, elbows and knees. It is worth to note that the patient did not receive any antenatal care on her 3rd and 4th pregnancies by her will. One year later, she was pregnant again and she admitted to our maternal-fetal unit on her 20th GW although she was referred on the 11th GW. Initially, a genetic consultation was obtained in which an autosomal recessive inheritance pattern was detected according to her pedigree analysis (**Fig. 1**). Ultrasonography revealed a single alive fetus where the fetal biometry was compatible with 18 weeks. A marked soft tissue edema was consistent with hydrops fetalis (**Figs. 2a** and **b**). The neck was shortened and widened. The chest appeared narrow and deformed with right pleural effusion complicated with pulmonary hypoplasia (**Figs. 2c** and **d**). A-polyhydramniotic state was recognized. There was no ascites. The posturing of the hands and feet were abnormal. No fetal movements were observed during the 30 minutes examination (even after stimulation). The upper and lower extremities were fixed, flexed and shortened. The feet were clubbed (**Figs. 3a** and **b**). All these findings were consistent with a recurrent LMPS. When the family was informed about the situation they requested the termination of pregnancy. The patient was discussed in our multidisciplinary clinical council and termination of pregnancy was decided. Labour was induced with misoprostol and a non-viable male fetus was delivered. Postmortem fetal head findings were; micrognatia, small mouth, flat nasal bridge, hypertelorism, epicanthal folds, scalp edema, low set ears and short neck (**Fig. 3c**). Upper and lower extremities showed flexion contractures with pterygia (**Figs. 3c** and **d**) and bilateral talipes equinavarus were present. Upon the request of the family, internal autopsy was not performed. Fetal karyotyping of the case was reported as 46-XY.

Discussion

Lethal multiple pterygium syndrome is the fatal form of multiple pterygium syndromes. LMPS is named for its typical fatality and for the presence of multiple pterygia and across a joint, which are associated with severe joint contractures (arthrogryposis). This autosomal recessive disorder is characterized by fetal movement loss leading to a cascade of events resulting of extremity contractures with multiple anomalies. This may be accompanied by lymphatic obstruction sequence leading to hydrops fetalis that is seen with subcutaneous edema, cystic hygroma, and pulmonary hypoplasia together.[3,5] The syndrome is fatal either in-



1. Multiple pterygium syndrome [46,XY]
2. Multiple pterygium syndrome [46,XY]
3. 3.5 years old healthy girl
4. Multiple pterygium syndrome [46,XY]

Fig. 1. Pedigree analysis of the family showing the autosomal recessive inheritance of recurrent multiple pytergium syndrome.

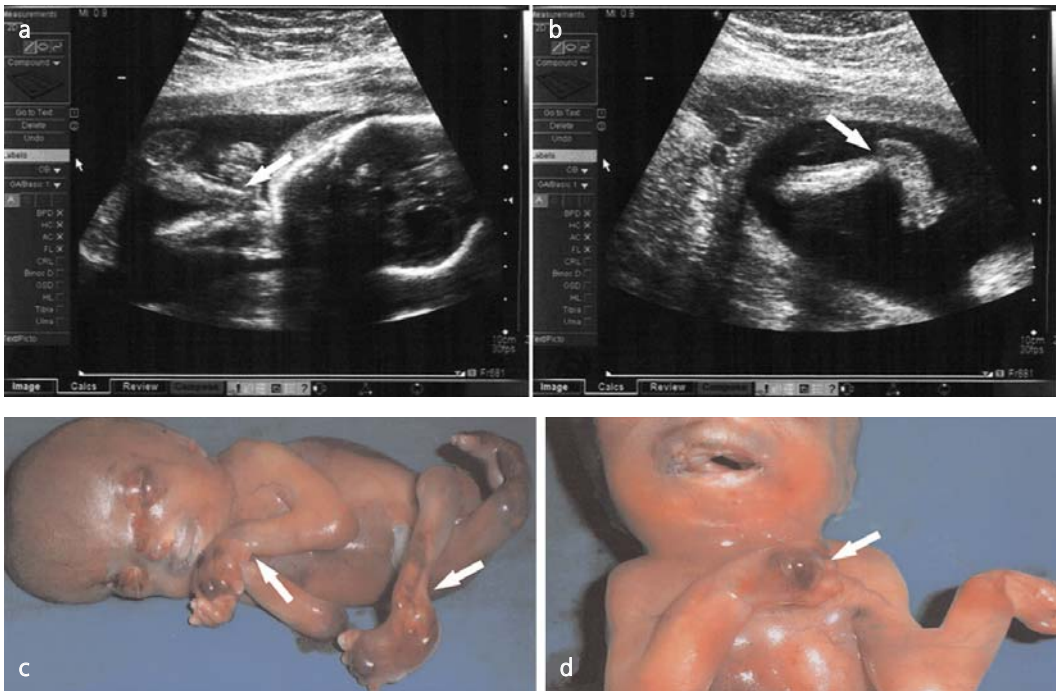


Fig. 2. (**a**) Upper extremity showing flexion deformity of the wrists (arrow) and (**b**) lower extremity showing talipes deformity of the foot (arrow). (**c**) Postmortem findings were micrognatia, small mouth, flat nasal bridge, hipertelorism, epicanthal folds, scalp edema, low set ears, short neck and flexion deformities of extremities (arrows). (**d**) The presence of a subcutaneous ptergia (web) at the forearm (arrow) associated with joint contractures. [Color figure can be viewed in the online issue, which is available at www.perinataljournal.com]

utero or shortly after delivery.[7] The inheritance may be X-linked recessive but most cases follow an autosomal recessive trait. Therefore establishing a diagnosis for LMPS is utmost important for the current and subsequent pregnancies. Common ultrasonographic findings are absence of fetal limb movements, limb flexures, hydrops fetalis and cystic hygroma. Moreover IUGR, lung and cardiac hypoplasia, diaphragmatic hernia, hydronephrosis, cerebral anomalies, polyhydramnios, abnormal faces with hypertelorism, low set ears, intestinal abnormalities and skeletal abnormalities may also be present.[8] Cystic hygroma is an early and important sign of LMPS.[9] Most of the reported cases in the literature are in the second or third trimester of the pregnancy.[6,8,10] but first trimester ultrasound diagnosis especially in the context of recurrence is also possible.[11] The risk of syndrome for the offspring is affected by the inheritance pattern; therefore a comprehensive genetic workup is mandatory.

Michalk et al. showed that complete or severe functional disruption of fetal acetylcholine receptor causes LMPS.[1] Recessive mutations of embryonal subunit of the acetylcholine G receptor (CHRNG) may cause both lethal and non-lethal MPS.[3,12] Vogt et al. stated in their study performed on 15 LMPS cases that they did not meet any CHRNA1, CHRNB1 or CHRND mutations; however, they reported a homozygote RAPSN frameshift mutation in a case with lethal fetal akinesia.[3] This information may provide great opportunities for understanding the pathogenesis of LMPS and diagnosing early and even developing some methods for establishing genetic diagnosis before implantation. In our case, it was not possible to show described genetic mutations due to the limitations on our genetic laboratory opportunities and since the family did not request an additional evaluation. The pedigree analysis of our case (**Fig. 1**) displayed an autosomal recessive inheritance and in this way, it was determined that both

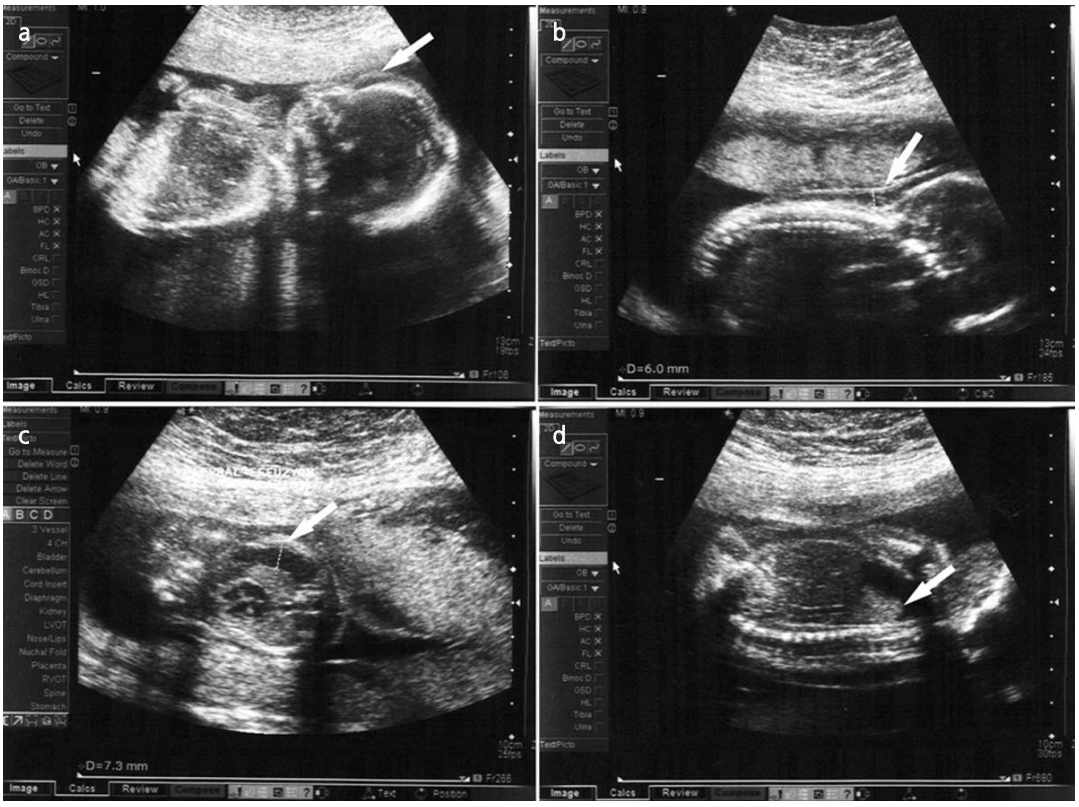


Fig. 3. (**a**) Prominent scalp edema consistent with hydrops fetalis. (**b**) Subcutaneous edema on transverse view. (**c,d**) Right pleural effusion with pulmonary hypoplasia.

mother and father were passive carriers. By means of a pedigree study, it is possible for physician to provide a better genetical consultancy to a family. As MPS is a genetical disease free of inheritance pattern, there is no method for avoiding to catch the disease for now. Although sperm donation is a method that can be recommended to families, it seems impossible to practice for many families.

Conclusion

This finding may offer an insight for the pathogenesis of LMPS leading to an earlier and even preimplantation genetic diagnosis of LMPS. Although these developments would be a potential for some form of interventional therapy in the future, today the gold standart diagnostic approach in such a rare case is obstetric ultrasound.

Conflicts of Interest: No conflicts declared.

References

1. Michalk A, Stricker S, Becker J, Rupps R, Pantzar T, Miertus J, et al. Acetylcholine receptor pathway mutations explain various fetal akinesia deformation sequence disorders. Am J Hum Genet 2008;82:464-76.
2. Parlakgümüş HA, Tarım E. Fetal akinezi / hipokinezi deformasyon sekansı (FADS): iki ve üç boyutlu ultrason bulguları. Türkiye Klinikleri J Gynecol Obst 2008;18:336-9.
3. Vogt J, Harrison BJ, Spearman H, Cossins J, Vermeer S, ten Cate LN, et al. Mutation analysis of CHRNA1, CHRNB1, CHRND, and RAPSN genes in multiple pterygium syndrome/fetal akinesia patients. Am J Hum Genet 2008;82: 222-7.
4. Lockwood C, Irons M, Troiani J, Kawada C, Chaudhury A, Cetrulo C. The prenatal sonographic diagnosis of lethal multiple pterygium syndrome: a heritable cause of recurrent abortion. Am J Obstet Gynecol 1988; 159:474-6.
5. Türkmen M, Süleymanova D. Multipl pterigium sendromu: bir olgu sunumu. Çukurova Üniversitesi Tıp Fakültesi Dergisi 1999;24:24-6.
6. Moerman P, Fryns JP, Cornelis A, Bergmans G, Vandenberghe K, Lauweryns JM. Pathogenesis of the lethal multiple pterygium syndrome. Am J Med Genet 1990; 35:415-21.

7. Martin NJ, Hill JB, Cooper DH, O'Brien GD, Masel JP. Lethal multiple pterygium syndrome: three consecutive cases in one family. Am J Med Genet 1986;24:295-304.
8. Hertzberg BS, Kliewer MA, Paulyson-Nunez K. Lethal multiple pterygium syndrome: antenatal ultrasonographic diagnosis. J Ultrasound Med. 2000;19:657-60.
9. Witters I, Moerman PH, Van Assche FA, Fryns JP. Cystic hygroma colli as the first echographic sign of the fetal akinesia sequence. Genet Couns 2001;12:91-4.
10. Gundogan M, Fong K, Keating S, Pierre-Louis J, Chitayat D. First trimester ultrasound diagnosis of lethal multiple pterygium syndrome. Fetal Diagn Ther 2006;21:466-470.
11. Bhargava N, Upreti L, Bhargava SK, Jain L. Case report: antenatal ultrasound diagnosis of multiple pterygium syndrome. Ind J Radiol Imag 2002;12:555-8.
12. Morgan NV, Brueton LA, Cox P, Greally MT, Tolmie J, Pasha S, et al. Mutations in the embryonal subunit of the acetylcholine receptor (CHRNG) cause lethal and Escobar variants of multiple pterygium syndrome. Am J Hum Genet 2006;79:390-5.