International Journal of Anatomy and Research,
Int J Anat Res 2016, Vol 4(4):3312-16. ISSN 2321-4287
DOI: http://dx.doi.org/10.16965/ijar.2016.474

Case Report

A RARE CASE OF FEMORAL HYPOPLASIA (PROXIMAL FOCAL FEMORAL DEFICIENCY) WITH OVERLAPPING PHENOTYPE OF MULLERIAN DUCT SYNDROME (MAYER-ROKITANSKY-HAUSER SYNDROME)

Cheryl Melovitz-Vasan [1], Hiroshi Kitoh [2], Nagaswami Vasan *[3].

[1] Assistant Professor, Department of Biomedical Sciences, Cooper Medical School of Rowan University, Camden, New Jersey, USA.

[2] Associate Professor, Department of Orthopedic Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan.

*[3] Professor of Anatomy, Department of Biomedical Sciences, Cooper Medical School of Rowan University, Camden, New Jersey, USA.

ABSTRACT

Background: Congenital deformities of the femur vary from minimal hypoplasia to total absence with or without other skeletal or organ system involvement. The proximal focal femoral deficiency is a rare congenital deformity with various degrees of involvement.

Materials and Methods: During physical examination of a donated body (willed body program) we observed a donor with extreme hypoplasia of the left femur with other musculoskeletal anomalies. The donor was a 77-year old Caucasian female, who died of coronary artery and peripheral vascular disease.

Results and Observations: We report here a rare case of proximal focal femoral deficiency with overlapping phenotype of Müllerian duct anomaly typifying congenital absence of uterus, fallopian tube, uterine cervix and vagina (Mayer-Rokitansky-Kuster-Hauser (MKRH) syndrome). Dissection of the cadaver revealed unilateral hypoplasia of the left femur with an aplastic acetabulum, femoral head and patella. The left tibia and fibula were anatomically normal but shorter. The ovaries were small and atrophied. The external genital structure was normal with blind ending vagina. We also observed involvement of vascular structures.

Conclusion: The features we observed are described in the literature as that of proximal focal femoral deficiency with overlapping phenotype of Mayer-Rokitansky-Kuster-Hauser syndrome. This is first report of coexistence of a proximal focal femoral deficiency and congenital absence of uterus, Fallopian tubes, uterine cervix and vagina is a rare defect.

KEY WORDS: Proximal focal femoral deficiency, Mayer-Rokitansky-Kuster-Hauser syndrome, Al-Awadi-Raas-Rothschild syndrome, Fuhrmann syndrome, vascular defect, femoral hypoplasia, Müllerian duct anomaly.

Address for Correspondence: Dr. Nagaswami Vasan, D.V.M., M.V.Sc., Ph.D. Professor of Anatomy, Department of Biomedical Sciences, Cooper Medical School of Rowan University 401 South Broadway, Camden, New Jersey 08103, USA. Phone: +1 (856) 361-2890, **E-Mail:** vasan@rowan.edu

Access this Article online

Quick Response code

DOI: 10.16965/ijar.2016.474

Web site: International Journal of Anatomy and Research
ISSN 2321-4287
www.ijmhr.org/ijar.htm

Received: 10 Dec 2016
Peer Review: 10 Dec 2016
Revised: None

Accepted: 02 Dec 2016
Published (O): 31 Dec 2016
Published (P): 31 Dec 2016

INTRODUCTION

Congenital deformities of the femur vary from minimal hypoplasia to total absence with or without other skeletal or organ system involve-

ment [1,2]. The proximal focal femoral deficiency (PFFD) is a rare congenital deformity with various degrees of involvement. Although the prevalence of PFFD is estimated to be 1 in 4500, females are more commonly affected than males [3] and left lower limb involvement seems to be more prevalent [4].

Aitken [5] described the congenital femoral deficit as 'proximal focal femoral deficiency' (PFFD) and distinguished four classes ranking A to D from the least severe form to the most severe form In class A femoral head is present with normal acetabulum with a short femoral shaft. In class B there is more severe defect of proximal femur, dysplastic acetabulum, the femoral segment is short with proximal bony tuft and no osseous connection between the head and shaft. In class C there is severely dysplastic acetabulum and femoral head, proximal femoral shaft usually tapered and without defined trochanter. The class D is the most severe form with aplasia of the acetabulum and proximal femoral components, extremely short femur which often has only an irregular ossified tuft of bone proximal to the distal femoral epiphysis. There is a similarity in the musculoskeletal deformity between the class D phenotype of PFFD and those with Al-Awadi-Raas-Rothschild syndrome and Fuhrmann syndrome [6]. We report here a rare case of class D phenotype PFFD [5] with overlapping phenotype of Mayer-Rokitansky-Kuster-Hauser (MKRH) syndrome typifying congenital absence of uterus, fallopian tube, uterine cervix and vagina (Müllerian duct anomaly).

During the fifth and sixth weeks of human embryo, two pairs of genital ducts the mesonephric (Wolffian) ducts that is important in the development of the male reproductive system and the paramesonephric (Müllerian) ducts important in the development of the female reproductive system are present. In the female fetus the paramesonephric duct differentiate into uterus, fallopian tubes, uterine cervix and the upper part of vagina while the mesonephric duct degenerate [7].

MATERIALS AND METHODS

During examination of a donated body to our 'Willed body program' we observed a severely shortened left lower limb. Before a whole body dissection was performed on the 77-year old Caucasian female, who died of coronary artery and peripheral vascular disease, a complete physical examination was conducted and plain film x-rays of both lower limbs were obtained.

Physical examination revealed the affected left side was bulkier and exhibited extremely short thigh, talipes valgus of the foot, and aplasia of the patella. The tibia and fibula were anatomically normal but shorter. The right lower extremity was unremarkable and no facial anomalies or other skeletal defects were observed. Further physical examination was unremarkable.

Radiographic assessment confirmed aplasia of the acetabulum and femoral head, and hypoplasia of the femur. We also observed a total right hip joint replacement with a titanium prosthesis (Figure 1). Dissection of the region revealed the hypoplastic femur was 14.5 cm long (Figure 2) and attached to the hipbone by the surrounding soft tissues. Aplasia of the acetabulum, patellar aplasia, the anatomically normal but shorter tibia and fibula, and deformed skeletal elements of the ankle and foot were also confirmed. Because of the thigh and the quadriceps muscles were rotated laterally and all hip and thigh muscles on the affected side were present but characterized by contracture and disuse atrophy.

Dissection also showed the heart, lungs, gastrointestinal tract, kidneys and suprarenal glands were normal and the ureters entered the bladder normally. The uterus, uterine tubes, uterine cervix and vagina, however, were absent and the vagina ended blindly. A pair of small atrophied ovary was present. Since a surgical scar indicative of a hysterectomy was not detected, a congenital defect associated with the PFFD likely accounted for the observed visceral aplasia. The external genitalia, on the other hand, were normal and the urethra entered the anterior aspect of the vaginal vestibule. Compared to the right side, the left common iliac artery, left internal iliac artery, left external iliac artery, and left femoral artery were smaller in diameter (Figure 3) but the left superior hypogastric artery and left inferior hypogastric artery were slightly enlarged. From the information published in the obituary notice, the donor

was gainfully employed in an international corporation indicating normal cognition and lived a normal life span of 77 years.

Fig. 1: Radiograph of the hip shows on the left side aplasia of the acetabulum and femoral head, hypoplasia of the femur and aplasia of the patella.

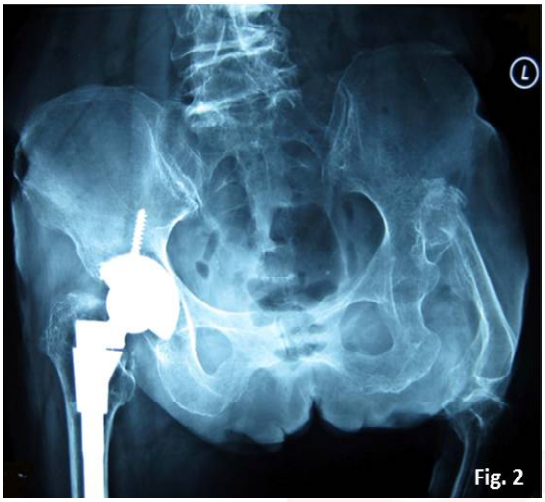

Fig. 2: Dissection of the left femur shows the aplasia of the femoral head, neck and severe hypoplasia of the femur.

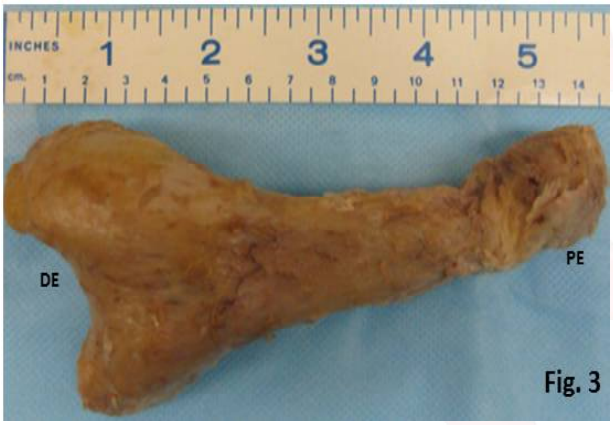

Fig. 3: Cadaveric specimen showing: **A:** Abdominal aorta; **B:** Right common iliac; **C:** Right external iliac; **D:** Right internal iliac; **E:** Left common iliac; **F** Left external iliac; **G:** Left internal iliac. Compared to the right normal side the size of the left common, external, internal iliac arteries and femoral artery are smaller in diameter.

RESULTS AND DISCUSSION

Congenital defects of the long bones and the extent of the defects varied from total absence to minor differences [1,2]. Unilateral femoral dysplasia accounts for 85-90% of congenital skeletal defects [8] and the affected individuals are mostly female [9].

The clinical appearance of PFFD is not subtle and easily recognized. The femur is shortened, flexed, abducted, and externally rotated [5,10,11]. The bulbous proximal thigh quickly tapers to the knee and flexion of the hip and knee typically causes dysfunction of the joints [12]. Small or vestigial patellae were observed in affected children [11]. Accordingly, we observed patellar aplasia in the present adult case of PFFD. A substantial reduction in length and diameter of the ipsilateral external iliac, femoral, and deep femoral arteries was observed in PFFD patients [13]. Similarly, we identified smaller diameters of the ipsilateral common iliac, internal iliac, external iliac, and femoral arteries in the present case of PFFD (Fig 3).

Congenital PFFD in combination with other anomalies such as unusual facies syndrome [14], Al-Awadi-Raas-Rothschild syndrome [15,6] and Al-Awadi-Raas-Rothschild syndrome Fuhrmann syndrome [16] have been well documented. However, PFFD (class D [5]) with overlapping phenotype of MKRH syndrome typifying congenital absence of uterus, fallopian tube, uterine cervix and vagina (Müllerian duct anomaly) hitherto has not been reported. Additionally, MKRH syndrome in association with other conditions such as Klippel-Feil and VATER has been observed [17]. Taken together, what we have presented is unique in that in addition to Müllerian dysgenesis the musculoskeletal deformity is only restricted to lower limb. The upper limb, thoracic and head and neck musculoskeletal and facial features were unaffected and the condition did not affect normal intelligence. It has been described that "femoral hypoplasia- an unusual facies syndrome" in infants with diabetic mothers [18]. Since we found no evidence of facial abnormalities, maternal diabetes may not be relevant in the present case; however, the family history of the donor is unknown. Exposure of the donor (born in 1935)

to thalidomide, a drug closely linked with congenital skeletal defects was unlikely as thalidomide was not available until 1957.

Number of causes for PFFD has been postulated. One theory implies PFFD results from injury to neural crest cells that form the precursors to sensory neurons of the spinal ganglia at L4 and L5 [10]. Another theory suggested that PFFD might result from a defect in the proliferation and maturation of chondrocytes of the proximal growth plate [19]. Element of ilium and proximal femur develop from a common anlage, with subsequent formation of joint space [20]. Taken together the musculoskeletal aplasia and hypoplasia suggests an alteration of the 'developmental field' [21]. Possibilities of a defective Hox gene family have been implemented in hypoplasia of the skeletal elements [22,1,23]. The expression of Hox genes in the Müllerian duct determines differential developmental identity, leading to the distinct morphological and functional components of the adult female reproductive tract. Diethylstilbestrol and several environmental xenoestrogens disrupt the development of the female reproductive tract by altering HOX gene expression, leading to structural and functional defects [24].

In 1985 Al-Awadi [25] described a new syndrome with profound limb and other deficiency. Since then, a host of phenotypic patterns in limb malformations have been recognized and given speciûc names. Mutations in WNT7A caused a range of limb malformations, including Fuhrmann syndrome and Al-Awadi-Rass-Rothschild-Schinzel phocomelia syndrome [23]. In 2006, Guerrier [26] described the MRKH syndrome with congenital absence of uterus and vagina. In 2011 Garavelli [11] and more recently Matsushita et al [6] described Al-Awadi–Raas-Rothschild (limb/pelvis/uterus–hypoplasia/aplasia) syndrome and without *WNT7A* mutations. Various forms of Müllerian duct anomaly that occurs 1 in 4500 women has been diagnosed [27]. The case presented here (aplastic acetabulum, femoral head and patella, severe hypoplsia of femur and absence of uterus, Fallopian tubes, uterine cervix and the upper part of vagina) represents what was described earlier [26]. Furthermore, as reported earlier [25] the donor in our case had normal intelligence as she was gainfully employed in an International corporation.

CONCLUSION

In conclusion, we have described an uncommon case of unilateral PFFD with overlapping phenotype of MKRH syndrome typifying congenital absence of uterus, fallopian tube, uterine cervix and vagina (Müllerian duct anomaly). In addition, we also observed compared to the right side, the left common iliac, internal iliac, external iliac and femoral arteries were smaller in diameter.

ABBREVIATIONS

MKRH- Mayer-Rokitansky-Kuster-Hauser

PFFD- Proximal focal femoral deficiency

ACKNOWLEDGEMENTS

The authors sincerely thank the donor for her generosity, which made this study possible and pave way for scientific and medical advancements.

Conflicts of Interests: None

REFERENCES

[1]. Ergin, H. Semerci, CN, Bican, M et al. A case with proximal femoral focal deficiency (PFFD) and fibular A/hypoplasia (FA/H) associated with urogenital anomalies. The Turkish Journal of Pediatrics 2006;48:380-382.

[2]. Hamanishi C. Congenital short femur. Clinical, genetic and epidemiological comparison of the naturally occurring condition with that caused by thalidomide. J Bone Joint Surg Br. 1980;62:307-320.

[3]. Ring, PA.Congenital abnormalities of the femur. Arch Dis Child 1961;36:410-417.

[4]. Emek D, Köpük SY, Çakýroðlu Y, Çakýr Ö, Yücesoy G. Unilateral Isolated Proximal Femoral Focal Deficiency. Obstetrics and Gynecology.2013;1-4. Article ID 637904 http://dx.doi.org/10.1155/2013/637904.

[5]. Aitken GT. Proximal femoral focal deficiency-Definition, classification, and management. In: Proximal Femoral Focal Deficiency. A Congenital Anomaly. Aitken GT (ed) Washington, DC. National Academy of Sciences. 1969. p 1.

[6]. Matsushita M, Kitoh H, Mishima K, Nishida Y & Ishiguro N. A case of severe proximal focal femoral deficiency with overlapping phenotypes of Al-Awadi-Ross-Rothschild syndrome and Fuihrmann syndrome. Pediatr Radiol 2014;44:1617-1619.

[7]. Moore KL, Persaud TVN, Torchia M. Urogenital system. In: The Developing Human, Clinically Oriented Embryology. Elsevier, Inc. 2016; p.241.

[8]. Goncalves, LF. De Lucca, DA. Vitorello, DA et al. Prenatal diagnosis of bilateral proximal femoral hypoplasia. Ultrasound in Obstetrics and Gynnecology 1996;8:127-130.
[9]. Lloyd-Roberts, GC. Stone, KH. Congenital hypoplasia of upper femur. J Bone and Joint Surg. 1963;45B:557-560.
[10]. Epps CH. Proximal femoral focal deficiency. J Bone Joint Surg Am 1983; 65:867-870.
[11]. Panting AL, Wiiliams PF. Proximal femoral focal deficiency. J Bone Joint Surg Br.1978;60:46-52.
[12]. Gillespie R, Torode IP. Classification and management of congenital abnormalities of the femur. J Bone Joint Surg Br. 1983;65:557-568.
[13]. Chomiak J, Horák M, Masek M, Frydrychová M, Dungl P. Computed tomographic angiography in proximal femoral focal deficiency. J Bone Joint Surg Am 2009;91:1954-64.
[14]. Daentl DL, Smith DW, Scott CI et al. Femoral hypoplasiaunusual facies syndrome. J Pediatr 1975;86:107–111.
[15]. Garavelli L, Wischmeijer A, Rosato S, Gelmini C, Reverberi S, Sassi S, Ferrari A, Mari F, Zabel B, Lausch E, Unger S, Superti-Furga A. Al-Awadi–Raas-Rothschild (limb/pelvis/uterus–hypoplasia/aplasia) syndrome and *WNT7A* mutations: Genetic homogeneity and nosological delineation. Am J Med Genet Part A 2011;155:332–336.
[16]. AlQattan MM, AlAbdulkareem I, Ballow M et al (2013) A report of two cases of Al-Awadi Raas-Rothschild syndrome (AARRS) supporting that "apparent" Phocomelia differentiates AARRS from Schinzel Phocomelia syndrome (SPS). Gene 527:371–375.
[17]. Varner RE, Younger JB, Blackwell RE. Mullerian dysgenesis. J Reprod Med. 1985;30:443-450.
[18]. Johnson JP, Carey JC, Manford Gooch III W, Petersen J, Beattie JF. Femoral hypoplasia-unusual facies syndrome in infants of diabetic mothers. J. Pedaitr. 1983;102:866-872.
[19]. Boden SD, Fallon MD, Davidson R, Mennuti MT, Kaplan FS. Proximal femoral focal deficiency. Evidence for a defect in proliferation and maturation of chondrocytes. J Bone Joint Surg Am 1989;71:1119-1129.
[20]. Laurenson R.D. Development of the Acetabular Roof in the Fetal Hip. J Bone Joint Surg Am. 1965;47:975-983.
[21]. Lewin SO, Opitz JM. Fibular a/hypoplasia: review and documentation of the fibular developmental field. Am J Med Genet. 1986;91:347-356.
[22]. Goodman FR. Limb malformation and the human Hox genes. Am J Med Genet 2002;112:256-265.
[23]. Woods CG, Stricker S**,** Seemann P**,** Stern R, Cox J, Sherridan E. et al. Mutations in WNT7A Cause a Range of Limb Malformations, Including Fuhrmann Syndrome and Al-Awadi/Raas-Rothschild/Schinzel Phocomelia Syndrome. Am. J. Hum. Genet 2006;79:402-408.
[24]. Taylor HS. Endocrine Disruptors Affect Developmental Programming of HOX Gene Expression. Fertil Steril 2008; 89 (2 Suppl):e57–e58.
[25]. Al-Awadi A, Teebi AS, Farag TJ, Naguib KM, El-Khalifa MY. Profound limb deficiency, thoracic dystrophy, unusual faces, and normal intelligence: a new syndrome. J Med Genet 1985;22:36-38.
[26]. Guerrier D, Mouchel T, Pasquier L, Pellerin I. The Mayer-Rokitansky-Küster-Hauser syndrome (congenital absence of uterus and vagina) – phenotypic manifestations and genetic approaches. Journal of Negative Results in BioMedicine 2006;5:1-8.
[27]. Griffin JE, Edwards C, Madden JD, Harrod MJ, Wilson JD. Congenital absence of the vagina. The Mayer-Rokitansky-Kuster-Hauser syndrome. Ann Intern Med 1976;85:224-236.

How to cite this article:

Cheryl Melovitz-Vasan, Hiroshi Kitoh, Nagaswami Vasan. A RARE CASE OF FEMORAL HYPOPLASIA (PROXIMAL FOCAL FEMORAL DEFICIENCY) WITH OVERLAPPING PHENOTYPE OF MULLERIAN DUCT SYNDROME (MAYER-ROKITANSKY-HAUSER SYNDROME).Int J Anat Res 2016;4(4):3312-3316. **DOI:** 10.16965/ijar.2016.474