INTRODUCTION

Ter Haar syndrome, also known as Frank-Ter Haar syndrome and Ter Haar-Hamel-Hendricks syndrome, is a rare genetic disorder inherited as autosomal recessive trait. The combination of the megalocornea, multiple skeletal anomalies, and developmental delay was first recognized as a separate entity by Frank et al. in 1973 and subsequently confirmed by Ter Haar et al. in 1982. The main characteristic features are brachycephaly, wide fontanels, prominent forehead, hypertelorism, prominent eyes, macrocornea with or without glaucoma, full cheeks, small chin, congenital heart defects, kyphoscoliosis, skeletal dysplasia, developmental delay, coccyegeal skin folds and flexion deformity of the fingers. This case report describes Frank-Ter Haar syndrome in a 4 months old girl suffering from club foot, dysmorphism, prominent coccyx with skin fold, atrial septal defect, patent ductus arteriosus and megalocornea.

CASE REPORT

A 4 months old infant was referred to the outpatient clinic for evaluation of club foot and dysmorphism. She was born as the first child of consanguineous healthy Saudi parents. The pregnancy was un-eventful and she was delivered spontaneously at 37 weeks of gestation. Her birth weight was 2461 g and Apgar scores was 6 and 9 after 1 and 5 minutes. At birth, club foot was noted and a cardiac murmur was heard on routine neonatal examination. She was referred to paediatric cardiologist for cardiac evaluation.

On examination her length was 58 cm (10th centile), weight was 4820 g (< 10th centile), and occipito-frontal head circumference (OFC) was 38 cm (at 10th centile). Her vital signs were stable and blood pressure was also normal. She had brachycephaly with frontal bossing, flat occiput, wide anterior fontanel, hypertelorism, large cornea, micrognathia, high arched palate, anteverted nostrils, broad alveolar ridges, and prominent coccyx bone with skin fold were present (Figures 1 and 2). Bilateral simian creases and mild flexion deformity of little finger were noted. She had short hands and talipes equinovarus. Ophthalmological examination, the cornea was large and circular (diameter ODS 14 mm) and intraocular pressure was found to be increased (> 36 mmHg). Her fundus examination was unremarkable. Routine CBC, blood chemistry and thyroid function tests were also normal. Skeletal roentgenograms showed foot deformity. X-rays of skull, vertebral column, long bones and pelvis were...
normal. No abnormality was detected on renal ultrasonography and CT brain was also normal.

She was operated for closed angle glaucoma and PDA. Clubfoot deformity was treated by orthopedic surgeon with gently manipulation and casting. It was not possible to conduct genetic analysis to confirm the diagnosis due to lack of facility.

**DISCUSSION**

The primary malformations of FTHS are craniofacial dysmorphism, glaucoma, congenital heart defects, coccygeal skin folds (tail bone), and generalized skeletal alterations. Since the first description of this syndrome in 1973, about 35 patients have been reported.3

The phenotype in this patient overlapped significantly with, but was not completely consistent with that of Melnick-Needles syndrome, another malformation with an X-linked dominant trait. Unfortunately, exact pathogenesis of the disorder has not clear yet. Genetic mapping in several families with FTHS linked the disease to an inherited mutation in the gene that codes for the protein TKS4.4 TKS4 was already known for its role in the formation of cellular projections known as podosomes, which allow cells to migrate. A mouse model that lacks the TKS4 gene shows all the symptoms of FTHS confirmed the hypothesis that TKS4 mutation is responsible for the disease.4,5 Autosomal recessive inheritance of Frank-Ter Haar syndrome was confirmed by Iqbal et al.4 TKS4, a protein implicated in cancer metastasis, also plays a significant role in Frank-Ter Haar syndrome (FTHS), a rare fatal disorder.4

Undoubtedly the craniofacial and radiological resemblance of both Frank-Ter Haar and Melnick-Needles is striking, but presence of congenital glaucoma, the prominent coccyx with skin fold, differentiates the former from Melnick-Needles syndrome (MNS).6 A remarkable difference in MNS is the mode of inheritance with lethality in affected males, although a few surviving males have been reported. Another noteworthy difference is prognosis; MNS is usually a benign condition, while FTHS has high mortality due to severe congenital heart diseases.7,8

Alkaissi et al. reported one brother and sister, with FTHS, but severe mental retardation was additional feature.8 The absence of family history indicates that this patient is a sporadic case. In this case, almost all malformations were present as described in previous literature. The presence of glaucoma and coccyx skin fold is essential for making the diagnosis of FTHS along with other craniofacial and skeletal malformations.8-10 There is no specific treatment for this condition except genetic counselling, and symptomatic care with multidisciplinary approach involving efforts of a team of cardiologists, orthopedic surgeons, ophthalmologists, physical therapists, paediatric surgeons, paediatric neurologists, and geneticists.

In conclusion, early recognition of FTHS is important because of congenital glaucoma and congenital heart defects mainly responsible for morbidity and mortality respectively.

**REFERENCES**

1. Frank Y, Ziprkowski M, Romano A, Stein R, Katznelson MB, Cohen B, et al. Megalocornea associated with multiple skeletal anomalies: a new genetic syndrome? J Genet Hum 1973; 21: 67-72.

2. Ter Haar B, Hamel B, Hendriks J, de Jager J. Melnick-Needles syndrome: indication for an autosomal recessive form. Am J Med Genet 1982; 13:469-77.

3. Hamel BC, Draaisma JM, Pinckers AJ, Boetes C, Hoppe RL, Ropers HH, et al. Autosomal recessive Melnick-Needles syndrome or Ter Haar syndrome? Report of a patient and a re-appraisal of an earlier report. Am J Med Genet 1995; 66:312-6.

4. Iqbal Z, Cejudo-Martin P, de Brouwer A, van der Zwaag B, Ruiz-Lozano P, Scimia MC, et al. Disruption of the podosome adaptor protein TKS4 (SH3PXD2B) causes the skeletal dysplasia, eye, and cardiac abnormalities of Frank-Ter Haar syndrome. Am J Hum Genet 2010; 86:254-61. Epub 2010 Feb 4.

5. Buschman MD, Bromman PA, Cejudo-Martin P, Wen F, Pass I, Courtenedge SA. The novel adaptor protein TKS4 (SH3PXD2B) is required for functional podosome formation. Mol Biol Cell. 2009; 20:1302-11. Epub 2009 Jan 14.

6. Krajewska-Walasek M, Winkielman J, Gorlin RJ. Melnick-Needles syndrome in males. Am J Med Genet 1987; 27:153-8.

7. Donnenfeld AE, Conard KA, Roberts NS, Borns PF, Zackai EH. Melnick-Needle syndrome in males: a lethal multiple congenital anomalies syndrome. Am J Med Genet 1987; 27:159-73.

8. AlKaisi A, Hammou A, Ghachem MB, Nacib MN, Chehida FB, Karoui H, et al. Siblings with glaucoma, mental retardation and short stature. Clin Dysmorph 2003; 12:191-4.

9. Megarbane A, Tomey K, Wakim G. Congenital glaucoma, limb deformities, skeletal dysplasia, and facial anomalies: report of another family. Am J Med Genet 1997; 73:67-71.

10. Maas SM, Kayseril H, Lam J, Apak MY, Hennekam RC. Further delineation of Frank-ter Haar syndrome. Am J Med Genet 2004; 131:127-33.