Case report

Floating–Harbor syndrome in a Kuwaiti patient: a case report and literature review

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Introduction

Floating–Harbor syndrome is a rare genetic disorder that was named by Robinson et al. in 1988 [*1*] from the first 2 identified patients seen at Boston Floating Hospital and Harbor General Hospital in California [*2,3*]. The main characteristic features of the syndrome are distinct facial features delay in using expressive language, short stature and delayed bone age [*4–7*]. The incidence of Floating–Harbor syndrome is unknown. To our knowledge, 29 cases have been identified in the literature [*3,8,9*]. Most of the reported cases were of female sex and the male:female sex ratio is 7:22. Here we report the first case of Floating–Harbor syndrome in Kuwait. The clinical picture and spectrum of the disease are discussed along with a review of the literature

Case report

A Kuwaiti female child, aged 8.5 years, was the product of the 4th pregnancy to nonconsanguineous phenotypically normal parents. At birth, the parental age was 27 and 37 years for mother and father respectively. The proband was referred to Kuwait Genetic Centre at the age of 5 days because of intrauterine growth retardation.

Pedigree study revealed that she has 3 phenotypically normal elder siblings (2 sisters and 1 brother). One of her sisters was found to have mosaic Turner syndrome.

The mother's preconception and 1st and 2nd trimester histories were irrelevant and the pregnancy was completed at term by spontaneous vaginal delivery and cephalic presentation. Apgar scores were 8 and 9, at 1 and 5 minutes respectively. Examination at birth revealed weight 2.15 kg, length 48 cm and occipito-frontal circumference 30.5 cm. No significant specific craniofacial dysmorphia could be detected at that time and chromosomal study was arranged to exclude the presence of any mosaicism.

Follow-up at the age 2 years 3 months revealed: weight 9 kg, length 78 cm, and occipito-frontal circumference 42 cm. All measurements were below the 3rd centile. She had a triangular face, microcephaly, bulging and narrow forehead, broad and prominent nasal bridge, wide columella, mild synophrys, deep-set eyes, short philtrum, thin upper lip, broad mouth, posterior rotated ears (Figure 1), short neck, low posterior hairline, small hands, bilateral clinodactyly

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of the 5th finger, bilateral shortening of the 4th and 5th fingers, bilateral shortening of the 4th and 5th toes, and bilateral partial cutaneous syndactyly between the 2nd and 3rd toes (Figure 2). There was delayed speech. At the age of 5 years 10 months she had height 105 cm, weight 12 kg, and occipito-frontal circumference 41 cm. All measurements were below the third centile for age.

Several investigations were carried out. Calcium, phosphorus, alkaline phosphatase, magnesium, blood glucose, ToRCH assay [*Toxoplasma gondii*, rubella togavirus, cytomegalovirus, and herpes simplex virus types 1 and 2], immunoglobulin electrophoresis, amino acid chromatography, organic acids assay, thyroid function and echocardiography were normal. IgA-antigliadin was negative. Growth hormone (GH) provocation test by clonidine revealed low baseline GH levels at 0 and 30 minutes. Normal response was observed after 60, 90 and 120 minutes (0.39, 0.36, 31.4, 19.0 and 14.1 mIU/L at 0, 30, 60, 90 and 120 minutes respectively) (normal range for females 0.4–26.7 mIU/L). Chromosomal study using peripheral blood and trypsin G banding was normal for both this child and her parents.

Developmental assessment at 14 months of age showed a maturity level of 6–7 months. IQ assessment at 4 years 7 months was 62 (mild mental retardation) and the language skill was severely affected. EEG showed low basic activity, low voltage in all stages of vigilance and a focus of spikes with phase reversal in the right centroparietal region showing a focally abnormal

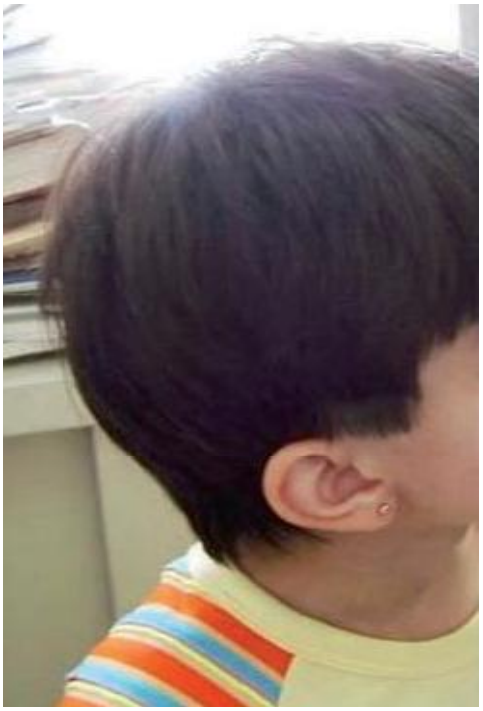

Figure 1 **Low-set, posterior rotated ear, one of the characteristic feature of Floating–Harbor syndrome**

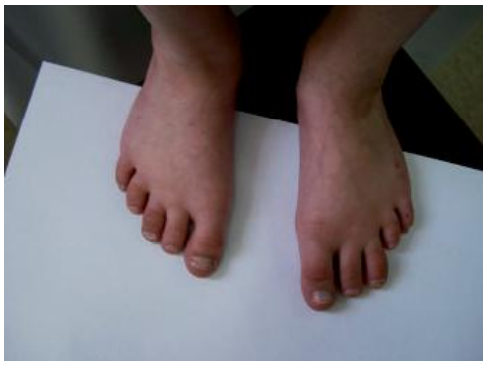

Figure 2 **Syndactyly between the second and third toes, shortening of the 4th and 5th toes and gap between big toe and second toe in an 8-year-old girl with Floating–Harbor syndrome**

record. Computerized tomography of the head and magnetic resonance imaging were normal.

Skeletal survey showed shortening of the 4th and 5th metacarpal bones bilaterally and minimal shortening of the 4th metatarsal bones.

Discussion

In the present case, most of the cardinal features of Floating–Harbor syndrome were present: triangular face, deep-set eyes, long eyelashes, broad nasal bridge, wide columella, short smooth philtrum thin upper lip, posterior rotated ears, low hairline, short stature and microcephaly. Gross deficits in verbal expression and perception (i.e. patient cannot understand and respond to what she hears), speech language problem, high-pitched voice and delayed bone age were present [*1,7,10–12*]. Trigonocephaly, atrial septal defects, supernumerary upper incisor, lateral asymmetry of the body and coeliac disease, which have been described infrequently, were missing in this case [*4–7,9,11–14*]. Trigonocephaly, described rarely, was considered an important craniofacial manifestation and has to be added to the cardinal features of Floating–Harbor syndrome [*7*].

The neuropsychological deficits recorded in this case are similar to what has been reported previously: mild mental retardation, constructive apraxia and comprehensive and expressive language impairment [*4*]. The use of sign language has greatly helped some parents. In addition, speech therapy has helped when the children are over 3 years old. Unfortunately it was not successful in this case.

GH deficiency and its role in the management of Floating–Harbor syndrome had been discussed previously [*15,16*]. However, its level was low to normal with adequate response in this girl. Cannavo et al. reported an affected female child with Floating–Harbor syndrome and impairment of GH responsiveness to administration of oral 150 μg clonidine and oral 4 mg dexamethasone [*15*]. Moreover, low mean GH levels (1.75 ng/mL) (normal value > 3.0 ng/mL) have been reported with successful treatment achieved by GH therapy [*16*].

The clinical diagnosis of Floating–Harbor syndrome may be unreliable or overlap with other dysmorphic syndromes such as velocardiofacial syndrome (Shprintzen syndrome), trichorhinophalangeal syndrome and De Lange syndrome [*17–19*].

Table 1 **Characteristic features of Floating–Harbor syndrome and this case**

Feature	Present
Short stature	+ve
Prenatal onset of short stature	+ve
Triangular face	+ve
Posterior rotated ears	+ve
Deep-set eyes	+ve
Long eyelashes	+ve
Prominent occiput	+ve
Wide columella	+ve
Smooth philtrum	+ve
Thin lips	+ve
Broad mouth	+ve
Short neck	+ve
Low posterior hairline	+ve
Delayed bone age	+ve
Joint laxity	–ve
Clinodactyly of 5th finger	+ve
Cone-shaped epiphysis	–ve
Hirsutism	+ve
Expressive language delay	+ve
Motor development delay	Normal

In velocardiofacial syndrome, the distinguishing characteristics are: prominent nose with squared-off nasal tip, notched ala nasi, significant cardiac anomalies, long tapering fingers, cerebral and ocular abnormalities. Both trichorhinophalangeal and Floating–Harbor syndrome are multiple congenital anomaly syndromes with involvement of craniofacial and skeletal structures. The main clinical features of trichorhinophalangeal syndrome are short stature, mid-facial dysmorphism, sparse hair, speech delay and genitourinary abnormalities [*17,20,21*]. Both autosomal dominant forms (types I, II, III) and recessive forms exist, associated with mutations in trichorhinophalangeal I, a zinc-transcription factor located at 8q24. The clinical basis of differentiation is: the shape of the nose, digital anomalies, sparse hair and long philtrum, which were missing in our case. The clinical overlap between De Lange syndrome and Floating–Harbor syndrome can be excluded by the presence of short philtrum, speech developmental delay, triangular face, lack of motor delay and absence of the De Lange phenotype at birth.

All reported cases of Floating–Harbor syndrome have been sporadic. Very few familial case have been reported in the literature, although affecting siblings of both sexes have been reported and other authors have reported Floating–Harbor syndrome in a mother and her daughter [*9,22,23*]. Recently Penaloza et al. reported a boy who had the clinical features of Floating–Harbor syndrome and coeliac disease [*9*]. His mother showed minor phenotypical features of Floating–Harbor syndrome, suggesting an autosomal dominant mode of inheritance [*9,24*].

In conclusion, Floating–Harbor syndrome is a very rare dysmorphic/mental retardation syndrome affecting both sexes but more frequent among the female sex. Most of the reported cases occur sporadically, but a few familial cases have been reported, raising the possibility of autosomal dominant mode of inheritance.

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