CLINICAL QUIZ (p277) ANSWER

What is the diagnosis?

The clinical features of this child (short stature, global developmental delay, delayed bone age, brachydactyly, typical facial features including triangular face, bitemporal narrowing, midface hypoplasia, prominent eyes, epicanthic fold, long nose with broad tip and short philtrum and thin lips) were suggestive of Floating Harbor Syndrome (FHS). FHS is a rare genetic disorder characterised by distinctive craniofacial features, short stature, delayed bone age, variable skeletal anomalies, expressive and receptive language delay and mild to moderate grade intellectual disability.[1] Molecular testing by Next Generation Sequencing (NGS) on extracted DNA from proband's peripheral blood detected a heterozygous pathogenic variant c.7330C>T in exon 34 of the *SRCAP* gene. This is a de novo nonsense mutation that changes the 2444th codon from Arginine to STOP. This variant has been reported multiple times in literatures as disease causing. The molecular diagnosis of FHS (OMIM#136140) was substantiated.

The exact prevalence of FHS is unknown. Over 100 cases have been reported worldwide.[2]

How is the clinical diagnosis established in FHS?

FHS should be suspected in individuals with the following clinical and radiographic features.[3]

Clinical features	**Radiological features**
Characteristic craniofacial appearance	Bone age delay (≥-2 SD) with= normalisation between 6-11 years old
Skeletal anomalies	
Short stature	
Speech and language delay	
Mild to moderate grade intellectual disability	

Characteristic craniofacial features include triangular face, deep-set eyes, short philtrum, wide mouth with thin lip, long nose with broad base and tip, low-hanging columella and low-set ears. Variable skeletal anomalies include brachydactyly, broad fingertips that give the appearance of clubbing, clinodactyly, prominent joints and clavicular abnormalities. Speech and language delay are commonly presented features. Severe receptive and expressive language impairment can be across all domains of function. Patients with FHS may also have dysarthria, verbal dyspraxia with phoneme imprecision, hypernasality and high-pitched voice.

Other features such as hyperopia, strabismus, conductive hearing loss, seizures, gastroesophageal reflux, renal anomalies (e.g., hydronephrosis. cysts, renal agenesis) and genital anomalies (e.g., hypospadias, micropenis, undescended testes) can also be present in FHS patients.

Molecular diagnosis of FHS and Genetic counselling

The diagnosis of FHS is established in a proband with aforementioned suggestive findings by identification of a heterozygous pathogenic variant in *SCRAP* on molecular genetic testing.

The *SRCAP* gene (OMIM*611421), located on chromosome 16p11.2, encodes an SNF2-related chromatin-remodelling ATPase which serves as a transcriptional activator via binding to CREB-binding protein. It is believed that the truncated *SRCAP* variant disrupts the binding of wild-type *SRCAP* to both DNA and chromatin targets, thus affecting gene expression that controls the onset of differentiation and developmental processes.[4]

Nearly all reported pathogenic variants were located in exons 33 and 34 of SRCAP that are predicted to cause truncation of the protein resulted in the FHS. FHS is inherited in an autosomal dominant manner, although most cases are sporadic. The offspring of an affected individual is at a 50% risk of inheriting the pathogenic variant. Once the pathogenic variant has been identified in an affected member, prenatal testing and preimplantation genetic diagnosis for a pregnancy at increased risk are possible. There are no silent carriers of FHS.

What are the management issues for FHS?

Management of FHS requires a multi-disciplinary approach. Depending on the clinical manifestations, paediatricians, endocrinologist, ophthalmologists, ENT specialists, audiologists, dental surgeons, urologists, clinical geneticists, speech therapists, clinical psychologists' inputs are important.
Treatment and surveillance are suggested as follows.[3]

Treatment	Surveillance
Treatment for refractive errors and strabismus, hearing loss, seizures, renal disease, cryptorchidism, orthopaedic complications and dental problems	Annual ophthalmologic, audiology, blood pressure and renal function evaluations
Growth hormone (GH) therapy	Growth evaluation for every visit
Early intervention programmes, special education and vocational training	Bone age examination
Communication rehabilitation	
Behaviour management	

To date, over 100 FHS cases have been reported worldwide, and only a few of these patients were GH deficient. Short stature is the core feature of FHS; however, there are limited data on the GH-IGF-1 axis in FHS. It was suggested that FHS may lead to impaired IGF-1 signalling because of the discrepancy between the modest growth response to GH therapy and serum IGF-1 level (upper limit of the normal level during therapy). For use of GH treatment in FHS, a few case reports have shown improvement in growth velocity and height. However, caution is indicated since further studies are necessary to clarify the real effectiveness and safety.[5]

Acknowledgement

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