Dilemmas on a Case with Craniosynostosis Diagnosed as Pfeiffer Syndrome by DNA Analysis

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Abstract

A case with craniosynostosis, facial dysmorphia, fingers, toes, and multiple skeletal anomalies syndrome is presented. The patient, a 28 years old female had normal growth and psychomotor development. All the family members were apparently normal. On a phenotypic basis alone, she put diagnostic dilemmas finally solved by DNA analysis.

Case Presentation

The patient, a 28 years old female, was born at term by normal delivery to apparently normal parents (mother 24, father 34) and weighed 3.500 gr. Her growth and psychomotor development were normal (walked at 11 months, spoke at 1 year of age) and she had never had any particular health problem. At approximately one year of age “her facial dysmorphia was not very much apparent” and did not bother her pediatrician, “who was more concerned for her mental and not her physical condition” and kept saying to the parents not to worry, “she has a strong mind and is going to be very smart”.

At 2.5 years of age she was operated for soft tissue syndactyly of the second and third right toes. At 18 years of age, she was hospitalized for acute tonsillitis, and for the first time she was diagnosed as having a syndrome, namely the Saethren-Cotzen syndrome. Her two brothers (31 years and 25 years) are apparently normal. She graduated the University School of Mathematics at the age of 23 years. After having a job, she decided to improve her facial appearance and, at first place, she visited a plastic surgeon to correct her nose. From there she was referred to the Department of Oral Pathology and Surgery, and to the Orthodontics Department at the School of Dentistry, University of Athens, to have an oral maxillary and orthodontic treatment first.

On physical examination, her height was 154 cm, weight 48 kg, head circumference 52.3 cm (3rd C). She had facial asymmetry, low set frontal hair line, hypertelorism, long down slanting palpebral...

Figure 1: Facial asymmetry, low set frontal hair line, hypertelorism, long down slanting palpebral fissures, retrusion of infraorbital rim, proptosis of eye globes with divergent strabismus of the right beak-like protruding nose deviated to the right, short neck.
fissures, retrusion of infraorbital rim, proptosis of eye globes with divergent strabismus of the right, beak-like protruding nose deviated to the right with difficulty in breathing, hyperbrachycephaly (C.I. 94.37), flat forehead and occiput, long narrow ears with hearing deficit of the right, long lower facial height (9.6 cm, 70.1% of the TFH, normal 55.8%), hypoplastic maxilla, relative mandibular prognathism, dental malocclusion with anterior open bite, narrow high palate, V shaped crowded upper dental arch, short neck, wide thumbs, wide halluces with valgus deformities, limited extension at elbows, limited mobility of shoulders, bowing of tibia (Figures 1-9).

Facial measurements

- Inner canthal distance 38 mm, above +2 S.D.
- Interpapillary distance 76 mm, 10 mm above 97th C.
- Palpebral fissure length 36 mm/36 mm above +2 S.D.
- Nasal length 48 mm, 5 mm below -1 S.D.
- Nasal protrusion 39 mm, 14 mm above +2 S.D.
- Nasal width 34 mm, mean a little above
- Ear length 69 mm/69 mm, 2 mm above +2 S.D.
- Ear width 32 mm/32 mm
- Philtrum length 18 mm, a little above 50th C.
- Mouth width 46 mm a little below -1 S.D.
- Limbs.
  - Hand length 16 cm/16 cm, 0.5cm below 3rd C.
  - Palm length 9 cm/9.5 cm, 0.5 cm below 3rd C.

Laboratory investigation showed that she had an iron deficiency anemia, but blood biochemical tests were within normal limits. HKG and ultrasonography of the upper abdomen did not disclose any abnormality.

Craniofacial, cervical and general radiologic examination revealed thick skull with increased digital markings more prominent in the frontal area, flat frontal and occipital bones, increased height of cranial cavity, short anterior (60 cm, -3SD) and posterior (34.5 cm, -3SD) cranial base, calcified stylohyoid ligament, fusion of cervical vertebrae and neural arches (C2 to C3, C5 to C6), bony hypertelorism, anterior open bite, straightness of thorax spine, hypoplastic humeral heads, thumb with rudimentary 1st and radially deviated 2nd phalanx without any visible joint in between, point finger with fused 1st and 2nd
phalanges, fusion of capitate-hamate-pyramidal carpal bones, small pelvis, thick and wide ischium bones, short femoral necks, fusion of 1st and 2nd metatarsals and of 1st toe phalange (Figure 10).

Discussion

The phenotypic Differential Diagnosis included Pfeiffer syndrome (broad thumbs and first toes), Crouzon for her facial appearance, and Apert syndrome for the severe skeletal abnormalities, (her high mental performance did not exclude the syndrome since, according to Renier, the IQ in Apert syndrome ranges between 10 to 114, and Cohen and Kreiborg had three patients who attended College [1,2].

We prepared the patient’s DNA and, accordingly, forwarded it to: Prof. Andrew Wilkie, Weatherall Institute of Molecular Medicine, John Radcliffe Hospital Headington, Oxford, UK.

From the above Institute, we received the results of DNA analysis, which showed that the patient is heterozygous for the splice acceptor site mutation 940-1G>A, immediately upstream of the IgIIIC exon 9 of FGFR2 [3]. This mutation has been described twice previously in association with Pfeiffer syndrome, while mutations of this syndrome have usually been located within the exons 7 and 9 [3]. Mutations of this splice site tend to be associated with relatively severe limb abnormalities, as explained by Oldridge [4]. Our case in addition had severe general skeletal abnormalities that created a phenotypic diagnostic problem [5]. The results of the molecular analysis lead to the final diagnosis of Pfeiffer syndrome.

References