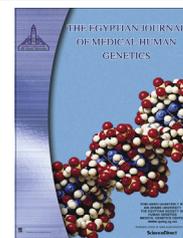




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CASE REPORT

Bilateral absence of fifth ray in feet, cleft palate, malformed ears, and corneal opacity in a patient with Miller syndrome

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Abstract *Background:* Miller syndrome is one of the acrofacial dysostosis syndromes, which are characterized by malformations of the craniofacial region and limbs.

Case report: A 26 month old male child, the product of healthy nonconsanguineous parents has many typical features of Miller syndrome. He has cleft lip and palate, malar hypoplasia, left crumpled cup shaped ear, and prominent nose together with the absence of the fifth ray in feet (postaxial) and fixation of interphalangeal joints of both thumbs (preaxial). However the limb affection is bilateral and symmetrical against what is usually reported (bilateral with more affection of one side) and the micrognathia is very mild. Our patient has also bilateral corneal opacities as well as underdeveloped external genitals.

Conclusion: There is phenotypic variability in Miller syndrome, and our patient may represent a new distinct subgroup in postaxial acrofacial dysostosis.

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1. Introduction

The acrofacial dysostosis syndromes, which are characterized by malformations of the craniofacial region and limbs, are a clinically heterogeneous group of disorders. Based primarily on the pattern of limb defects, two major groups have

emerged: Nager syndrome with predominantly preaxial malformations plus mandibulofacial dysostosis (severe micrognathia and malar hypoplasia) and Miller syndrome with predominantly post axial malformations plus mandibulofacial dysostosis [1].

Miller (Genée–Weidemann) syndrome represents a clinically and biochemically distinct subgroup of postaxial acrofacial dysostosis (POADS). The facies can be strikingly similar to Treacher Collins syndrome [2].

Ng et al., reported that the pattern of malformations observed in individuals with Miller syndrome is similar to those in individuals with fetal exposure to methotrexate. Methotrexate is a well-established inhibitor of de novo purine biosynthesis, and its antiproliferative actions are thought to be due to its

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inhibition of dihydrofolate reductase and folate-dependent transmethyations. Accordingly, defects of both purine and pyrimidine biosynthesis appear to be capable of causing a similar pattern of birth defects [3].

We report an Egyptian patient who has many typical features of Miller syndrome with subtle facial changes, and few associated congenital malformations after taking consent of the parents.

2. Case report

The patient was a 26-month old male child, the third in order of birth of healthy non consanguineous Egyptian parents. The patient was delivered at full term by cesarean section. His birth weight was appropriate for gestational age. No history of drug intake by the mother during pregnancy. The patient was referred to the Genetics Clinics, Pediatric Hospital, Ain Shams University because of abnormal features.

On examination the skull circumference is 47 cm (-1.65 SDS), height is 86.5 cm (-0.15 SDS), weight is 10 kg (-2.41 SDS), BMI is 13.36 kg/m^2 (-3.07 SDS) [4,5]. The patient has an open anterior fontanel 2×2 cm, and there is hypertelorism. The eyes show transverse slant as well as small corneal opacity. The patient has broad bulbous nose, with broad nasal tip, and wide nares. The right ear is low set, malformed, cup shaped, and posteriorly rotated. The left ear lobule is small and slightly everted upwards. Also he has long philtrum which shows a scar of cleft lip operation, thin upper lip, and high arched palate (Figs. 1 and 2). The upper limbs show that the interphalangeal joints of both thumbs were fixed in extension, with clinodactyly of the little fingers. The lower limbs show bilateral postaxial oligodactyly (the fifth toes are absent), long second toe, and medial deviation of the third and fourth toes (Fig. 3).

The patient has normal mentality. Genital examination shows small uncircumcised penis measuring 3.1 cm in full stretched length (-2.3 SDS) [6], with bilaterally undescended small testes both felt in the inguinal canal, (left testes < 1 ml and right testes 1.5 ml in volume), and underdeveloped scrotum (Fig. 4). Chest, cardiac, abdominal, and neurological examinations are normal. Hearing and vision are also normal.



Figure 1 Facial features including transverse slant of palpebral fissures, broad bulbous nose, with broad nasal tip, and wide nares, bilateral corneal opacities at the medial lower quadrant, long philtrum which shows a scar of cleft lip operation, and thin upper lip.



Figure 2 The right ear is low set, malformed, cup shaped, and posteriorly rotated.



Figure 3 Bilateral postaxial oligodactyly (absence of the fifth toe), long second toe, and slight medial deviation of third and fourth toes.



Figure 4 Small uncircumcised penis, with underdeveloped scrotum, bilaterally undescended small testes both felt in the inguinal canal.

There was suboptimal testosterone response to the HCG test (Human Chorionic Gonadotropin 5000 IU intramuscular, with serum testosterone measured after 72 h). Peak testosterone level was 0.3 ng/ml, and there was absence of three fold rise of serum testosterone from baseline level. Also the test did not result in testicular descent. Skeletal survey was normal apart from bilateral absence of the fifth metatarsal, and fifth



Figure 5 Bilateral absence of the fifth metatarsal, and fifth toe bones.

toe bones (Fig. 5). ECHO cardiography, and pelvi-abdominal ultrasonography are normal.

The patient had two operations one for correction of cleft palate at the age of 3 months, and the other at 6 months for correction of cleft lip.

The patient has an older normal female sib, and no history of similarly affected family member.

3. Discussion

Miller syndrome is a rare condition that mainly affects the development of the face and limbs. The facial features include micrognathia, orofacial clefts, malar hypoplasia, aplasia of the medial lower lid eye lashes, coloboma of the lower eye lid, ectropion, and cupshaped ears as well as hearing deficit [7,8].

The main features in our patient include cleft lip and palate, malar hypoplasia, sparse medial lower eye lid lashes, left crumpled cup shaped ear, small everted lobule of the right ear, and prominent nose. However the micrognathia is very mild with no coloboma or ectropion of the eye lids. Hearing is also normal. Our case is very similar to that described by Murthy [9]. Other cases of Miller syndrome with mild micrognathia was also reported by Kinoshita et al., [10], and Al Kaissi et al., [11].

Miller in 1979 reported postaxial absence or incomplete development of the fifth digital rays in both upper and lower limbs [7]. Lower limb anomalies vary from hypoplasia of fifth toe to total absence of the fifth, and occasionally third, and forth toes, polydactyly, syndactyly, and malposition of toes [8,12]. Upper limb defects may result in phocomelia with a hypoplastic pectoral girdle [12], shortened radius and ulna, and radiological evidence of ulner hypoplasia. Abnormalities of other digits are also reported and include absent forth digits, various degrees of syndactyly, and clenched hypoplastic thumbs [8,2].

Limb affection is usually reported as bilateral with more affection of one side than the other [13–15]. As regards limb affection in our patient, they are mainly symmetrical and post-axial in lower limbs. There is bilateral absence of fifth ray which is also confirmed by X-ray picture. As regards the upper limbs there is fixation of interphalangeal joints of both thumbs (preaxial).

Congenital anomalies are rare in Miller syndrome. In our patient there is underdevelopment of penis, scrotum with undescended testis. The same was also reported by Murthy

[9]. In our patient there are also bilateral corneal opacities which were also reported by Oglivy-Stuart, and Parsons. However they reported other anomalies including mid gut malrotation, gastric volvulus, renal anomalies, skin defects, congenital heart disease, accessory nipples, single umbilical artery, absence of hemidiaphragm, choanal atresia, supernumerary vertebrae, and other vertebral segmentation and rib defects, inguinal hernia and pectus excavatum [12].

Mentality as well as growth and development are usually normal. Oglivy-Stuart, and Parsons reported that this syndrome may be associated with mild mental retardation [12]. Our patient has normal mentality, however his growth is retarded.

Our patient was a male and third in the order of birth. Males usually out number females by three to eight times and the majority are first borne [16]. In our patient the karyotype was normal and there is no consanguinity between parents, although the consanguinity rate is high in Egypt [17], and there is no family history which points most probably to a sporadic case or a new mutation of an autosomal dominant inherited syndrome.

To our knowledge it is the first case of Miller syndrome to be reported in Egypt, and Arab countries. Only few patients with Miller syndrome had been reported (about 30 cases), and so every patient needs to be reported in order to establish and document the clinical finding of this syndrome in a possibility to identify the presence of major, minor criteria, and mode of inheritance.

Miller syndrome was the first Mendelian disorder whose molecular basis was identified via whole exom sequencing [18]. It is due to biallelic mutations in the gene encoding DHODHase [dihydroorotate dehydrogenase (DHODH)], an enzyme required for de novo pyrimidine biosynthesis [2,19]. A total of 14 different mutations in the coding region of DHODH including two nonsense mutations, have been identified. All affected individuals reported to have compound heterozygous DHODH mutations [2]. The primary known function of dihydroorotate dehydrogenase is to catalyze the conversion of dihydroorotate to orotic acid, an intermediate in the pyrimidine de novo biosynthesis pathway. Orotic acid is subsequently converted to uridine monophosphate (UMP) by UMP synthase. Pyrimidine biosynthesis might be particularly sensitive to the step mediated by dihydroorotate dehydrogenase [3]. Reduction of this enzyme DHODH is expected to produce an elevation of the precursor DHO and a deficiency of orotic acid (OA) in affected cases. However mutation positive cases had no detectable dihydroorotate (DHO), but had significant orotic aciduria, and as OA is the product of the DHODH reaction, it represents a paradoxical result. It is possible that DHO may be converted very efficiently to OA in the extracellular fluids, perhaps via other NADH-linked dehydrogenase enzymes that recognize DHO as an alternative substrate or via the action of gut bacteria. This may represent a simple biomarker for Miller syndrome. In all affected individuals, the genotype predicts that there should be significant residual DHO dease activity. Miller syndrome associated malformations result from a rare limiting effect on cell division during specific developmental stages in the limb bud and facial processes. A threshold of DHODH activity and ultimately pyrimidine synthesis (or availability) is required during human and mammalian development, below which manifests the clinical features of miller syndrome and further reduction still may result in embryonic lethality [2].

From the previous discussion it is evident that there is phenotypic variability as well as severity in craniofacial development as well as in postaxial and preaxial upper and lower limb reduction anomalies. This variability has been also reported by Chrzanwka et al., [20]. In the group of patients carrying the DHODH mutations, the phenotypes are strikingly similar and typical of Miller syndrome. In the mutation negative cases, the cases may have upper limb only or lower limb only in postaxial rays or post and preaxial rays, facial clefting without cleft palate, and subtle facial involvement with no residual mandibular hypoplasia [2].

There has been speculation that Miller syndrome is an autosomal dominant disorder and the rare occurrence of affected siblings is the result of germline mosaicism, as only three multiplex families, each consisting of two affected siblings born to unaffected, non consanguineous parents, have been described among a total of ~30 reported cases of Miller syndrome [3].

To conclude: our patient had bilateral symmetrical affection of both upper and lower limbs, cup shaped left ear, subtle facial features as well as bilateral corneal opacities, and underdeveloped gonads and thus may represent a new distinct subgroup in POADS.

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