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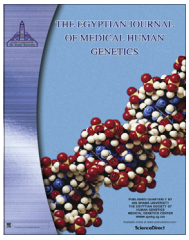

CASE REPORT

Meier-Gorlin syndrome: Report of an additional patient with congenital heart disease

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KEYWORDS

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Absent patella

Abstract We report a 7 year old female child with the classical triad of Meier-Gorlin syndrome (MGS), (microtia, absent patella and short stature). She had the characteristic facial features, with normal mentality and defective speech, skeletal abnormalities, conductive hearing loss, cystitis and normal growth hormone level. She suffered from recurrent chest infection during the first year of life which improved gradually with age. Although congenital heart is rarely observed in MGS, our patient had in addition fenestrated interatrial septal defect.

1. Introduction

Meier-Gorlin syndrome (MGS) is included in a group of disorders known as primordial dwarfism. These disorders share similar characteristics including skeletal malformations, growth deficiency in the intrauterine period as well as during infancy and childhood, ultimately resulting in varying degrees of short stature. This group of disorders includes five disorders: ear-patella-short stature (Meier-Gorlin) syndrome, Seckel syndrome, Russell–Silver syndrome, and Majewski osteodysplastic bird-head dwarfism type I/II/III [1].

Meier-Gorlin syndrome (MGS) is a rare autosomal recessive disorder characterized by primordial dwarfism, bilateral microtia and patellar aplasia/hypoplasia [2]. It was first described by Meier and Rothschild in 1959 [3], and the second case was reported by Gorlin et al. [4], so named after the two.

Mutations in five different pre-replication complex genes (ORC1, ORC4, ORC6, CDT1, and CDC6) crucial in cell-cycle progression and growth were identified in 67% of patients with MGS described in the literature [5,6]. Mutations in ATR, which functions during replication can cause Seckel syndrome, a clinically related disorder. These findings suggest that impaired DNA replication could underlie the developmental defects which characterize these disorders [7].

The pre-replication complex consists of the origin recognition complex (subunits ORC1–ORC6), two regulatory proteins (CDT1 and CDC6), and the MCM helicase complex. The complex forms at origins of DNA replication and is essential for initiation of genome replication, a crucial step in cell cycle and cellular growth [8,9].

ORC1-deficient cells from MGS patients and siRNA-mediated depletion of origin licensing proteins also have impaired centrosome and centriole copy number. They also display a

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defect in the rate of formation of primary cilia which impacts sonic hedgehog signaling in ORC1-deficient primary fibroblasts. Additionally, reduced growth factor-dependent signaling via primary cilia affects the kinetics of cell cycle progression following cell cycle exit and re-entry, highlighting an unexpected mechanism whereby origin licensing components can influence cell cycle progression. Defects in cilia function impair chondroinduction. The reduced efficiency in forming cilia could contribute to the clinical features of MGS, particularly the bone development abnormalities, and could provide a new dimension for considering developmental impacts of licensing deficiency [7].

Reductions in growth as a whole as well as of specific tissues are evident in MGS most notably affecting the patella and ears, given that microtia and patellar aplasia/hypoplasia are defining features of MGS [10]. Compound heterozygous mutations have a more severe effect on phenotype than homozygous missense mutations [11].

Here we report the first Egyptian patient with MGS, who had many typical features of the syndrome, in addition to congenital heart disease after taking consent of the parents.

2. Case report

The study involved a 7 year old female child, third in the order of birth of remote consanguineous Egyptian parents. The patient was delivered at full term by vaginal delivery after uncomplicated pregnancy with no history of drug intake by the mother. Her birth weight was 1.5 kg (< 5th centile). The patient was referred to the Genetics Clinic, Pediatric Hospital, Ain Shams University complaining of short stature, very small ears and poor weight gain since birth, and repeated chest infections started at one month old. There was no improvement of weight gain in spite of nutritional management for several years. Six months ago she complained of hearing difficulty.

Family history was unremarkable. She had four healthy sibs with no craniofacial anomalies. Her mother had spontaneous abortion at 4 months of pregnancy. Her parents were normal. Psychomotor development had been satisfactory apart from some delay in speech development. She had a cheerful and friendly personality.

On examination, her weight was 9 kg (< 5th centile), her height was 83 cm (< 5th centile), her span was 74 cm, weight for stature (< 5th centile) and skull circumference was 46 cm (< 5th centile). The girl is slim. She had small triangular face, long peaked nose, high nasal bridge, bilateral low set very small ears (microtia), microstomia, retromicrognathia, high arched palate, maxillary hypoplasia and decayed teeth (Figs. 1 and 2). There were bilateral clinodactyly of fifth finger and mild pectus carnitum. The 3rd, 4th and 5th toes were incurved medially. The back, abdominal and cardiac examinations were apparently normal. The genitalia were also normal. Neurologic examination demonstrated normal tone and reflexes.

Abdomino pelvic ultrasonography demonstrated urinary bladder cystitis. ECHO cardiography demonstrated fenestrated interatrial septum at foramen ovale with minimal shunting. Audiometry revealed bilateral moderate conductive hearing loss. Extended metabolic screen, karyotype, MRI brain, and growth hormone provocation test were normal.

Skeletal survey revealed an increase in the occipitofrontal diameter of the skull (dolichocephalic skull), with relatively small size of the face and mandible. Both hands showed marked delay in bone age (presence of ossific center of two carpal bones only, capitate, hamate), and small radial ossific center for patients age (bone age 18–20 month). There was hyperextensibility of the metacarpophalyngeal joints of both thumbs more on the left side. Both Knees lateral view showed the absence of the patellar ossific center (absent patella). Long bones of both upper and lower limbs were slender and the ribs were also slender (Figs. 3–7).

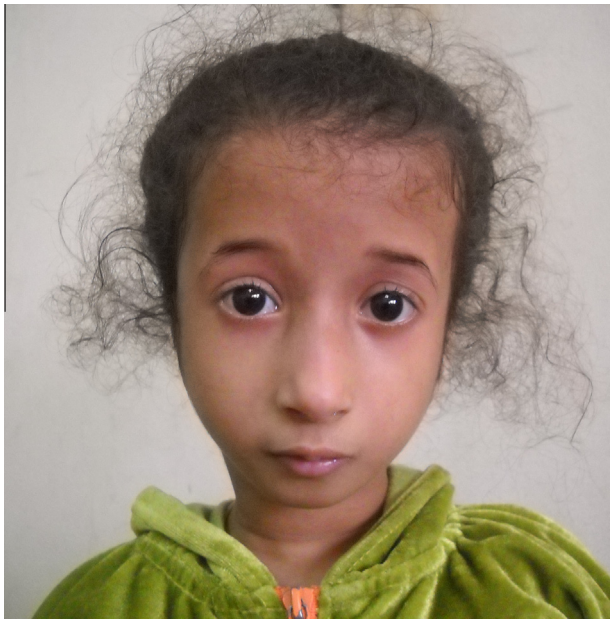

Figure 1 Facial features, small triangle face, long peaked nose, high nasal bridge, micrognathia and microstomia.

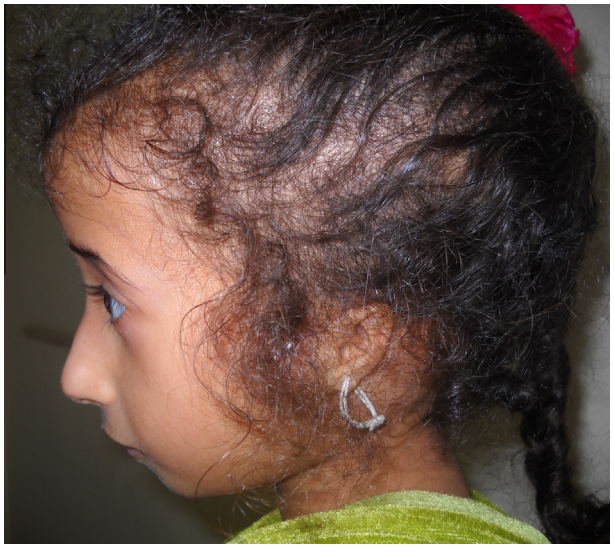

Figure 2 Low set very small ear.

3. Discussion

We report a 7 year old female child with the classic triad of MGS (microtia, absent or hypoplastic patella and short