The Egyptian Journal of Medical Human Genetics (2014) 15, 393–398

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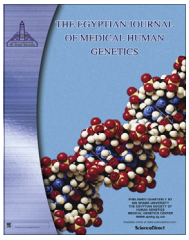

CASE REPORT

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

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Received 7 April 2014; accepted 17 April 2014
Available online 16 May 2014

KEYWORDS

Meier-Gorlin syndrome;
Ear-patella-short stature syndrome;
Primordial dwarfism;
Microtia;
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.

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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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Peer review under responsibility of Ain Shams University.

http://dx.doi.org/10.1016/j.ejmhg.2014.04.003
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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).

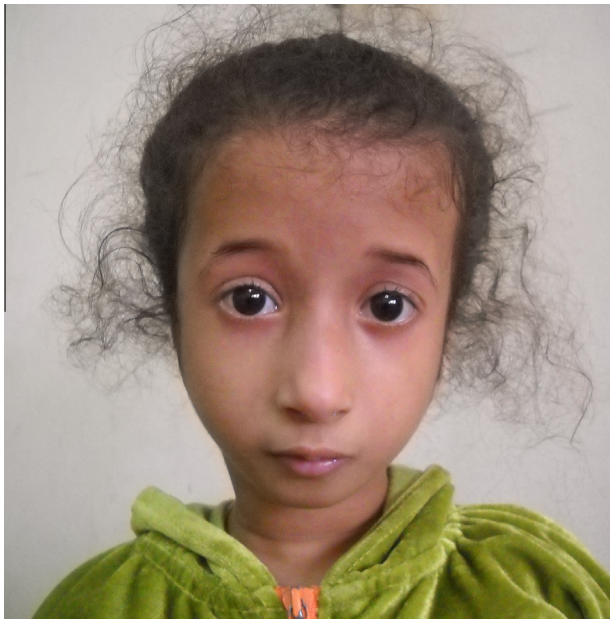

Figure 1 Facial features, small triangle face, long peaked nose, high nasal bridge, micrognathia and microstomia.

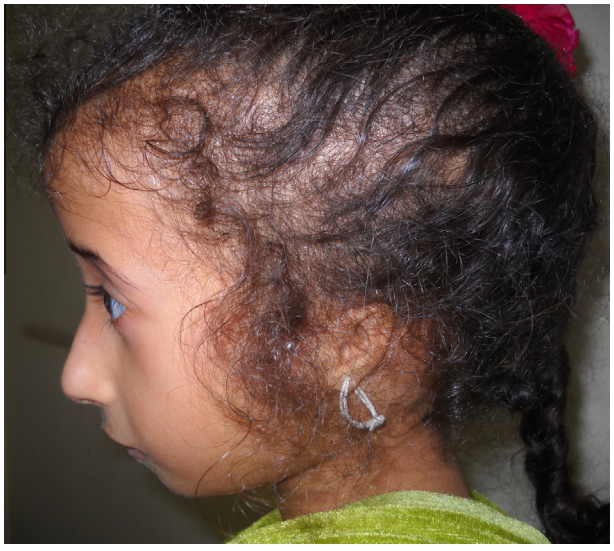

Figure 2 Low set very small ear.

3. Discussion

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

stature). However this triad was reported in 82% of patients with MGS. This means that not all three features had to be present to diagnose MGS and there is a broader range of phenotypes in MGS than previously expected [11]. Our patient had short stature as well as prenatal and postnatal growth retardation. Terhal et al. [12], reported disproportionate short stature in two patients.

She also had the characteristic facial features of MGS including microcephaly, narrow nose with high nasal bridge, bilateral low set small ears, microstomia and microretrognathia as reported in MGS.

Less frequent findings reported in MGS and not detected in our patient include strabismus, bifid uvula and cleft palate [11]. The mentality in our patient was normal, however she had speech defect. Ninety-five percent of patients with MGS had normal intellect despite the presence of microcephaly [5], while 74% display normal motor and speech development [11]. So intelligence is variable in MGS ranging from normal to moderately retarded in few patients. Expressive language delay which may be related to conductive hearing loss was found in some cases [13–15]. The personality of these patients is often described as cheerful and friendly as detected in our patient.

Our patient had absent patella, delayed bone age, slender long bones, slender ribs, dolichocephaly and clindactly. Other musculoskeletal features reported in MGS and not detected in our patient included hooked clavicles, genu recurvatum, club foot or other joint contractures, craniosynostosis, mandibular osteochondroma, short ribs, lack of sternum ossification and chest asymmetry and in some cases brachydactly, and cutaneous syndactyly of 2nd and 3rd or 4th and 5th toes [14].

Our patient suffered from repeated chest infections since birth which improved gradually with age. No specific respiratory disorders had been noted previously in MGS apart from congenital pulmonary emphysema [16], but early non specific respiratory problems were not uncommon especially in the neonatal period which improve with age. Structural abnormalities of the respiratory tract including laryngomalacia, tracheomalacia and bronchomalacia are relatively frequent in these patients while tracheoesophageal fistula was reported in only one patient [11].

Our patient had fenestrated interatrial septum. Congenital heart defects were rarely observed in MGS. However some patients demonstrated perimembranous ventricular septal defects and others patent ductus arteriosus [11], as well as atrial defect with left–right shunt [17]. Also our patient suffered from bilateral conductive hearing loss. Deafness was also reported by Loeys et al. [15], in two brothers with MGS, and severe deafness with congenital labrynthine anomalies was also seen in one patient with MGS [18].

Our patient had normal genitalia. In females hypoplastic labia majora/minora were reported in some MGS patients and in males small testis, cryptorchidism, micropenis as well as hypospadias were reported [11].

Eye and fundus examinations were normal in our patient however Kalappanavar et al. reported MGS with papilledema [18].

Abdominal ultrasonography demonstrated urinary bladder cystitis in our patient. Structural renal anomalies were uncommon in MGS; however unilateral kidney aplasia and kidney stones were reported [11], as well as hypoplasia of corpora cavernosa and the medial segment of the urethra in some patients [19].

Our patient suffered from prenatal and postnatal growth retardation; however her growth hormone level was normal. Growth hormone level showed a broad range of subnormal, normal or elevated levels in these patients. Therefore it is unlikely that short stature is only related to growth hormone deficiency in MGS. In MGS global growth as reflected by both height and head circumference was influenced by the underlying molecular cause. ORC1 mutations caused the most severe growth retardation, followed by ORC4 mutations. This might represent a differential sensitivity to efficient DNA replications, of mutations in different pre-replication complex subunits, or simply reflects the strength of specific mutations, of which there are a limited number in each subunit so far reported. Therefore, testing of ORC1 first should be considered in individuals with a severe growth retardation and microcephaly [11].

De Munnik et al. [10], reported that growth velocity (length) is impaired in MGS during pregnancy and first year of life, but thereafter, height increases in parallel normal

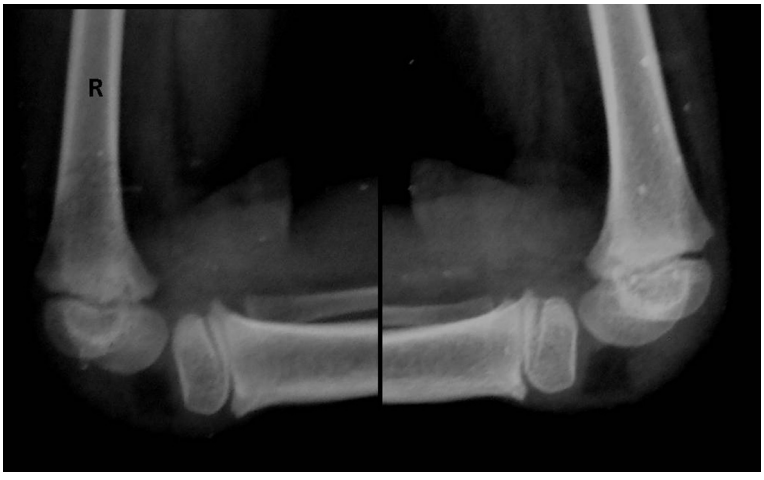

Figure 3 Plain X-ray of both Knees lateral view shows the absence of the patellar ossific center (R is for the right side).

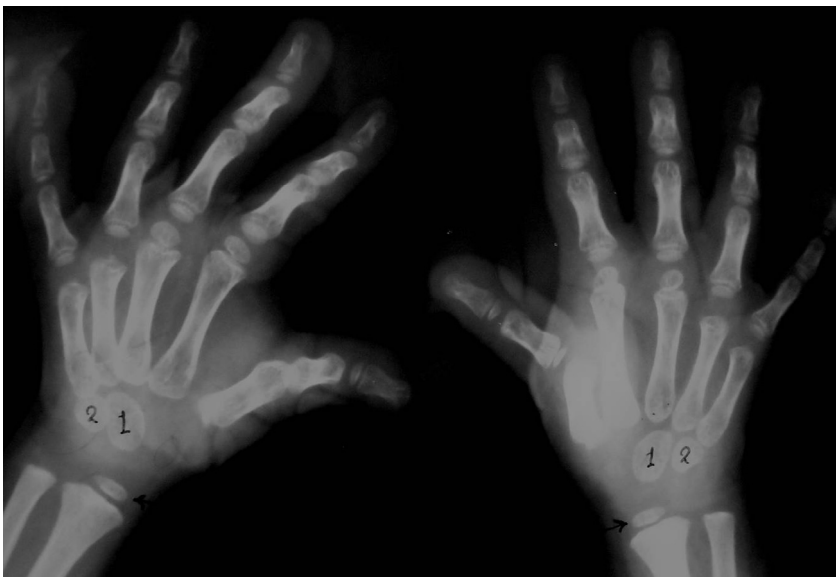

Figure 4 Plain X-ray of both hands shows marked delay in bone age (presence of ossific center of two carpal bones only, capitate (1) and hamate (2)), associated with hyperextensibility of the metacarpophalyngeal joint of both thumbs more on the left side (white arrows). Small radial ossific center for patient's age (Black arrows) (R: right side).

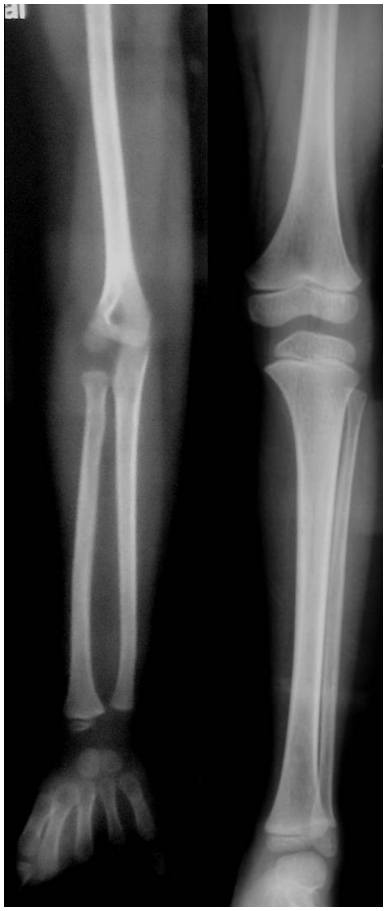

Figure 5 Plain X-ray of the left upper limb and left lower limb shows slender long bones.

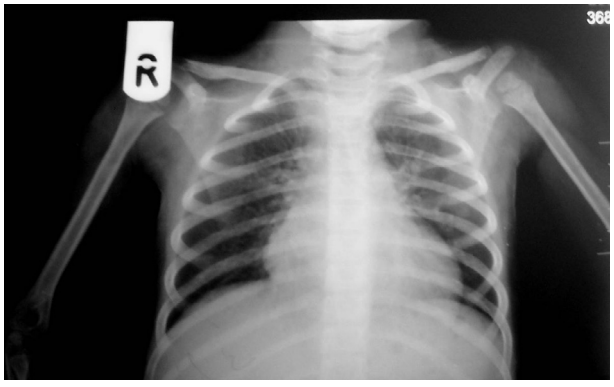

Figure 6 Plain X-ray of the thoracic cage and both arms shows slender ribs and both humeri.

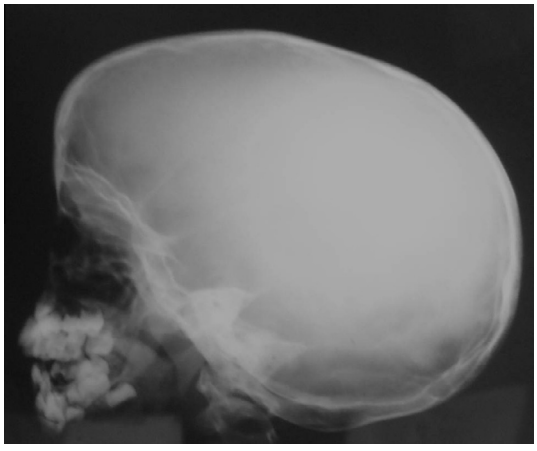

Figure 7 Plain X-ray of the skull lateral view shows increase in the occipitofrontal diameter of the skull that is associated with relatively small size of the face and mandible.

reference centiles resulting in a mean adult height of −4.5 SD. Growth hormone therapy was generally ineffective though in two patients with significantly reduced IGF1 level, growth substantially improved by GH treatment with 2 SD and 3.8 SD improvements in height.

Lacombe [20], followed up a male patient, originally described by Gorlin et al. [4] as an adult. He had degeneration of the knees due to absent patellae, with bilateral aseptic necrosis of lateral femoral condyles.

Differences in facial features were also reported between patients in early infancy (micrognathia, microstomia and full lips) and those described at older age (high vertical forehead, narrow nose and high nasal bridge) [19].

There are reports of consanguinity in some patients as reported in our patient as well as the occurrence of affected sibs. This provides evidence for autosomal recessive inheritance [14,21]. Consanguineous marriages are very common in Egypt (35.3%) and thus help the appearance of autosomal recessive syndromes [22].

MGS should be differentiated from several well known syndromes with proportionate short stature and small ears. Disorders characterized by aplasia/hypoplasia of the patellae accompanied by short stature are RAPADILINO syndrome [23], and Coffin Siris syndrome [24], but microtia has never been observed in these syndromes. Aplasia/hypoplasia of the patellae in association with pelvic anomalies are cardinal manifestations of the small patella syndrome [25], and nail patella syndrome, the latter being accompanied by hypo/dysplastic nails and nephropathy [26]. Nail anomalies and renal anomalies are absent in the MGS. Aplasia/hypoplasia of the patellae without other skeletal anomalies have been found in autosomal dominant patella aplasia-hypoplasia [27].

Follow up of the patients is indicated as there is a change in facial appearance (high vertical forehead, narrow nose and high nasal bridge), accentuated nasolabial folds, hypoplastic breasts and normal menstruation [2].

To conclude this is the first report of an Egyptian patient with the diagnostic triad of MGS (microtia, absent patella and short stature) with associated congenital heart disease. In three quarters of patients with MGS, diagnosis can be confirmed by molecular diagnosis.

Conflict of interest

The authors declare conflict of interest.

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