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Case Report

Meier-Gorlin syndrome with prenatal ultrasound findings and successful growth hormone therapy: Six years follow-up of a rare case ☆,☆☆,★

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ABSTRACT

Meire-Gorlin syndrome (MGS) is a rare autosomal recessive disorder characterized by a triad of short stature, microtia, and absent or hypoplastic patella. We report a 5-year-old male affected with the subtype MGS1, secondary to c.c2292t mutation of ORC1 gene. Our patient's features included a triangular face, micrognathia, and delayed motor development. To the edge of our knowledge, this is the first diagnosed Iranian MGS patient and sixth case in the middle east. MGS1 subtype has never shown improvement to growth hormone therapy, therefore underlying molecular defect was suggested to be responsible for patients' short stature rather than growth hormone deficiency. However, our patients' growth velocity was improved by growth hormone. We recommend more studies to specify the role of ORC1 gene in this syndrome. In addition, this case report describes the prenatal investigations and sonographic examinations of MGS1 for the first time.

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Introduction

Meire-Gorlin syndrome (MGS), is a rare autosomal recessive disorder, characterized by the classical triad of overall short

stature, microtia, and patellar hypoplasia/dysplasia. The first patient was described in 1959 by Meier and the second patient was reported in 1975 by Gorlin[1,2]. To date, less than 80 patients are reported in the literature[3]. In our opinion, the prevalence is underestimated due to missed diagnoses[4].

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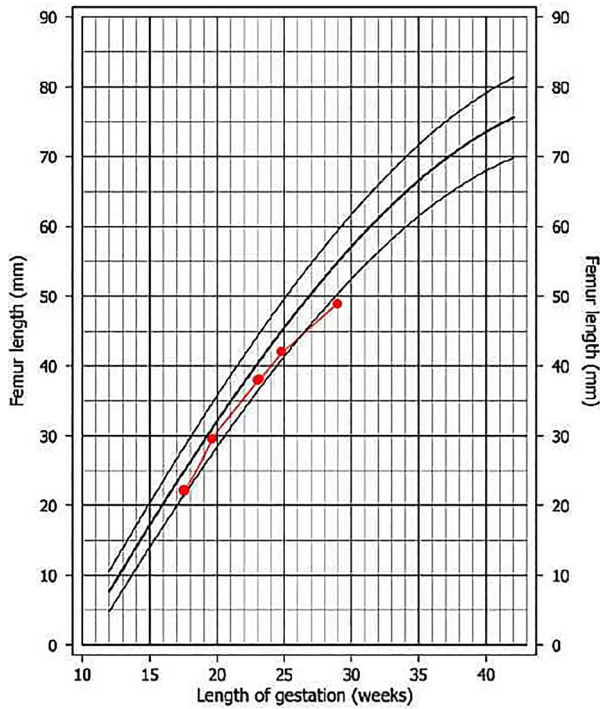


Fig. 1 – Biometric data of fetus affected with Meiere-Gorlin syndrome: femur length. Fetal femur length was in normal range up to 26 weeks, nevertheless it was always under the 50th percentile.



Fig. 3 – An anteroposterior x-ray of both lower limbs of a 2-year-old male affected by MGS1 shows an absence of the patellar ossific center.

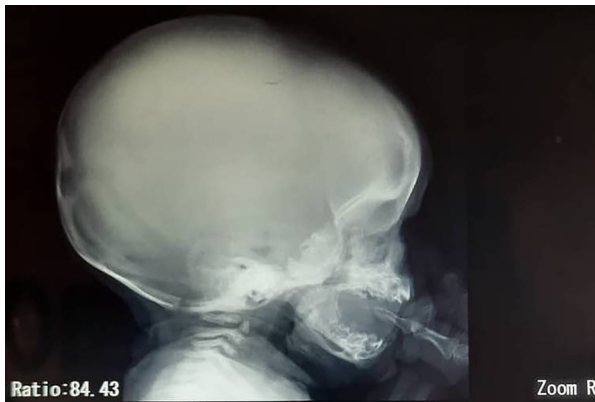


Fig. 2 – A lateral view of the skull in a 2-year-old male affected by MGS1, shows enlarged occipitofrontal diameter, small-sized face, mandible, and maxilla.

So far, most frequent features are intrauterine growth restriction (IUGR) (97%), microtia (94%), patellar anomalies (94%),



Fig. 4 – Knees lateral view x-ray of a male affected by MGS1 at 2 years old, the patellar ossific center is absent.



Fig. 5 – Plain x-ray of thoracic cage shows slender ribs in a 2-year-old MGS1 patient.

Table 1 – Biometric values for gestational age (by ultrasound target anomaly scan.)

GA	12W	17 W 4 D	19 W 5 D	23 W	24 W 6 D	29 W	30 W
FL (mm)		22	29.3	37.7	42	48.4	
HUM (mm)		21.9	28.1	34	38	44	
TIB (mm)		20	25	31	36	42.8	
GA based on BPD		18 W 3 D	20 W 4 D	24 W	25 W 3 D	31 W 4 D	33 W
AC (cm)				17.9	20	24.9	
Weight (gr)		204	289	520	702	1230	1250
NT (mm)	0.98						
NB (mm)	2.3	5.3					

Abbreviations: FL, femur length; HUM, humerus length; TIB, The thermal index for bone; GA, gestational age; BPD, bi-parietal diameter; mm, millimeters; W, weeks; D, days

microcephaly (92%) micro/retrognathia (90%), infancy feeding problems (86%), congenital pulmonary emphysema (83%), and craniosynostosis (80%)[4–6].

Eight different genetic mutations are known to be associated with MGS; each mutation is responsible for a type of syndrome. These 8 genes are responsible for DNA replication, and among them all, ORC1 mutations cause the most severe form of growth failure[3,7]. As yet, patients with ORC1 mutation have not shown any improvement to growth hormone (GH) therapy. Therefore, unknown underlying molecular defects were deemed to cause global growth retardation rather than GH deficiency[7]. However, the hypothesis is not confirmed by molecular studies and there is a doubt about the gene effects. To the edge of our knowledge, there is no previous report on the prenatal screening of MGS1 patients and herein, we present the first case report. In this report,

we will discuss the whole diagnostic odyssey in chronological order.

Case presentation

Our patient was a 5-year-old male, the first child of healthy consanguineous Iranian parents, at the age of 29 and 34 years for mother and father, respectively. The patients' mother had no previous medical, drug, or family history, attended for routine ultrasound screening examination at 12 weeks of gestation. The first sonography revealed normal crown-rump length (CRL), nuchal translucency (NT), and biparietal diameter (BPD) for the gestational age (GA). Ultrasonographic exploring of chromoso-



Fig. 6 – Anteroposterior x-ray of the left hand at 26 months age MGS patient, shows pseudo epiphysis of the second metacarpal base. Hand bone age: 18 months.

normal markers abnormalities revealed normal nasal bone, normal tricuspid doppler, and normal ductus venous doppler. It showed regular anatomy of the skull, spine, heart, abdomen, and extremities as well. Therefore, the report demonstrated a low risk of Down's (1:1010), Edward's (1:11915), and Patau's (1:28048) syndromes which are trisomies 21,18 and 13, respectively.

The mothers' first-trimester hormone analysis showed free Beta-hCG (81 IU/L) and pregnancy-associated plasma protein-A (2335 mIU/L) within the normal ranges. Targeted anomaly scan performed at the gestational age of 17 weeks (Table 1) showed femur length (FL) was in 10th percentile for GA, humerus length (HUM) was in 22nd percentile, and tibial length (TIB) was in 36th percentile, the radiologist suggested follow-up, therefore 5 more ultrasonography scans were performed (all sonographies performed by a single expert radiologist; the Medison Accuvix XQ ultrasound system was used with a Voluson 730 probe, and the visualization was good). At 19 and 23 weeks of gestation, ultrasound showed lower biometric data in percentile for GA (Fig. 1). The serial sonographic follow-up was performed at 24 and 29 weeks of gestation (all data shown in Table 1). Ultrasonography at 29 weeks revealed FL/abdominal circumference (AC) of 19% and FL/head circumference of 17%, both in pathologic range, it also showed FL, HUM, and TIB, all below fifth percentile for GA (Table 1). Neurogram and color doppler examination happened to be normal (fetal transverse cerebral diameter was 36mm). Further sonographic findings included shortening of long bones as well as frontal bossing and widening of the nasal bridge representing constitutional growth delay, skeletal dysplasia,

and atypical IUGR. The latest ultrasound examination was at the 30th week and revealed gestational age of 33 weeks, 28 weeks and 3 days, 26 weeks based on BPD, AC, and FL, respectively.

At term, a 38-weeks intrauterine growth-restricted male was delivered using cesarean section with a birth weight of 2230 grams (under third percentile), birth length of 42 cm (under fifth percentile), and head circumference of 35.5 mm (75th percentile for age). The Apgar score was normal.

The patient was first referred to our center at 2 years old due to his short stature with a height value of 72 cm and weight of 8 kgs, both under the third percentile for age. Clinical manifestations included a small triangular face, micrognathia, bilateral low-set ears, small external auditory canals, and also delayed motor development (Fig. 2). Throughout the examinations, we suspected an absent patella which was further confirmed by radiographic studies (Fig. 3,4). Radiographs revealed a normal pelvic bone and articular structure, normal vertebrae, and delayed bone age of 18 months. Besides, hand x-ray radiography showed second metacarpal pseudo epiphysis (Fig. 5,6). According to our examinations, there was no evidence of neurological disorders or motor retardation, as well as no pulmonary, cardiac, renal, and abdominal abnormalities based on electrocardiogram, echocardiography, and abdominal and pelvic sonography. In addition, the sonogram showed an accessory spleen which might be a normal variation as it presents in 16% of the healthy population[8]. The nails were clinically normal. The growth chart of the first years is represented in Figure 7.

Material and methods

Diagnosis

Chromosomal karyotyping reported 46-XY karyotype (Fig. 8). DNA was extracted from patients' peripheral blood sample and whole-exome sequencing (WES) was performed using Agilent SureSelect V6 target enrichment kit, followed by next generation sequencing using Illumina HiSeq 4000 platform. WES showed c.c2292t heterozygous mutation of ORC1 gene on chromosome 1 (chr1: 52841113), and also reported c.G1874A mutation in ACAN gene on chromosome 15 (chr15: 89392809). ORC1 gene is responsible for an autosomal recessive disease developing MGS1 [MIM: 224690]. c.G1874A variant in ACAN gene is responsible for spondyloepiphyseal dysplasia with autosomal dominant inheritance. We ruled out spondyloepiphyseal dysplasia based on neurological examinations, thus the diagnosis of MGS became more likely regarding the patient's clinical phenotype.

Treatment

Growth hormone (somatropin) 0.05 mg/kg/day was prescribed at 25 months old. We could not find any reports in the literature that confirm growth improvement in ORC1 patients in response to the same treatment. Nonetheless, there was

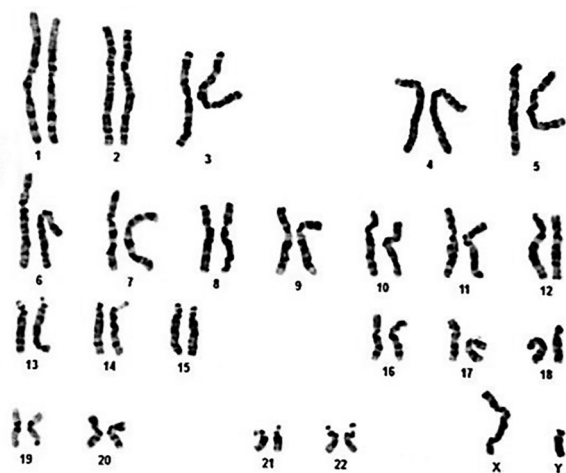


Fig. 8 – Chromosome karyotype of a patient with Meier-Gorlin syndrome, ORC1 mutation.

drome[3]. ORC1 mutation appears to present with extreme growth retardation and microcephaly, we reviewed the patient's prenatal sonographic screenings and anomaly scans and noticed HUM and TIB were under 50th percentile in the first anomaly scan (Table 1). Therefore, the radiologist asked for further follow-up and serial examination. Five ultrasonographic anomaly scans were performed and the last one revealed shortening of long bones and intrauterine growth restriction. Hence, prenatal anomaly scans are essential for screening, particularly in consanguineous parents' pregnancy.

Our patient was a 5-year-old male with the classic triad of MGS, microtia, absent patella, and short stature, nevertheless there are reports of MGS patients with the normal patella[3]. WES revealed a c.c2292t mutation in the ORC1 gene, which highly recommends the MGS1 subtype owing to his phenotype. MGS1 subtype patients have significantly shorter stature and smaller head circumferences[5]. They also should be considered for chromosomal breaks, and malignancies[10]. Height is highly affected by ethnic origin, as Middle Eastern patients were the shortest among all known patients[5]. Also, our patient had low-set ears (63% prevalence), small external auditory canal, triangle face, mandibular hypoplasia (90% prevalence), microcephaly (41% prevalence), and despite his normal intellect, delayed motor milestones (24% prevalence), delayed bone age, and thin skin[5]. There are other skeletal manifestations of MGS syndrome that were not presented in our patient, namely craniosynostosis, detected in the majority of (80%) CDC45 related MGS, hooked clavicles, genurecurvatum, club foot, and clinodactyly, as well as brachydactyly and cutaneous syndactyly have been reported frequently[3,6,7]. Yet in our case, we noticed 2nd metacarpal pseudo epiphysis [Fig. 6], reported for the first time in an MGS patient which could be either a normal variation or a symptom in syndromes[11]. Many cases have experienced congenital pulmonary emphysema (34%) or other respiratory disorders during infancy (48%)

which did not apply to our patient[3]. Subsequently, we also performed the pulmonary examination in addition to exploring any abnormalities and the outcome was normal for any respiratory problems. Cardiac anomalies are not common among MGS cases, although ventricular septal defect and ductus arteriosus have been reported formerly[4]. In this case, cardiac examination, electrocardiogram, and echocardiography were normal. He also underwent abdominal and pelvic ultrasonography and was free of renal or abdominal abnormalities; however, they are not very often presented in MGS. There is a large number of reports indicating poor feeding during infancy (86%), which did not include our patient. Urogenital anomalies are very common among these patients that did not concern our case[3].

In a study by Demunnik et al., 9 out of 45 MGS patients underwent GH therapy, and 2 male patients both with unknown mutations, and clinical diagnosis showed increased height velocity[5]. In contrast, in 2002 GH treatment was considered for an Italian MGS1 patient, yet without beneficial results[12]. Of all the confirmed MGS patients that have been previously reported, the MGS1 subtype was never along with any improvement to GH therapy. Thus, understanding the exact underlying molecular defects and their mechanism contributing to patients' phenomenon is essential for developing novel therapeutic targets and options[7].

Conclusion

We described a rare case of Meire-Gorlin syndrome, an autosomal recessive disorder. WES revealed c.c2292t mutation of ORC1 gene, responsible for MGS1 subtype. Our patient is the first reported case of MGS1 who benefited from GH therapy, through which we learnt that the early detection of this disease is important. Treatment should begin at the earliest opportunity to improve their quality of life, however there is no certain cure. More molecular studies should be designed to specify the ORC1 gene action on this syndrome. In addition, this case report describes the prenatal investigations and sonographic examinations of MGS1 for the first time. We hope our data will help early diagnosis of MGS during pregnancy and routine ultrasound screening examinations.

Consent to publication

Written informed consent was obtained from patient and his family for the publication of this report and any accompanying images.

Availability of data and materials

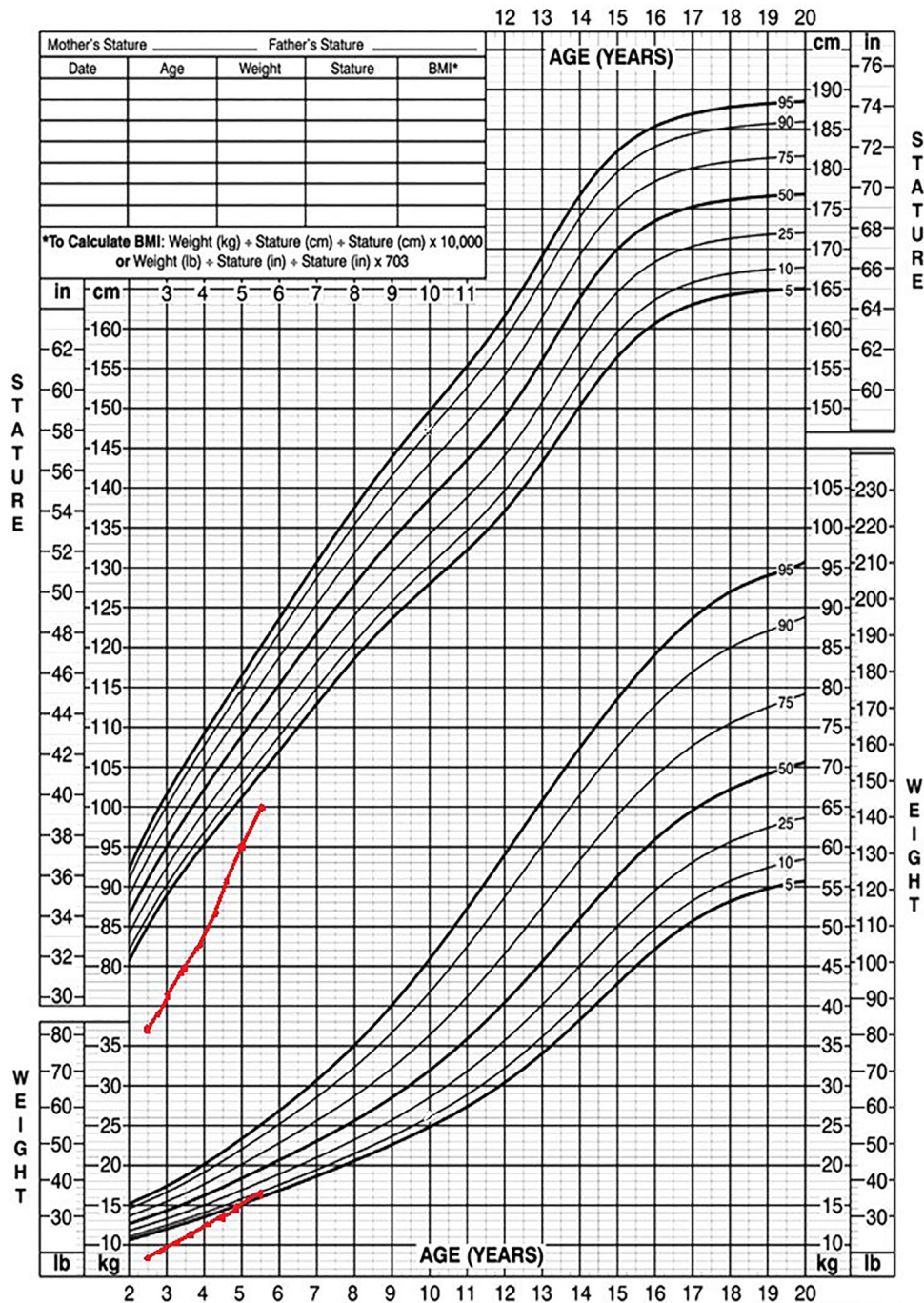
The datasets of the current study are available from the corresponding author on reasonable request.

2 to 20 years: boys

Stature-for-age and weight-for-age percentiles

NAME _____

RECORD # _____



Published May 30, 2000 (modified 11/21/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with
the National Center for Chronic Disease Prevention and Health Promotion (2000).
<http://www.cdc.gov/growthcharts>



Fig. 9 – Growth chart, shows improvement in growth velocity, due to growth hormone therapy in a MSG case.



Fig. 10 – A 5-years-old male with Meier-Gorlin syndrome: (A) short stature (100 cm height), (B) micrognathia, (C) small triangular face, low set ears.

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