An 11-Year-Old Girl With Rare Diagnosis of Meier-Gorlin Syndrome Accompanied by Neonatal Seizure, Mental Retardation, and Attention Deficit Hyperactivity Disorder: A Case Report and Review of Literature

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Abstract- Meier-Gorlin syndrome (MGS) is a rare autosomal recessive disorder with homozygous or heterozygous mutations in one of the five following genes (ORC1, ORC4, ORC6, CDT1, and CDC6). This syndrome is characterized by the triad of short stature (pre/postnatal), microtia, and patella hypoplasia/aplasia. Special features included microcephaly, microstomia, full lips, micrognathia, narrow convex, and high nasal bridge nose. Also, it may be accompanied by feeding problems, skeletal disorders, urogenital or respiratory anomalies, and intelligence disorders. This case report describes the first Persian MGS accompanied by neonatal seizure, mental retardation, and attention deficit hyperactivity disorder.

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Keywords: Meier-Gorlin syndrome; Seizures; Intellectual disability; Neonatal seizure; Attention deficit disorder with hyperactivity

Introduction

Meier-Gorlin syndrome (MGS) or Ear patella short stature syndrome (EPS) is a rare disorder manifested by proportionate growth retardation (pre/post natal), microtia, and patella hypoplasia/aplasia (1). The first MGS patients were reported by Meier in 1959 and Gorlin in 1975 (2). Although its prevalence is estimated to be less than 1-9/1,000,000, undiagnosed or unreported cases should be considered as well. To the best of our knowledge, about 70 cases of this syndrome have been reported to date (1).

MGS is an autosomal recessive disorder with homozygous or heterozygous mutations in one of the following five genes (ORC1, ORC4, ORC6, CDT1, and CDC6) (1-3), which encode members of the pre-replication (pre-RC) and pre-initiation (pre-IC) complexes. Mutation of these genes disrupts cellular proliferation resulting in total cell number reduction and, thereby, retardation of overall growth (4-7). These patients have special facial features, including bilateral microtia, narrow convex, and high bridge nose aggravating with age, microstomia, full lips, and micrognathia. Associated manifestations are microcephaly, patellar aplasia or hypoplasia, feeding problems, and rare skeletal disorders (delayed bone age, club foot, joint contracture, genu recurvatum, and dislocation of knee). In addition, Cryptorchidism in males and mammary hypoplasia, small uterus, hypoplastic major/minor labia, or polycystic ovaries in female cases could be detected (1,8). This case report aimed to present an 11-year-old girl with the classic triad of MGS and associated anomalies.

Case Report

An 11-year-old girl was referred to the endocrinology clinic of 17 Shahrivar hospital, Rasht, Iran. Short stature and developmental delay were the main complaints. She was the first living birth in the family. Her mother's previous pregnancy was terminated at 6 months of gestation due to severe hydrocephalus,

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myelomeningocele, and lumbosacral spinabifida in prenatal sonography. Parents were consanguineous and healthy, and no other family member was affected.

She was born at 32 weeks of gestation by cesarean section due to severe symmetric intrauterine growth retardation and moderated to severe oligohydramnios. Her birth height, weight, and head circumference were 38 cm (<3% percentile), 790 grams (<3% percentile), and 26 cm (<3% percentile), respectively. After birth, the neonate was admitted to the NICU department due to respiratory distress and very low birth weight status. On the twentieth day of her life, she experienced a subtle seizure for 1 minute, including eyelid blinking, staring, and sucking, accompanied by tachycardia and reduction of oxygen saturation in pulse oximetry. Therefore, she was treated with intravenous phenobarbital. A sepsis workup was done, and other evaluations showed no hydrocephalus, intraventricular hemorrhage, or other abnormalities in brain sonography and CT scan. Cerebrospinal fluid analysis, serum calcium, glucose, blood gas, and metabolic study were all normal. Electroencephalography was performed after the seizure and in repeated visits and revealed no abnormal findings. Oral daily phenobarbital continued and tapered until three years without recurrence of seizure.

Due to the high level of TSH hormone in premature neonatal screening, levothyroxine was started and is continued to this day (9). Due to microcephaly and abnormal facies (receding forehead, prominent nose, clinodactyly in 5th finger of right hand, low set ear, and microtia), karyotype testing was done and revealed 23 pairs of chromosomes, compatible with normal female (46 XX) (Figure1).

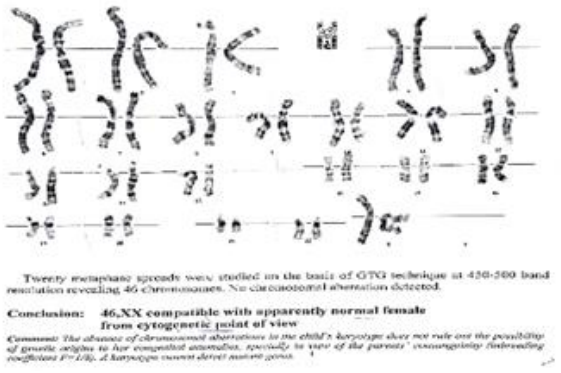

Figure 1. Patient karyotype compatible with normal female (46 XX)

An orthopedic consultation was done in the neonatal period due to left knee dislocation. She received related treatment, and plastering was done for 2 months. Developmental milestones and speech were acquired with great delay. The growth trend of weight and height, and head circumference, were all <5% of WHO child growth standard percentiles in frequent visits by pediatricians. Also, she had an impaired growth hormone (GH) stimulation test and low serum level of insulin growth factor 1 (IGF-1) along with poor growth in anthropometric indices during her first years of life; therefore, GH therapy was started for her by an endocrinologist at the age of 18 months and continued for 2 years. Currently, at the age of 11 years, anthropometric characteristics included height (127 cm, Height z score -2.4), weight (22 kg, Weight z score -3.26), and head circumference (42 cm, Z score >-5) were deficient for age according to the WHO child growth standards. Also, due to the combination of symptoms, including inattention, hyperactivity, and impulsivity, she was under treatment for risperidone from the age of 5 with the diagnosis of attention deficit hyperactivity disorder (ADHD). Her intelligence quotient is low, and she has not finished the first grade yet. Facial characteristics included bilateral microtia, large convex nose, microcephaly, full lips, and micrognathia were evident (Figure 2, 3). The left patella was not palpable, and as shown in figure 4, its absence was confirmed by radiography. As shown in figure 5, clinodactyly was seen in the 5th finger of the right hand. Bone age on left wrist radiography was equivalent to chronological age (Figure 6).

Figure 2. Special facies including microcephaly, large convex nose, microcephaly, full lips, and micrognathia

Figure 3. Bilateral microtia in patient

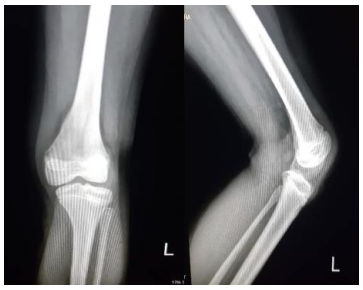

Figure 4. Absence of left patella

Figure 5. Clinodactyly in the 5th finger of the right hand

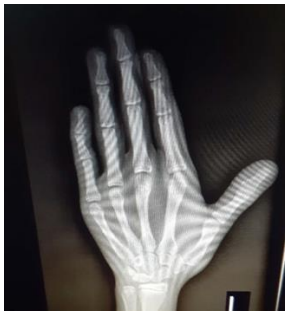

Figure 6. Bone age on the left wrist radiograph was equivalent to chronological age (11 years)

Chest and abdominal exams were normal. There were some degrees of hypermobility and hyperextension in both knee joints, preferably on the left side.

Breasts were at the first tanner stage of puberty (Figure 7), and spare pubic hair was seen in the genitalia examination. Neurologic examination demonstrated normal tone and forces. Other exams were all normal and revealed no specific abnormality. All laboratory tests showed normal results except for G6PDd (Glucose 6 phosphatase dehydrogenase deficiency) and high TSH level compatible with hypothyroidism. Echocardiography and abdominopelvic sonography were normal. Audiometry at 6 months of age revealed some degrees of left ear conductive hearing loss (Figure 8), but at the age of 11 years, audiometry revealed bilateral conductive hearing loss. The ophthalmologic exam was normal. The intelligence quotient was performed by the Wechsler test and was revealed as 51.

DNA extraction identified a homozygote variant of ORC1gene (c313c>T, P, R105W) compatible with MGS.

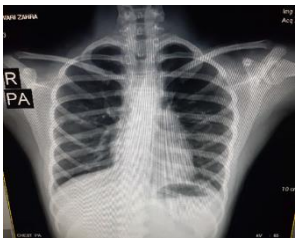

Figure 7(A-B). Chest radiography and breast examination (breasts at stage1 tanner)

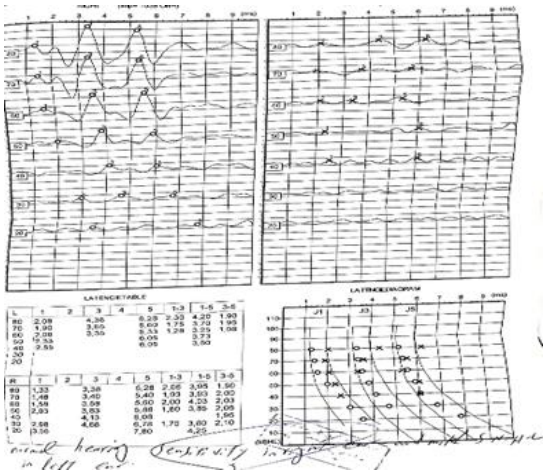

Figure 8. The patient's neonatal audiometry revealed some degrees of left ear conductive hearing loss

Discussion

MGS should be considered in patients with short stature, microtia, and patella hypoplasia as a triad that is not seen in any other diseases (5). In 97% of patients, two out of three findings are seen. The most common findings include patellar hypoplasia and microtia (1,10). However, it is worth noting that MGS clinical phenotype might be varied to the extent that short stature can be the only manifestation of MGS (2). The present patient had the triad manifestations of the disease.

Although Seckel syndrome is one of the important differential diagnoses in short stature, its height and head circumference are much smaller than MGS. Other syndromes such as Russell-Silver, Majewski osteodysplasia-tic bird-head dwarfism type I/II/III, Rapidilinio, nail patella, and Coffin-Siris can mimic MGS signs as well (10,11). It is noteworthy that nail dysplasia is absent in MGS, which can differentiate it from nail-patella syndrome (9).

Mild to severe microtia or low set ear is seen in the majority of MGS patients as well as the current case. Narrow ear canals and conductive hearing loss may be present in combination with microtia as exist in both ears of the present case. Patellar abnormalities, including absent or hypoplastic patella, are the other common finding in MGS compatible with the current case. Growth problems begin before birth and continue after birth. Intrauterine growth retardation (IUGR) and birth weight Z score <-3.8 Standard Deviation (SD) is a common finding in this disorder (2) as mentioned in this patient and 3 other case reports (12,13), Which led to the termination of the pregnancy in 32 weeks of gestation.

Severe microcephaly (< −3SD) is an associated problem that is especially correlated with a mutation in ORC4 and ORC1, the same gene that was mutated in the present case (1). A review of the literature did not mention a definite association between MGS and seizure disorders, but two previous reports, as well as the present one, mentioned it (5,12). The occurrence of seizure in our patient may be an accidental finding, not a common manifestation of the MGS. The association of ADHD with this syndrome in our patient may also be a coincidence because no similar accompaniment was found in any of the reported cases.

These patients are usually normal in intelligence, but some degrees of developmental delay or speech skills may be present, as well as in the current case. Respiratory tract anomalies are other finding in this syndrome, including congenital pulmonary emphysema, bronchomalacia, laryngomalacia, tracheomalacia, and recurrent respiratory tract infections (1,5). Cardiac anomalies such as patent ductus arteriosus or ventricular septal defect are seen rarely in MGS (13).

The other problems in MGS are feeding problems, including small appetite, gastroesophageal reflux, needing a gastrostomy tube, or even ophthalmologic disorders such as papilledema in rare reported cases of MGS (1,14,15). None of these findings were present in the current case report.

Knee examination should be considered in patients with microtia accompanied by growth retardation. Radiography of the left knee of the current case confirmed the absence of the left patella. Since the patellae are radiolucent in the first years of life, radiography of the patella is diagnostic after 4 years old, and ultrasonography has a diagnostic value at this age range. Although the recurrence risk for a couple with an affected child is about 25%, prenatal diagnosis is recommended by chorionic villus sampling or amniocentesis and prenatal ultrasound if the patient's mother intends to become pregnant again (5).

The management of MGS is supportive. MGS patients should be examined by an ear-nose-throat (ENT) specialist due to conductive hearing loss with microtia. ORC1 and ORC4 mutations causing more severe short stature and prevention and treatment of growth retardation after GH stimulation test, serum IGF-1 level measurement, and GH therapy may be in consideration if growth velocity continued to be low after the first year of birth or low levels of IGF1 be present; however, the efficacy of this treatment in MGS is controversial (14). Relief of knee pain as present and prevention of instability of the knee joints are necessary. Following the patient in terms of the occurrence of early knee joint arthrosis is recommended. Treatment of accompanied lung or feeding problems (gastrostomy tube-proton pomp inhibitor if gastroesophageal reflux is present) might be in consideration. Cardiac echocardiography should be done in all MGS cases. Exogenous estrogen or Breast augmentation surgery in mammillary hypoplasia in female cases are the other treatments that might be in consideration.

This is the first Persian MGS-reported case accompanied by a neonatal seizure, intelligential disorder, and ADHD. The presence of microtia, growth retardation, and patellar aplasia/hypoplasia together should raise diagnostic suspicion of MGS syndrome. A thorough examination of the knee is necessary for patients with small ears and short stature.

Early diagnosis can greatly prevent complications and lead to better growth and quality of life with proper management and supportive treatments.

References

1. De Munnik SA, Hoefsloot EH, Roukema J, Schoots J, Knoers NV, Brunner HG, et al. Meier-Gorlin syndrome. Orphanet J Rare Dis 2015;10:114.
2. Guernsey DL, Matsuoka M, Jiang H, Evans S, Macgillivray C, Nightingale M, et al. Mutations in origin recognition complex gene ORC4 cause Meier-Gorlin syndrome. Nat Genet 2011;43:360-4.
3. Bicknell LS, Bongers EM, Leitch A, Brown S, Schoots J, Harley ME, et al. Mutations in the pre-replication complex cause Meier-Gorlin syndrome. Nat Genet 2011;43:356-9.
4. Klingseisen A, Jackson AP. Mechanisms and pathways of growth failure in primordial dwarfism. Genes Dev 2011;25:2011-24.
5. Morankar RG, Goyal A, Gauba K, Kapur A. Dentofacial characteristics in a child with Meier–Gorlin syndrome: A rare case report. Saudi Dent J 2018;30:260-4.
6. Kuo AJ, Song J, Cheung P, Ishibe-Murakami S, Yamazoe S, Chen JK, et al. The BAH domain of ORC1 links H4K20me2 to DNA replication licensing and Meier–Gorlin syndrome. Nature 2012;484:115-9.
7. Vetro A, Savasta S, Raucci AR, Cerqua C, Sartori G, Limongelli I, et al. MCM5: a new actor in the link between DNA replication and Meier-Gorlin syndrome. Eur J Hum Genet 2017;25:646-50.
8. Kruglov I, Rumyantsev N, Omarov G, Rumyantseva N, Kagantsov IM. Meyer-Gorlin syndrome in combination with congenital dislocation of the knee: a clinical case. Pediatr Traumatol Orthop Reconstr Surg 2021;10.
9. Dalili S, Mohammadi H, Rezvany SM, Dadashi A, Novin MH, Gholaminejad H, et al. The relationship between blood pressure, anthropometric indices and metabolic profile in adolescents: a cross sectional study. Indian J Pediatr 2015;82:445-9.
10. Shawky RM, Elabd HS, Gamal R, Mohammad SA, Gad S. Meier-Gorlin syndrome: Report of an additional patient with congenital heart disease. Egypt J Med Hum Genet 2014;15:393-8.
11. Al-Dosari MS, Shaheen R, Colak D, Alkuraya FS. Novel CENPJ mutation causes Seckel syndrome. J Med Genet 2010;47:411-4.
12. Khan AA, Reddy C, Saini AG, Vyas S. Meier-Gorlin syndrome presenting as early infantile epileptic encephalopathy. BMJ Case Rep 2020;13:e235468.
13. Stenzel M, Schulz S, Fiedler A, Vilser C, Doerfel MH. Meier-Gorlin syndrome type 1 in a 3 years old female-clinical, radiologic and genetic data. ISDS Meeting Bologna, 2013.
14. de Munnik SA, Bicknell LS, Aftimos S, Al-Aama JY, Van BY, Bober MB, et al. Meier-Gorlin syndrome genotype-phenotype studies: 35 individuals with pre-replication complex gene mutations and 10 without molecular diagnosis. Eur J Hum Genet. 2012;20:598-606.
15. Kalappanavar NK, Gouli C, Syed Nasiruddin I. Meier-Gorlin syndrome with papilloedema. J Pub Health Med Res 2013;1:53-4.