A Case of Concurrent Miller-Dieker Syndrome (17p13.3 Deletion) and 22q11.2 Deletion Syndrome

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J Pediatr Genet 2015;4:201–203.

Abstract

Features of Miller-Dieker syndrome (MDS, 17p13.3 deletion syndrome, LIS1-associated lissencephaly) include classic lissencephaly, microcephaly, cardiac malformations, growth restriction, and characteristic facial changes. Individuals with 22q11.2 deletion syndrome (DiGeorge syndrome or velocardiofacial syndrome) are known to have congenital cardiac malformations (in particular conotruncal defects), palatal abnormalities (especially velopharyngeal insufficiency), hypocalcemia, immune deficiency, learning disabilities, and characteristic facial features. This case report describes phenotypic characteristics of a patient with extremely rare instance of having both MDS and 22q11.2 deletion syndrome that is unique in the medical literature. Prognosis in this concurrent phenotype is poor with our patient suffering from several malformations seen in both conditions and expiring in the neonatal period.

Keywords

- Miller-Dieker syndrome
- 17p13.3 deletion
- 22q11.2 deletion syndrome

Introduction

Features of Miller-Dieker syndrome (MDS, 17p13.3 deletion syndrome, LIS1-associated lissencephaly) include classic lissencephaly, microcephaly, cardiac malformations, growth restriction, and characteristic facial changes, including the prominent forehead, downslanting palpebral fissures, short nose with upturned nares, protuberant upper lip, and micrognathia. Death usually occurs in the first few years of life and development remains at the 3- to 6-month level.¹ Individuals with 22q11.2 deletion syndrome (DiGeorge syndrome or velocardiofacial syndrome) are known to have congenital cardiac malformations (in particular conotruncal defects), palatal abnormalities (especially velopharyngeal insufficiency), hypocalcemia, immune deficiency, learning disabilities, and characteristic facial features, including narrow palpebral fissures, hypertelorism, short philtrum, bulbous nose, and low-set ears.^{2,3} This case report describes phenotypic characteristics of a patient with extremely rare instance of having both MDS and 22q11.2 deletion syndrome that is unique in the medical literature.

Case Report

The patient was an ex-32 week Hispanic male born to a 20-year-old G1P1 mother. Parents were both of Mexican descent and consanguinity was denied. Prenatal complications included significant polyhydramnios, a fetal echocardiogram that demonstrated D-transposition of the great arteries (d-TGA), a ventriculoseptal defect (VSD), and significant subpulmonic stenosis. Additionally, ultrasound demonstrated a small stomach, symmetric intrauterine growth restriction (IUGR), micrognathia, mild ventriculomegaly, and an enlarged fetal bladder. He was born by spontaneous vaginal delivery with Apgar scores of 1 and 8 at 1 and 5 minutes, respectively. Postnatal growth parameters at birth included length 38 cm (3rd percentile), weight 1.44kg (10th percentile), and head circumference 26.5 cm (3rd percentile). Delicate features were noted in the physical examination; the cranium was normocephalic with a mild occipital shelf and open anterior fontanelle; ear helices were overfolded, short and malformed bilaterally; micrognathia was noted.

received

March 10, 2015

accepted after revision

April 9, 2015

published online

October 14, 2015

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DOI <http://dx.doi.org/10.1055/s-0035-1565267>.
ISSN 2146-4596.

The fingers were tapering with a broad left thumb, and feet were edematous particularly over the dorsal aspect and there was persistence of fetal fat pads on the feet. Head ultrasound showed a dysplastic and possible absent corpus callosum, and nodular, septated, hyperechoic material was noted in the cavum septum pellucidum. The dorsal midline cerebellum was not seen, which was suggestive of hypogenesis or dysplasia of the vermis. Last, the brain was globally underdeveloped and even corrected for gestational age. Renal ultrasound showed mild pelviectasis in the left kidney with bilateral hydronephrosis. Echocardiogram showed d-TGA, VSD, subpulmonic stenosis, and a large patent ductus arteriosus.

Karyotype result was 45, XY, der(17)t(17;22)(p13.2;q11.2)-22. There was loss of the distal arm of chromosome 17 from band 17p13.2 to the 17p terminus (17pter, including 17p13.3) as well as loss of the proximal portion of the long arm of chromosome 22, including the centromere of chromosome 22 and a part of band 22q11.2 (→Fig. 1). There was only one copy of chromosome 22, thus resulting in partial monosomy 17p and partial monosomy 22q. Maternal karyotype was performed and was normal 46, XX with no evidence of apparent rearrangements, and paternal karyotype was unavailable. An array comparative genomic hybridization showed 17p13.3(13,073–2,777,588)x1,22q11.1q11.21(16,054,713–20,238,236)x1. The 17p13.3 deletion observed in the patient was obviously a terminal deletion (due to the nature of the unbalanced translocation) and included most of band 17p13.3 to the 17pter. This deletion was at least 2.76 Mb in size and included at least 36 RefSeq genes from *DOC2B* to *RAP1GAP2*. Of interest in this region are *PAFAH1B1* (formerly *LIS1*), *YWHAE*, and *CRK*. Deletions that are associated with MDS are variable and can range from 0.1 to 2.9 Mb in size; however, all include the *PAFAH1B1* locus that is thought to be responsible for the lissencephaly associated with this disorder.⁴ *YWHAE* is believed to play a role in the developmental delay and facial dysmorphism observed in MDS, whereas *CRK* is a candidate gene for the growth

restriction that is typically seen.^{5,6} The 22q11.1 to 22q11.23 deletion observed in this patient included loss of the chromosome 22 short arm (repetitive material) and the centromeric region of chromosome 22 to the proximal half of band 22q11.21. There was only one normal copy of chromosome 22 present in this patient, as per the karyotype performed earlier. This deletion was at least 4.18 Mb in size and includes at least 42 RefSeq genes from *CCT8L2* to *RTN4R*. Of interest in this region are *HIRA* (formerly *TUPLE1*) and *TBX1*. Though this is not the typical deletion observed in velocardiofacial syndrome (due to its derivation via a translocation), it still includes the minimally deleted region (or critical region) for this syndrome. Both *HIRA* and *TBX1* have been suggested as candidate genes for the disorder.^{7,8}

Discussion

This report describes the only case documented in the medical literature describing the phenotype of concurrent MDS and 22q11.2 deletion syndrome. Given there are two distinct genetic syndromes with well-described phenotypes, we felt it is important to distinguish the likely cause of the congenital malformations. The dysplastic or possibly absent corpus callosum anteriorly and possible agenesis of dorsal midline cerebellum are both well described in MDS and are not typical of 22q11.2 deletion syndrome.⁹ The cardiac findings of d-TGA, VSD, and subpulmonic stenosis are not typical of MDS while they are seen in less than 10% of 22q11.2 deletion syndrome. Hydronephrosis is not typical of MDS; however, it is well described in 22q11.2 deletion syndrome. Prognosis in this concurrent phenotype is difficult. A previous report of MDS with VACTERL (vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities) association highlights a severe phenotype noted in a patient with blended phenotypes.¹⁰ MDS typically has severe developmental delay with development at the 3- to 6-month level with death in first few years of life whereas 22q11.2 deletion syndrome has a milder phenotype with generally only mildly reduced intellect. Given the structural brain abnormalities described in this patient, we were conservative with our prognosis; the patient expired in the neonatal period. In conclusion, we describe the only known case of concurrent MDS and 22q11.2 deletion syndrome. The phenotype appears severe and this case highlights the importance of thorough investigation when presented with multiple congenital abnormalities in the newborn period.

Fig. 1 Ideogram of chromosomal imbalance.

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