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REVIEW ARTICLE

Prenatal Sonographic Features of Miller-Dieker Syndrome

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Miller-Dieker syndrome (MDS) is a contiguous gene deletion disorder involving genes on chromosome 17p13.3. Clinical manifestations include central nervous system (CNS) anomalies (mainly Type I lissencephaly), facial dysmorphism, growth restriction, profound mental retardation, seizure, and extracranial anomalies. The affected individuals often die in infancy or early childhood. Owing to the poor prognosis of MDS, early diagnosis of fetuses with MDS is important. Currently, ultrasound is regarded as a useful tool in prenatal detection of MDS, in addition to fetal magnetic resonance imaging. This article provides an overview of the reported prenatal sonographic features of MDS, including CNS anomalies (ventriculomegaly, agyria or lissencephaly, abnormal sylvian fissures, agenesis or dysgenesis of corpus callosum, and microcephaly), intrauterine growth restriction, polyhydramnios, cardiac anomalies, omphalocele, facial anomalies, and rare anomalies. Several diseases may have phenotypic overlaps with MDS, including Type I lissencephaly (Lissencephaly 1, Lissencephaly 2, and X-linked lissencephaly) and Type II lissencephaly. Increasing the awareness and knowledge of fetal structural anomalies associated with MDS on prenatal ultrasound will be helpful in the early detection, thus allowing appropriate genetic counseling and optimize clinical management.
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Introduction

Miller-Dieker syndrome (MDS, OMIM 247200), described by Miller [1] and Dieker et al [2], is a contiguous gene deletion syndrome characterized by central nervous system (CNS) anomalies, facial dysmorphism, growth restriction, profound mental retardation, and extracranial anomalies. The CNS anomalies include cerebral agyria or Type I lissencephaly, ventriculomegaly, absent or hypoplastic corpus callosum, and microcephaly. The facial features may present prominent forehead with bitemporal narrowing, furrowed brow, small nose with anteverted nostrils, low set ears, prominent upper lip, and micrognathia. Seizure is often developed in early childhood. Life expectancy is significantly shortened and patients usually die during early childhood [3]. Associated extracranial anomalies may be present, such as cardiac anomalies, omphalocele, and genitourinary anomalies [4,5].

The normal six-layered brain cortex is formed by neuronal migration beginning at 8 weeks of gestation. Impairment or arrest of neuronal migration at about 3—4 months of gestation can result in lissencephaly. On the basis of clinicopathological classification, two types of lissencephaly have been proposed. Type I lissencephaly seen in MDS is often associated with a microdeletion of chromosome 17p13.3. Three genes, *LIS1* (*PAFAH1B1*; OMIM 601545), *14-3-3ε* (*YWHAE*; OMIM 605066), and *CRK* (OMIM 164762), are mapped to this locus [6,7]. Deletion or mutations in these genes can cause the lissencephaly. Lissencephaly is also present in several other diseases such as Norman-Roberts syndrome and Walker-Warburg syndrome. Therefore, differential diagnosis including Type I and Type II lissencephaly is discussed here.

Prenatal diagnosis is important due to the poor outcome in MDS-affected cases. Magnetic resonance imaging is considered to be a useful tool in the diagnosis of CNS anomalies in fetuses of MDS. However, it is more expensive and sedation of the fetus may be required during examination. At present, ultrasound is thought to be another possible tool in the prenatal detection of characteristic findings associated with MDS. To date, there have been approximately 25 reported cases of MDS having prenatal sonographic findings. Here, we review the sonographic features in these fetuses of MDS. Early diagnosis of MDS is significantly beneficial for prenatal counseling and obstetric management.

Prenatal Sonographic Features

The prenatal sonographic features of published MDS cases are summarized in Table 1 [5,8—23]. They include CNS anomalies (ventriculomegaly, agyria or lissencephaly, abnormal sylvian fissures, agenesis or dysgenesis of corpus callosum, and microcephaly), intrauterine growth restriction (IUGR), polyhydramnios, cardiac anomalies, omphalocele, facial anomalies, and rare anomalies.

Table 1. Prenatal sonographic features of reported cases with Miller-Dieker Syndrome [8—23]

Cases	Microdeletion	CNS anomalies			
		Ventriculomegaly	Lissencephaly (agyria)	Abnormal sylvian fissure	Agenesis of corpus callosum
Sermer et al [8]	del(17p)				
Greenberg et al [9]	del(17)(p13)				
Saltzman et al [10]	del(17)(p13.3)mat		(+)		
	del(17)(p13.3)		(+)		
Blass et al [11]	del(17)(p13.2)	(+)	(+)		(+)
Okamura et al [12]	(−)	(+)	(+)	(+)	
	(−)	(+)	(+)	(+)	
Alvarado et al [13]	del(17)(p13.3)pat				
Holzgreve et al [14]	(−)	(+)			
McGahan et al [15]	del(17)(p13.3)	(+)			
Chitayat et al [5]	del(17)(p13.3)	(+)	(+)		
Greco et al [16]	(−)	(+)	(+)		
Fong et al [17]	del(17)(p13.3)	(+)	(+)	(+)	
	del(17)(p13.3)	(+)	(+)	(+)	
	del(17)(p13.3)mat	(+)		(+)	
	del(17)(p13.3)	(+)	(+)	(+)	(+)
	del(17)(p13.3)pat	(+)	(+)	(+)	
	del(17)(p13.3)		(+)	(+)	
	del(17)(p13.3)	(+)	(+)	(+)	
Pastorino et al [18]	(−)	(+)	(+)		
Lenzini et al [19]	del(17)(p13.3)	(+)	(+)		(+)
Herman and Siegel [20]	distal 17p deletion				
Aslan et al [21]	(−)		(+)	(+)	
Lin et al [22]	del(17)(p13.3)	(+)	(+)		
Chen et al [23]	del(17)(p13.2)	(+)			

Central nervous system anomalies

The CNS anomalies reported in fetuses of MDS include ventriculomegaly, agyria, abnormal sylvian fissures, agenesis or dysgenesis of corpus callosum, and microcephaly. Ventriculomegaly is the most common finding in the reported cases of MDS, and it has been shown to be an important prenatal ultrasound marker for MDS [17,18,24]. Agyria or smooth brain is the key feature of MDS. During the early period, prenatal sonographic diagnosis of agyria and MDS is rare as routine survey of fetal cerebral cortex is not included in anatomic evaluation. Clinically, fetal cerebral sulci can be demonstrated by sonography as early as 18 weeks' gestation, and by 30—32 weeks, most of the main sulci can be demonstrated [25—27]. However, ventriculomegaly may obscure the visualization of the sulcal pattern because there is a mean lag of 2 or more weeks in the development of sulci/fissures in ventriculomegaly. Fong et al [17] reported that mild ventriculomegaly could be the first sign of abnormal or delayed brain maturation and suggested to carefully evaluate cerebral sulci at 24—26 weeks of gestation by sonography, when a fetus had an apparently isolated mild ventriculomegaly. In general, severe forms of lissencephaly, such as complete agyria, are easily detected on prenatal ultrasound, but milder forms of pachygyria and subcortical band heterotopia (SBH) are difficult to diagnose. Agenesis or dysgenesis of corpus callosum and microcephaly are also observed in cases of MDS [11,19,21]. Lenzini et al [19] reported that a fetus with a 4-Mb microdeletion at 17p13.3 had the prenatal sonographic findings of CNS anomalies, including microcephaly, ventriculomegaly, dysgenetic corpus callosum, hypoechoic cerebral parenchyma, and pachygyria, at 29 weeks of gestation.

Intrauterine growth restriction

Intrauterine growth restriction (IUGR) is a common finding associated with reported fetuses of MDS. They are associated with microdeletion of 17p13 (Table 1).

Polyhydramnios

Polyhydramnios is also a common feature associated with fetuses of MDS (Table 1). It is usually detected beyond the mid-second trimester.

Cardiac anomalies

The cardiac anomalies reported in fetuses of MDS include tetralogy of Fallot (TOF), atrial septal defects (ASD), ventricular septal defects (VSD), double-outlet right

Table 1. (continued)

CNS anomalies Microcephaly	IUGR	Polyhydramnios	Cardiac anomalies	Omphalocele	Facial anomalies	Rare anomalies	Outcome
			(+)	(+)		Neural tubal defects	
	(+)	(+)	(+)			Thymic hypoplasia	IUFD
	(+)	(+)					Alive at delivery
			(+)	(+)			TOP
	(+)	(+)			(+)		Alive at delivery
							Neonatal death
							Neonatal death
				(+)			TOP
							Neonatal death
	(+)	(+)					Alive at delivery
				(+)			Alive with seizure at 4 m/o
							Alive with seizure at 24 m/o
				(+)			Died at 23 m/o
							Neonatal death
		(+)					IUFD
	(+)						IUFD
	(+)						Alive with seizure at 12 m/o
		(+)			(+)		Died at 11 m/o
	(+)	(+)					Died at 3 m/o
							TOP
(+)	(+)	(+)				Equinovarus foot, hyperechoic renal parenchyma	IUFD
	(+)	(+)					Alive at delivery
(+)					(+)		TOP
	(+)	(+)					Alive with seizure at 10 m/o
	(+)			(+)			Alive with seizure at 18 m/o

CNS = central nervous system; IUFD = intrauterine fetal death; IUGR = intrauterine growth restriction; TOP = termination of pregnancy.

ventricle, and cardiomegaly. Saltzman et al [10] reported a fetus of MDS with a deletion of 17p13.3 having TOF at 31 weeks' gestation. Greenberg et al [9] reported a fetus with a deletion of 17p13 having double-outlet right ventricle. Chen et al [23] reported a fetus of congenital heart defect with ASD, VSD, and TOF at 36 weeks of gestation in association with monosomy 17p (17p13.2 → pter). Sermer et al [8] reported a case of 17p deletion associated with prenatally detected cardiomegaly.

Abdominal wall defect

Omphalocele can be a prenatal sonographic feature associated with MDS [5,8,13,17]. Alvarado et al [13] reported MDS and omphalocele in a family with multiple affected offsprings with monosomy 17p (17p13.3 → pter) using fluorescence *in situ* hybridization study. They concluded that omphalocele should be one of the listed malformations that make up the MDS.

Facial anomalies

Facial features in MDS may characterize prominent forehead with bitemporal narrowing, furrowed brow, a small nose with anteverted nostrils, low set ears, prominent upper lip, and micrognathia. However, not all of the features can be easily detected on a prenatal ultrasound. The prenatally reported facial anomalies associated with MDS include micrognathia [11,17], hypotelorism [21], low-set ears, and a small nose [11].

Rare anomalies

The reported rare anomalies in MDS include thymic hypoplasia, neural tubal defects, talipes eqinovarus, and hyperechoic renal parenchyma. Greenberg et al [9] reported a case of 17p13 deletion associated with thymic hypoplasia. Sermer et al [8] reported a case of 17p deletion associated with prenatally detected neural tubal defects. Lenzini et al [19] reported that a fetus with a 4-Mb microdeletion at 17p13.3 had the prenatal sonographic findings of talipes eqinovarus and hyperechoic renal parenchyma.

Molecular and Cytogenetic Diagnosis

MDS is often associated with microdeletion of chromosome 17p13.3. About 90% of MDS patients have visible or submicroscopic deletions of 17p13.3 [28]. Families with multiple affected MDS children have been noted to have parental balanced translocations between 17p and other chromosomal segments [4,29]. Familial chromosomal rearrangement is reported in about 20% MDS patients [30]. Clinically, an approach to laboratory diagnosis of MDS should include traditional G-banded chromosome analysis to detect visible deletions and translocations and then molecular diagnostic tools such as DNA markers, fluorescence *in situ* hybridization, or array-based comparative genomic hybridization to identify submicroscopic deletions. If a deletion is found, parental studies are required to determine whether the deletion is *de novo* or inherited from a cryptic translocation. Thus, genetic counseling about the recurrence risk can be accurately provided to the affected families.

Differential Diagnosis

Lissencephaly is divided into two types. Classical or Type I lissencephaly is characterized by an abnormally thick and poorly organized four-layered cortex, enlarged ventricles, and often hypoplasia of the corpus callosum. Type II or cobblestone lissencephaly is characterized by a disorganized unlayered cortex, overmigration of neurons into the subpial space and gliovascular proliferation near the surface of the cortex resulting in the formation of a granular surface, and effacement of gyri showing a bumpy cobblestone-like appearance [31]. Owing to the lissencephaly commonly seen in MDS, differential diagnosis should include Type I lissencephly (Lissencephaly 1, Lissencephaly 2, and X-linked lissencephaly) and Type II lissencephaly.

Type I lissencephaly

Lissencephaly 1 (LIS 1; OMIM 607432)
LIS 1 includes isolated lissencephaly sequence, classic lissencephaly, subcortical laminar heterotopia (SCLH), and subcortical band heterotopia (SBH). It is characterized by smooth or nearly smooth cerebral surface, encompassing a spectrum of brain surface malformations ranging from complete agyria to subcortical band heterotopia [32]. SBH represents the less severe end of the LIS spectrum of malformations [32]. LIS 1 caused by mutations in the *PAFAH1B1* gene is also called "isolated" lissencephaly to distinguish it from the accompanying features of MDS.

Lissencephaly 2 (LIS 2; OMIM 257320) or Norman-Roberts syndrome
It is caused by mutations in the *RFLN* gene (OMIM 600514) mapped to 7q22. It belongs to Type I lissencephaly with distinctive features such as a low slopping forehead and a prominent nasal bridge, which are not seen in MDS [33]. In addition, it has been observed to have multiple affected sibs and parental consanguinity.

X-linked lissencephaly
X-linked lissencephaly 1 (LISX1) includes lissencephaly and agenesis of the corpus callosum, X-linked SCLH, X-linked SBH, and double cortex syndrome. LISX1 can be caused by mutations in the *DCX* gene (OMIM 300121) mapped to Xq22.3-q23. Male patients generally have a more severe phenotype compared to females. The gyral patterns are different in LIS 1 and LISX1. Those with *PAFAH1B1* mutations are associated with more severe malformations posteriorly, and those with *DCX* mutations are associated with more severe malformation anteriorly. In addition, hypoplasia of the cerebellar vermis was more common in LISX1 [32]. X-linked lissencephaly 2 (LISX2) includes X-linked lissencephaly with ambiguous genitalia and hydranencephaly and abnormal genitalia, and can be caused by mutations in the *ARX* gene (OMIM 300382) mapped to Xq22.13.

Table 2. Prenatal sonographic features of Miller-Dieker Syndrome and differential diagnosis

Prenatal sonographic features
    Central nervous system anomalies
      Ventriculomegaly, agyria or lissencephaly, abnormal sylvian fissures, agenesis or dysgenesis of corpus
      callosum, microcephaly
    Intrauterine growth restriction
    Polyhydramnios
    Cardiac anomalies
      Tetralogy of Fallot, atrial septal defects, ventricular septal defects, double-outlet right ventricle, cardiomegaly
    Abdominal wall defect
      Omphalocele
    Facial anomaly
      Micrognathia, hypotelorism, low-set ears, a small nose
    Rare anomalies
      Thymic hypoplasia, neural tubal defects, talipes eqinovarus, hyperechoic renal parenchyma

Differential diagnosis
    Type I lissencephaly
    Lissencephaly 1
    Lissencephaly 2 (Norman-Roberts syndrome)
    X-linked lissencephaly
    Type II lissencephaly
    Walker-Warburg syndrome
    Fukuyama-type congenital muscular dystrophy
    Muscle-eye-brain disease and muscular dystrophy
    Muscular dystrophy, congenital, Type IC

Type II or cobblestone lissencephaly

Type II lissencephaly occurs with four prototypic autosomal recessive disorders: Walker-Warburg syndrome (WWS, OMIM 236670), Fukuyama-type congenital muscular dystrophy (OMIM 253800), muscle-eye-brain disease (OMIM 253280), and muscular dystrophy, congenital, Type IC (MDC1C, OMIM 606612) [24,31]. WWS or HARD ± E syndrome is characterized by hydrocephalus (H), agyria (A), retinal dysplasia (RD) with or without encephalocele (±E), and congenital muscular dystrophy. CNS anomalies associated with WWS include Type II lissencephaly (100%), cerebellar malformation (100%), ventriculomegaly (95%), Dandy-Walker malformation (53%), and occipital encephalocele (24%) [34]. WWS can be caused by mutations in these genes, including *POMT1* (OMIM 607423), *FKTN* (OMIM 607440), *FKRP* (OMIM 606596), *POMT2* (OMIM 607439), and *LARGE* (OMIM 603590). Fukuyama-type congenital muscular dystrophy has an overlapping phenotype with mild WWS and is caused by mutations in the *FKTN* gene. Muscle-eye-brain disease also has phenotypic similarities with WWS and can be caused by mutations in the *FKRP* gene and the *POMGNT1* gene (OMIM 606822). MDC1C is characterized by muscle weakness and structural brain defects and can be caused by mutations in the *FKRP* gene. All the above diseases may present with more severe lissencephaly, marked ventriculomegaly, and hydrocephalus. One fetus has been diagnosed with WWS as early as 18 weeks because of the marked ventriculomegaly [35]. Therefore, Type II lissencephaly may be more easily detected in prenatal period than Type I because of the marked ventriculomegaly.

Conclusion

This article provides an overview of prenatal sonographic features of MDS. Prenatal detection of CNS anomalies (ventriculomegaly, agyria or lissencephaly, abnormal sylvian fissures, agenesis or dysgenesis of corpus callosum, and microcephaly), IUGR, polyhydramnios, cardiac anomalies, omphalocele, facial anomalies, and rare anomalies should alert clinicians to the possibility of MDS and prompt molecular cytogenetic analyses and counseling for MDS (Table 2). Differential diagnosis should include Type I lissencephaly (Lissencephaly 1, Lissencephaly 2, X-linked lissencephaly) and Type II lissencephaly (Table 2). Early diagnosis of MDS is important because of extremely poor prognosis in affected cases. Prenatal diagnosis of MDS is helpful for accurate genetic counseling and appropriate obstetric management.

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