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Taiwanese Journal of Obstetrics & Gynecology 51 (2012) 12–17

www.tjog-online.com

Review Article

Prenatal diagnosis and genetic analysis of fetal akinesia deformation sequence and multiple pterygium syndrome associated with neuromuscular junction disorders: A review

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Accepted 6 January 2012

Abstract

Fetal akinesia deformation sequence is a clinically and genetically heterogeneous disorder characterized by a variable combination of arthrogryposis, fetal akinesia, intrauterine growth restriction, developmental abnormalities such as cystic hygroma, pulmonary hypoplasia, cleft palate, cryptorchidism, cardiac defects and intestinal malrotation, and occasional pterygia of the limbs. Multiple pterygium syndrome is a clinically and genetically heterogeneous disorder characterized by pterygia of the neck, elbows and/or knees, arthrogryposis, and other phenotypic features such as short stature, genital abnormalities, craniofacial abnormalities, clubfoot, kyphoscoliosis, and cardiac abnormalities. Fetal akinesia deformation sequence may phenotypically overlap with the lethal type of multiple pterygium syndrome. This article provides a comprehensive review of prenatal diagnosis and genetic analysis of fetal akinesia deformation sequence and multiple pterygium syndrome associated with neuromuscular junction disorders. Prenatal diagnosis of fetal akinesia along with cystic hygroma, increased nuchal translucency, nuchal edema, hydrops fetalis, arthrogryposis, pterygia, and other structural abnormalities should include a differential diagnosis of neuromuscular junction disorders. Genetic analysis of mutations in the neuromuscular junction genes such as *CHRNA1*, *CHRND*, *CHRNG*, *CNTN1*, *DOK7*, *RAPSN*, and *SYNE1* may unveil the pathogenetic cause of fetal akinesia deformation sequence and multiple pterygium syndrome, and the information acquired is helpful for genetic counseling and clinical management.

Keywords: *CHRNA1*; *CHRND*; *CHRNG*; *CNTN1*; *DOK7*; fetal akinesia deformation sequence; multiple pterygium syndrome; prenatal diagnosis; *RAPSN*; *SYNE1*

Introduction

Fetal akinesia deformation sequence (FADS; OMIM 208150) is a clinically and genetically heterogeneous disorder characterized by a variable combination of arthrogryposis, fetal akinesia, intrauterine growth restriction (IUGR), developmental abnormalities such as cystic hygroma, pulmonary hypoplasia, cleft palate, cryptorchidism, cardiac defects and intestinal malrotation, and occasional pterygia of the limbs [1–5]. In a retrospective population-based study in Demark, Bayat et al [6] reported that the incidence of FADS was 1:15,000. FADS was originally reported by Pena and Shokeir [1] and Lindhout et al [3] to describe a disorder called Pena–Shokeir syndrome consisting of the symptoms of IUGR, polyhydramnios, facial dysmorphism, pulmonary hypoplasia,

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1028-4559/$ - see front matter
doi:10.1016/j.tjog.2012.01.004

a short umbilical cord, and supplementary symptoms of cleft or high-arched palate and bell-shaped chest. The pathogenetic mechanisms of FADS include neuropathy, muscular disorders, neuromuscular junction (NMJ) disorders, maternal myasthenia gravis, restrictive dermopathy, and others [5,7−12]. FADS may phenotypically overlap with the lethal type of multiple pterygium syndrome (LMPS; OMIM 253290). Multiple pterygium syndrome (MPS) is a clinically and genetically heterogeneous disorder characterized by pterygia (webbing) of the neck, elbows and/or knees, arthrogryposis (joint contractures), and other phenotypic features such as short stature, genital abnormalities, craniofacial abnormalities, clubfoot, kyphoscoliosis, and cardiac abnormalities [13−15]. MPS can occur in autosomal-recessive [12,16−18], autosomal-dominant [19], or X-linked-dominant [20] transmission.

Genetic analysis of mutations in the genes associated with NMJ in fetuses with FADS/MPS

FADS and/or MPS have been reported to be caused by mutations in the genes associated with NMJ such as *CHRNA1* (OMIM 100690), *CHRND* (OMIM 100720), *CHRNG* (OMIM 100730), *RAPSN* (OMIM 601592), *DOK7* (OMIM 610285), *CNTN1* (OMIM 600016), and *SYNE1* (OMIM 608441).

CHRNA1

CHRNA1, *CHRNB1* (OMIM 100710), *CHRND*, *CHRNG*, and *CHRNE* (OMIM 100725) encode the acetylcholine receptor (AchR) subunits of α1, β1, δ, γ, and ε, respectively. The AchR of fetal type consists of α1 (two) subunits and one of each β1, δ, and γ subunits, whereas the AchR of adult type consists of two α1, β1, δ, and ε subunits because of replacement of the fetal γ subunit by the adult ε subunit after 33 weeks of gestation [21−23]. Heterozygous mutations of *CHRNA1* can cause autosomal dominant congenital slow-channel myasthenic syndrome (OMIM 601462) and congenital fast-channel myasthenic syndrome (OMIM 608930). Homozygous mutations of *CHRNA1* have been reported to cause autosomal-recessive LMPS [12]. Michalk et al [12] reported two male sib fetuses in a consanguineous Pakistani family with LMPS and a homozygous mutation of c.761 G→T in *CHRNA1* that predicts R234L in mature protein and R245L in precursor. The first fetus was stillborn at 24 weeks of gestation with IUGR, edema, cystic hygroma, decreased movements, joint contractures, faciocranial dysmorphism, cleft palate, micrognathia, reduced muscle bulk, scoliosis, contractures, and pterygia. The second fetus was terminated at 20 weeks of gestation with similar phenotypic features as the first fetus and an additional finding of rocker-bottom feet. Michalk et al [12] reported another two male sib fetuses in a non-consanguineous African family with LMPS and a homozygous mutation of c.117_133dup17 in *CHRNA1* that predicts H25RfsX19 in mature protein or H45RfsX19 in precursor. The first fetus was stillborn at 28 weeks of gestation. The second fetus was terminated at 17 weeks of gestation with IUGR, edema, cystic hygroma at 7 weeks of gestation, decreased movements, joint contractures, faciocranial dysmorphism, down-slanting palpebral fissures, a depressed nasal bridge, micrognathia, low-set ears, contractures, and pterygia.

CHRND

Heterozygous mutations of *CHRND* can cause autosomal-dominant congenital slow-channel myasthenic syndrome and congenital fast-channel myasthenic syndrome. Homozygous or compound heterozygous mutations in *CHRND* have been reported to cause autosomal recessive LMPS [12]. Michalk et al [12] reported two male sib fetuses in a consanguineous Turkish family with LMPS and a homozygous mutation of c.234 G→A in *CHRND* that predicts W57X in mature protein or W78X in precursor. Both fetuses were terminated at 15 weeks of gestation and manifested IUGR, edema, cystic hygroma, decreased movements, and joint contractures. One fetus additionally showed cystic hygroma, muscle hypoplasia, scoliosis, contractures, pectus excavatum, broad ribs and clavicles, and pterygia. Michalk et al [12] also reported five sib fetuses in a non-consanguineous German family with LMPS and compound heterozygous mutations of c.283 T→C/c.1390C→T in *CHRND* that predict F74L/R443X in mature protein or F95L/R464X in precursor. The first female fetus was delivered at 23 gestational weeks with neonatal death, generalized edema, a depressed nasal bridge, low-set ears, a big atrial septal defect, lung hypoplasia, hydrothorax, and ascites. The second female fetus was terminated at 19 gestational weeks with cystic hygroma, joint contractures, faciocranial dysmorphism, hypertelorism, a depressed nasal bridge, micrognathia, low-set ears, contractures, pterygia, rocker-bottom feet, lung hypoplasia, hydrothorax, pericardial effusion, and shortened ribs. The third male fetus was terminated at 12 gestational weeks with cystic hygroma, decreased movements, joint contractures, contractures, and pterygia. The fourth male fetus was terminated at 13 gestational weeks with IUGR, cystic hygroma, decreased movements, joint contractures, micrognathia, low-set ears, contractures, and pterygia. The fifth male fetus was terminated at 19 gestational weeks with IUGR, edema, cystic hygroma, joint contractures, faciocranial dysmorphism, down-slanting palpebral fissures, hypertelorism, a depressed nasal bridge, micrognathia, low-set ears, contractures, and pterygia.

CHRNG

Homozygous and compound heterozygous mutations in *CHRNG* have been reported to cause autosomal-recessive Escobar syndrome (OMIM 265000) and LMPS [18,24]. Morgan et al [18] reported two sibs of different sex in a consanguineous Arab family with LMPS and a homozygous missense mutation of c.320 T→G in *CHRNG* that predicts p.Val107Gly. The sister died at age 3 months because of congenital heart disease, and the brother died at age 3 days because of lung hypoplasia. Morgan et al [18] also reported a male fetus in a consanguineous Turkish family with LMPS and a homozygous frameshift mutation of c.753_754delCT in

CHRNG that predicts p.Val253AlafsX44. The fetus manifested hydrops at 13 weeks of gestation and was terminated at 15 weeks of gestation with down-slanting palpebral fissures, low-set ears, micrognathia, deviation of the wrists, bilateral talipes, unfixed colon, mild thoracic scoliosis, and reduced muscle bulk. Morgan et al [18] additionally reported a 37-gestational-week female fetus in a non-consanguineous family with hydrops, bilateral pleural effusions, skin edema, hydronephrotic right kidney, pterygia, rocker-bottom feet, lung hypoplasia, neonatal death, and a homozygous frameshift mutation of c.459dupA in *CHRNG* that predicts p.Val154SerfsX24.

RAPSN

The *RAPSN* gene encodes a postsynaptic protein that functions as a link between AchR and the agrin-binding dystrophin-associated glycoprotein complex to stabilize AchR at the NMJ [25]. Homozygous or compound heterozygous mutations in *RAPSN* can cause autosomal recessive FADS and congenital myasthenic syndrome associated with AchR deficiency (OMIM 608931). Michalk et al [12] reported two sibs of different sex with FADS in a non-consanguineous Pakistani family. The sibs were born at term with severe respiratory problems, inborn contractures, down-slanting palpebral fissures, mild hypertelorism, a wide nasal bridge, low-set ears, micrognathia, a small mouth, tented lips, hypotonia, but no pterygia. The brother had cryptorchidism and died of respiratory problems at age 10 months, and the sister had cleft palate but was alive at age 10 months. Both sibs had compound heterozygous mutations of c.416 T→C/ c.566C→T in *RAPSN* that predict F139S/A189 V. Vogt et al [5] reported three sibs (two twin males and one female) with FADS and a homozygous mutation of c.1177_1178delAA in *RAPSN* that predicts a frameshift after residue 392 of rapsyn resulting in 82 C-terminal missense amino acids. The monozygotic twin males were found to have FADS, micrognathia, fixed position of the extremities, a small thorax, no respiratory movements, and mild hydrops at 19 weeks of gestation. The pregnancy was terminated at 23 weeks of gestation, and the fetuses manifested a flat facial profile, hypertelorism, moderate micrognathia, a short broad neck, mild hydrops, hydrothorax, subcutaneous edema, hypoplastic lungs, abnormal posture, hyperextension of the wrists, flexion of the fingers, fixed ankles, hyperextended toes, but no pterygia. The female singleton was found to have FADS at 19 weeks of gestation, and the pregnancy was terminated at 23 weeks of gestation. The fetus postnatally manifested micrognathia, low-set ears, a short nose, a short philtrum, thin lips, a short broad neck, subcutaneous edema of the head, neck and shoulders, abnormally fixed elbows, hyperextended wrists, and overlapping fingers, but no pterygia.

DOC7

The *DOC7* gene encodes a muscle protein that is essential for synaptogenesis through its interaction with MuSK (OMIM 601296), a skeletal muscle receptor tyrosine kinase that orchestrates postsynaptic differentiation including the clustering of receptors for the neurotransmitter acetylcholine [26]. Homozygous or compound heterozygous mutations in *DOC7* can cause autosomal recessive FADS and familial limb-girdle myasthenia (OMIM 254300). Vogt et al [5] identified a homozygous *DOC7* splice site mutation of IVS3+1 G > T or c.331 + 1 G > T in a consanguineous Bengali family with three fetuses affected with FADS but no pterygia. The first fetus was stillborn at 32 weeks of gestation with a neuromuscular disorder. The second fetus was miscarried at 22 weeks of gestation with down-slanting palpebral fissures, a small jaw, a short neck, extended extremities, overlapping fingers, bilateral talipes, rocker-bottom feet, bilateral hydrothorax, severe generalized edema, and reduced muscle bulk. The third fetus was found to have no fetal movements on prenatal ultrasound at 24 weeks of gestation.

CNTN1

The *CNTN1* gene encodes a neural adhesion and NMJ protein that is restricted to the NMJ and function for NMJ adhesion [27]. Homozygous mutations in *CNTN1* can cause severe fetal akinesia and Compton−North congenital myopathy (OMIM 612540). Compton et al [27] identified a homozygous 1-bp duplication (c.871dupT) in exon 8 of *CNTN1* that results in a frameshift and premature truncation (S291fsX296) within the third Ig domain and predicts a nonsense-mediated mRNA decay.

SYNE1

The *SYNE1* gene encodes a synaptic nuclear envelope protein 1 or nesprin 1. Nesprin 1 anchors specialized myonuclei underneath NMJ, binds lamin A and emerin, and interacts with the cytoplasmic domain of MuSK [28−31]. Mutations in *SYNE1* can cause autosomal-recessive spinocerebellar ataxia 8 (OMIM 610743), autosomal-dominant Emery−Dreifuss muscular dystrophy 4 (OMIM 612998), and autosomal-recessive myogenic arthrogryposis multiplex congenita [32]. Attali et al [32] identified homozygosity for an acceptor site mutation 2-bp 5′ to exon 137 in *SYNE1* (IVS136-2 A > G) that predicts retention of intron 136 in mRNA and generates a premature stop codon and loss of the C-terminal transmembrane KASH domain in a two-generation consanguineous family with arthrogryposis, decreased fetal movements, hypotonia, delayed motor milestones, and progressive motor decline after the first decade. In that family, a brother of affected children married his first cousin who had two pregnancies that manifested bilateral clubfeet and decreased fetal movements at 28 and 16 weeks of gestation in the first and second fetuses, respectively.

Prenatal diagnosis of FADS/MPS by ultrasound and magnetic resonance imaging

Prenatal diagnosis of reduced or absent fetal movements in association with abnormal fetal posture should include

a differential diagnosis of spina bifida, trisomy 18, arthrogryposis, FADS, fetal constraint, body stalk anomaly, caudal regression sequence, fetal hypoxia/severe hypotonia, amniotic bands, fetal neck masses, joint dislocations, vertebral segmentation abnormalities, iniencephaly, and MPS [33]. Fetal akinesia/arthrogryposis can result from primary defects of brain, spinal cord, peripheral nerves, NMJ, skeletal musculature and connective tissues, vascular compromise, restricted intrauterine space, teratogenic exposures, ischemia, maternal illness, and circulating maternal antibodies to neurotransmitters, myelin, and muscle proteins [34,35]. Fetal akinesia can be detected by prenatal ultrasound as early as 12 weeks of gestation [36]. Prenatal ultrasound findings of fetal akinesia/arthrogryposis include lack of extremity motions, persistent abnormal posture of the limbs, lack of facial movements, polyhydramnios due to decreased fetal swallowing, pulmonary hypoplasia, a short umbilical cord due to decreased fetal movements, IUGR, increased nuchal translucency, nuchal edema or cystic hygroma in the first trimester, and hydrops fetalis [36–65]. Fetal magnetic resonance imaging can be a useful adjunct to prenatal ultrasound in evaluating central nervous system findings [62,65]. The abnormal neurological magnetic resonance imaging findings include agenesis of the corpus callosum, lissencephaly, hydrocephalus, and spinal cord abnormalities [37]. Prenatal ultrasound findings of Escobar MPS include small stature, multiple pterygia of neck, axillae, elbows and knees, micrognathia, digital hypoplasia, camptodactyly, syndactyly, and scoliosis [66]. Prenatal ultrasound findings with LMPS include IUGR, flexion contractures of the limbs, multiple extensive pterygia, cystic hygroma, hydrops, and hypoplastic lungs [67–77].

In summary, this article provides a comprehensive review of prenatal diagnosis and genetic analysis of FADS/MPS associated with NMJ disorders. Prenatal diagnosis of fetal akinesia along with cystic hygroma, increased nuchal translucency, nuchal edema, hydrops fetalis, arthrogryposis, pterygia, and other structural abnormalities should include a differential diagnosis of NMJ disorders. Genetic analysis of mutations in the genes associated with NMJ may unveil the pathogenetic cause of FADS/MPS, and the information acquired is helpful for genetic counseling and clinical management.

Acknowledgments

This work was supported by research grants NSC-97-2314-B-195-006-MY3 and NSC-99-2628-B-195-001-MY3 from the National Science Council, and MMH-E-100-04 from Mackay Memorial Hospital, Taipei, Taiwan.

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