



Clinical characteristics of pregnancies complicated by congenital myotonic dystrophy

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Objective

Although the conventional prevalence of myotonic dystrophy is 1:8,000, the prevalence in Korean population was recently reported as 1:1,245. With higher domestic result than expected, we aimed to investigate the clinical characteristics of pregnancies complicated by congenital myotonic dystrophy in our institution.

Methods

We have reviewed 11 paired cases of neonates diagnosed with congenital myotonic dystrophy and their mothers between July 2004 and May 2014, with clinical features including maternal history of infertility, prenatal ultrasonographic findings, and neonatal outcomes. Cytosine-thymine-guanine (CTG) repeat expansion in the myotonic dystrophy protein kinase gene of both neonates and their mothers was also examined.

Results

None of mother was aware of their myotonic dystrophy traits before pregnancy. History of infertility followed by assisted reproductive technology accounted for 57.1% (4/7). Distinctive prenatal ultrasonographic finding was severe idiopathic polyhydramnios (66.7%, 4/6) with median amniotic fluid index of 43 (range, 37 to 66). In 37.5% (3/8) cases, decreased fetal movement was evident during prenatal ultrasound examination. For neonatal outcomes, more than half (6/11) were complicated with preterm birth and the proportion of 1-minute Apgar score <4 and 5-minute Apgar score <7 was 44.4% (4/9) and 66.7% (6/9), respectively. Most of neonates were admitted to the neonatal intensive care unit (9/10) because of hypotonia with respiratory problems and there was one infant death. Median number of cytosine-thymine-guanine repeats in mothers and neonates was 400 (range, 166 to 1,000) and 1,300 (range, 700 to 2,000), respectively.

Conclusion

Our data suggest that severe idiopathic polyhydramnios with decreased fetal movement in pregnant women, especially with a history of infertility, requires differential diagnosis of congenital myotonic dystrophy.

Keywords: Fetal movement; Infertility; Myotonic dystrophy; Polyhydramnios; Prenatal diagnosis

Introduction

Myotonic dystrophy is the most common inheritable neuromuscular disorder in adults. It is inherited as an autosomal dominant condition and its clinical features include progressive muscular weakness, myotonia (especially, failure of muscular relaxation after contraction), cataracts, and endocrine abnormalities [1].

Myotonic dystrophy 1 is caused by an expansion of cytosine-thymine-guanine (CTG) trinucleotide repeats in the myotonic dystrophy protein kinase (*DMPK*) gene locus at 19q13.3 [2]. The expansion is observed in parent-to-child transmission,

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which is called anticipation. The anticipation is more frequent and critical when inheritance occurs from the mother rather than the father [3]. Moreover, the size of abnormal CTG repeats correlates with time of onset and severity of symptoms [4].

Congenital myotonic dystrophy is the most severe form of myotonic dystrophy presenting as generalized hypotonia, respiratory failure, and neonatal or infantile death in most severe cases. Clinical features of affected infants are a “fish-shaped mouth” resulting from weakness of facial muscles, weak cry, and poor sucking. Mortality from respiratory failure is rather high, and most of the affected neonates need to be treated in an intensive care unit after birth [5,6]. Women at reproductive age who are mildly affected by myotonic dystrophy 1 may be symptom-free, but are at a risk of passing the abnormal CTG repeats with expansion to their offspring, resulting in a severe myopathic condition of the neonates. When marked exacerbation of muscle weakness happens during pregnancy, the pregnancy is more likely to result in complications like fetal or neonatal loss, premature delivery, and labor abnormalities [7].

The prevalence of myotonic dystrophy has been considered to be 1:8,000 among Western Europeans, based on the clinical picture; however, after identification of the distinct genetic mutation, it is presumed to vary among different populations. The estimated prevalence in some areas of Japan is approximately 1:20,000 and in Iceland, approximately 1:10,000, while higher prevalence has been shown in northern Sweden, Quebec in Canada, and the Basque region of Spain [5,8,9]. Recently, it was reported in Korea that the frequency of pre-mutation carriers and the prevalence of myotonic dystrophy 1 among women at reproductive age were 1/415 and 1/1,245, respectively [10]. Although these domestic results suggest that there is a possibility of myotonic dystrophy 1 being more common in Korea than expected, most obstetricians are not acquainted with clinical manifestations of pregnancies in patients with myotonic dystrophy 1. With this background, we aimed to define the clinical characteristics of pregnancies complicated by congenital myotonic dystrophy diagnosed in our institution and to discuss the clinical picture suggestive for this disease entity.

Materials and methods

1. Information of clinical characteristics

This is a retrospective review of all newborns diagnosed with

congenital myotonic dystrophy in our institution, and their mothers, between July 2004 and May 2014. We obtained available medical records including maternal history of infertility and standard obstetric data, with details about maternal age, parity, gestational age at birth, mode of delivery, and the indications for cesarean section. Prenatal ultrasonographic findings were reviewed in all available cases and, in case of polyhydramnios, we investigated the onset of polyhydramnios, maximum amniotic fluid index, and the presence of other anatomical abnormalities or maternal diabetes mellitus that could cause polyhydramnios. Data on neonatal outcomes such as Apgar score, neonatal intensive care unit (NICU) admission, the cause of NICU admission, the length of NICU stay, the need for ventilator care, and infant death were also collected. Besides, the results from *DMPK* gene mutation test with the number of CTG repeat expansion from mothers and neonates were assessed, as well.

2. *DMPK* gene mutation test

The CTG trinucleotide repeat expansion in the *DMPK* gene was tested by conventional fluorescence polymerase chain reaction and Southern blotting according to the technical standards and guidelines for myotonic dystrophy 1 testing [2,11,12].

3. Ethics statement

This study was approved by institutional review board approval from Samsung Medical Center, the Sungkyunkwan University School of Medicine, South Korea (SMC 2016-02-099).

Results

During the study period, there were 11 cases affected by congenital myotonic dystrophy, which consisted of 6 inborn and 5 outborn neonates. Based on the number of total births in our institution during that period, the prevalence of congenital myotonic dystrophy was roughly presumed to be 1:3,263 (6:19,579).

We summarized clinical characteristics of pregnancies complicated by congenital myotonic dystrophy (Table 1). Of note, none of the mothers in our study population were aware of their own myotonic dystrophy traits before their pregnancies. Although 2 mothers had mild symptoms before getting preg-

Table 1. Summaries of clinical characteristics of pregnancies complicated by congenital myotonic dystrophy

Case	Age	ART	Maternal symptom	Prenatal ultrasonographic findings				Birth weight (g)	Apgar score		NICU hospital day	Mortality	No. of CTG repeats			
				Polyhydramnios	GA at detection	Maximum AFI	Decreased FM		Mode of delivery	GA at birth			1-min	5-min	Maternal	Neonatal
1	37	IVF	Foot drop	+	32+5	37	+	CS	34+6	2,058	2	4	397	-	NA	2,700
2	29	-	Grip myotonia	+	30+4	66	+	CS	36+6	2,985	5	6	29	-	1,000	1,300
3	29	NA	-	NA	NA	NA	+	CS	38+0	3,600	NA	NA	20	-	166	1,100
4	31	IUI	-	NA	NA	NA	-	CS	38+2	3,140	9	9	21	-	670	1,300
5	33	NA	-	NA	NA	NA	NA	CS	29+1	1,380	2	2	260	-	350	1,000
6	30	-	-	-	22	22	-	CS	38+5	3,450	8	9	24	-	300	700
7	34	-	-	+	30+0	43	-	CS	31+5	1,710	1	4	91	-	NA	1,700
8	NA	NA	-	NA	NA	NA	NA	CS	40+0	3,200	NA	NA	+	-	NA	NA
9	29	NA	-	NA	NA	NA	NA	CS	37+0	2,850	8	9	5	-	400	1,270
10	40	IVF	-	+	30+2	45	-	CS	31+0	1,640	4	6	45	+	NA	2,000
11	33	IVF	-	-	24	24	-	CS	34+5	2,100	2	6	75	-	500	NA

ART, assisted reproductive technology; AFI, amniotic fluid index; GA, gestational age; FM, fetal movement; NICU, neonatal intensive care unit; CTG, cytosine-thymine-guanine; IVF, *in vitro* fertilization; CS, cesarean section; NA, not available; IUI, intrauterine insemination.

nant, such as foot drop and grip myotonia, and one of them had a familial history of myotonic dystrophy, the definite diagnosis of myotonic dystrophy was not made before pregnancy. Considering grip myotonia is one of important symptom which enables clinicians to make diagnosis for myotonic dystrophy of mother, according to our data, there was one mother who presented the symptom. This result does not suggest that grip myotonia is an inconsequential symptom, but the perspective that this is retrospective study depending on past medical records so that there were insufficient data for symptoms of mothers is required. Two mothers experienced the loss of their child earlier, one from generalized hypotonia 40 days after birth and the other from a respiratory problem immediately after birth; however, the definite cause of these neonatal compromises remained undiagnosed. Interestingly, women getting pregnant through assisted reproductive technology (ART) due to infertility accounted for 57.1% (4 of 7) of the total number of cases. The median maternal age at the time of delivery was 32 years (range, 29 to 40 years). Median gestational age at delivery was 35+6 weeks (range, 29+1 to 38+5 weeks), with the preterm delivery rate of 54.5% (6/11). The median neonatal birth weight was 2,850 g (range, 1,380 to 3,600 g).

Regarding prenatal ultrasonographic findings, severe polyhydramnios was the most distinguishing manifestation, demonstrated in 66.7% (4/6) of cases with a median amniotic fluid index of 43 (range, 37 to 66). The median gestational age when polyhydramnios was first detected was 30+6 weeks (range, 30+0 to 32+5 weeks). In 37.5% (3/8) of cases, a notably decreased fetal movement was observed during prenatal ultrasound examination. As no associated anomalies explaining the increased amniotic fluid were found, the causes of polyhydramnios were considered as "idiopathic."

All neonates were born by cesarean section because of reasons such as previous cesarean section (4/9), previous myomectomy (1/9), fetal breech presentation (1/9), placenta previa (1/9), fetal hydrops (1/9), and others (1/9). The proportion of 1-minute Apgar score under 4 was 44.4% (4/9) and that of 5-minute Apgar score under 7 was 66.7% (6/9), indicating the worsening of neonatal condition after birth. Most of the newborns were admitted to the NICU, (9/10) immediately after birth, because of respiratory problems, weak initial crying with cyanosis, or generalized hypotonia. The median hospital stay in the NICU was 37 days (range, 5 to 397 days), and there was 1 infant death on the 45th day after birth. This

case was complicated by fetal hydrops with intrauterine onset. Therefore, the mortality of congenital myotonic dystrophy diagnosed in our institution was approximately 9% (1/11).

Since most neonates in this study admitted NICU immediately after birth with symptoms of generalized hypotonia or respiratory suppression, based on these neonatal symptoms or familial history, some workups under suspicions such as congenital myotonic dystrophy, Prader-Willi syndrome were underwent. The *DMPK* gene mutation test was carried out within 1 month after birth in six of them and 1 year after birth in four of them. According to the records, there was tendency that hypotonic symptoms were more severe the test was taken earlier. The test was checked for all eleven neonates which results showed abnormal expansion of CTG repeats on their each gene by comparison with 5 to 37 repeats in normal. The genotype-phenotype correlation of myotonic dystrophy 1 is widely known, on the specifics, the patient with higher numbers of CTG repeats shows more severe or earlier onset of clinical symptoms. Our results seem to match with this correlation, the one who expired after 45 days had the highest CTG repeat number which was 2,000. Also, while the median number of CTG repeats in the mothers was 400 (range, 166 to 1,000), that in the neonates was 1,300 (range, 700 to 2,000), which shows inheritance with anticipation and explains the difference between the severity of clinical symptoms in mothers and neonates.

Discussion

Through this study, we provide useful clinical information about pregnancies complicated by congenital myotonic dystrophy, which is a rare, but clinically serious disease entity for both obstetricians and pediatricians. Our data showed that severe polyhydramnios and decreased fetal movement were distinct characteristics of pregnancies complicated by congenital myotonic dystrophy. In detail, severe idiopathic polyhydramnios was presented in 66.7% of the cases, with median amniotic fluid index of 43 and median detection time at approximately 30 weeks of gestation. These results are similar to those of other studies stating that 77% to 78% of polyhydramnios cases during late 2nd and early 3rd trimester were observed in pregnancies affected by congenital myotonic dystrophy [13,14]. Polyhydramnios in affected pregnancies is considered a consequence of decreased or absent fetal

swallowing [15]. Decreased fetal movements as a result of reduced muscle tone and polyhydramnios were also notable findings in our study, accounting for 37.5%. Several studies have described that talipes and ventriculomegaly were common findings in affected fetuses [13,14], but were not evident in our study. Like the 9% mortality rate of congenital myotonic dystrophy observed in our study, congenital myotonic dystrophy is associated with high perinatal morbidity and mortality because of severe respiratory failure. Therefore, most of the affected neonates need immediate transfer to the intensive care unit after birth, including ventilator-assisted respiration.

As previously stated, accurate diagnosis for myotonic dystrophy 1 has become possible nowadays with the *DMPK* gene mutation test, and the reported prevalence varies in different areas and ethnicities, ranging from 0.5 to 18.1 per 100,000 [16]. Based on our study, the crude prevalence of congenital myotonic dystrophy was calculated as 1:3,263, which is quite higher than the prevalence reported by other investigators (1:8,000) [10]. We should be aware that our study population may include a relatively larger proportion of high-risk pregnant women, characteristic of a tertiary hospital referral. However, given the recent study reporting that the frequency of *DMPK* mutation carriers among Korean women at child-bearing age was 1:415 and estimated prevalence of myotonic dystrophy was 1:1,245, the prevalence of congenital myotonic dystrophy (1:3,263) may be accurate. Rather, it should be considered that the prevalence of myotonic dystrophy in Korea is underestimated, especially when neonates or infants having a respiratory problem with an unknown cause are left with incomplete diagnosis because of insufficient evaluations.

The association between subfertility in men and myotonic dystrophy is an established phenomenon in the reproduction field [17]. However, there are conflicting data about the effect of myotonic dystrophy on female fertility. Recently, a study reported diminished ovarian function and less favorable response to *in vitro* fertilization-preimplantation genetic diagnosis in women with myotonic dystrophy [18]. It was also noticed recently that the development of ART helps women with myotonic dystrophy traits to conceive more easily and with better a success rate [19]. Consequently, these women with *DMPK* gene mutation can bear offspring affected by congenital myotonic dystrophy even without being themselves diagnosed with this disease. In this context, our data showed that none of the mothers whose babies were diagnosed with

congenital myotonic dystrophy were aware of their own myotonic dystrophy traits before their pregnancies.

Since prenatal genetic diagnosis of congenital myotonic dystrophy is available through chorionic villi sampling or amniocentesis these days, appropriate awareness is important for clinicians. Based on our data, undiagnosed pregnant women may have prior history of subfertility or infertility, familial history of myotonic dystrophy, prior miscarriage, or loss of a child. If clinicians suspect myotonic dystrophy 1 in an undiagnosed women presenting with these details in her history, accurate diagnosis can be made before pregnancy and proper genetic counseling can be provided, especially before ART. Even when these histories or symptoms are absent, idiopathic severe polyhydramnios and reduced fetal movement during prenatal ultrasonographic examination, especially in the third trimester, can be critical keys to suspect or diagnose congenital myotonic dystrophy.

Pregnancies affected by congenital myotonic dystrophy tend to have preterm labor, as is the case with severe polyhydramnios. In our study, the preterm delivery rate was 54.5%, and most of these deliveries were complicated by preterm labor or preterm premature rupture membranes. It is noteworthy that in such a situation, clinicians should be cautious about the use of tocolytics. Ritodrine, a widely used tocolytic, may worsen or precipitate myotonia in pregnant women with myotonic dystrophy. Ritodrine can also provoke myotonic dystrophic symptoms in asymptomatic pregnant women [20]. Another study reported that even oral ritodrine for tocolysis in a pregnant patient caused rhabdomyolysis, which is an extremely rare disease during pregnancy. In that particular case, the patient improved gradually after immediately stopping ritodrine [21]. In addition, it was recently reported that infusion with $MgSO_4$ in a pregnant patient could result in maternal respiratory compromise, and the patient recovered after discontinuation of this treatment [22].

Although congenital myotonic dystrophy is the most severe form of myotonic dystrophy, clinicians have difficulties in suspecting this disease when neonates present with hypotonia after birth. Manifestations of symptoms in neonates affected by congenital myotonic dystrophy include muscle hypotonia, weak crying, poor sucking, and cyanosis or respiratory failure. Hypotonia is a common cause for neonatal admission to the intensive unit care, but identifying the reason can be challenging. The differential diagnosis for neonatal hypotonia encompasses primary muscular dystrophies, numerous chromo-

somal abnormalities, neuropathies, and metabolic disorders [23]. This is another reason that underlines the importance of mother's obstetric data including prenatal ultrasonographic findings, previous obstetric event, prior history of infertility, or familial history of any genetic disorder for an accurate diagnosis. We conclude that the clinical characteristics of pregnancies complicated by congenital myotonic dystrophy presented in this study could be helpful in the differential diagnosis of neonatal hypotonia.

In summary, concerning the possibility of underestimated prevalence of myotonic dystrophy in Korea, clinicians should consider congenital myotonic dystrophy as a diagnosis when idiopathic severe polyhydramnios and/or decreased fetal movement is detected on prenatal ultrasonographic examination.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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