CLINICAL/SCIENTIFIC NOTE OPEN ACCESS

Fetal Brain MRI Findings in Myotonic Dystrophy and Considerations for Prenatal Genetic Testing

Matthew A. Shear, MD, Monica Penon-Portmann, MD, Joseph T. Shieh, MD, PhD, Orit A. Glenn, MD, Mari-Paule Thiet, MD, Shilpa Chetty, MD, Teresa N. Sparks, MD, MAS, and Dawn Gano, MD, MAS

Correspondence
Dr. Shear
matthew.shear@ucsf.edu

Neurol Genet 2024;10:e200171. doi:10.1212/NXG.0000000000200171

Abstract

Background

Congenital myotonic dystrophy type 1 (DM1) is a rare congenital neuromuscular disorder associated with high morbidity and potential early mortality requiring lifelong symptomatic management. Prenatal presentations of DM1 have been associated with nonspecific ultrasound findings such as clubbed foot, polyhydramnios, ventriculomegaly, and decreased fetal movement, but many cases of DM1 have no ultrasound anomalies.

Methods

We sought to compare the clinical course and prenatal imaging findings in two cases of DM1 using retrospective chart review.

Results

This report demonstrates potential expansion of the prenatal phenotype of DM1 including fetal SVT and frontal bossing. Both cases shared unique prenatal imaging features of lateral ventricle dilation involving the anterior bodies and frontal horns on fetal MRI.

Discussion

Because congenital DM1 is most often maternally inherited, attention to maternal symptoms, physical examination, and family history can be helpful in recognizing cases. Molecular diagnosis of DM1 requires specialized testing of the 3′ untranslated region of the DMPK gene, and DM1 will not be detected by current standard prenatal genetic testing with microarray, karyotype, or exome sequencing.

Introduction

Myotonic dystrophy type 1 (DM1) is a genetic neuromuscular disorder presenting with variable findings: facial and generalized muscle weakness, inability to relax muscles (myotonia), posterior subcapsular cataracts, and progressive muscle degeneration.[1,2] DM1 may be categorized as mild, classic, or congenital, with the latter being most severe. Newborns with congenital myotonic dystrophy (CMD) have hypotonia with variable weakness and may require neonatal intensive care for respiratory failure.[2] Mortality within the first year of life has been estimated at 25% among those who require prolonged intubation and approaches 50% by the fourth decade of life.[2,3] Treatments are primarily symptomatic and focus on respiratory support and quality of life, with no effective therapy currently available for the progressive muscle weakness.[4] Prenatal diagnosis of CMD is challenging, as phenotypes that have been associated with DM1 are nonspecific and can include polyhydramnios, clubbed foot, and decreased fetal movement.[5,6] Few published cases include prenatal neuroimaging findings, and ventriculomegaly has been described.[6-8] Like other congenital

From the Department of Obstetrics, Gynecology, and Reproductive Sciences (M.A.S., M.-P.T., S.C., T.N.S.); Division of Medical Genetics (M.A.S., M.P.-P., J.T.S.), Department of Pediatrics, University of California, San Francisco; Division of Genetic Medicine (M.P.-P.), Department of Pediatrics, University of Washington, Seattle; Fetal Treatment Center (M.A.S., S.C., T.N.S.), Division of Maternal-Fetal Medicine and Reproductive Genetics; Center for Maternal Fetal Precision Medicine (M.A.S., D.G.); Departments of Neurology and Pediatrics (O.A.G., D.G.); and Department of Radiology and Biomedical Imaging (O.A.G.), University of California, San Francisco.

Go to Neurology.org/NG for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by the authors.

myopathies and dystrophies, there can often be an absence of abnormal prenatal imaging findings.[9] Prenatal diagnosis of congenital DM1 has implications for obstetric and neonatal management given risk of complications such as uterine atony and postpartum hemorrhage in women with mild or classic DM1, who are often undiagnosed until CMD is recognized in an affected neonate.[2,3,10]

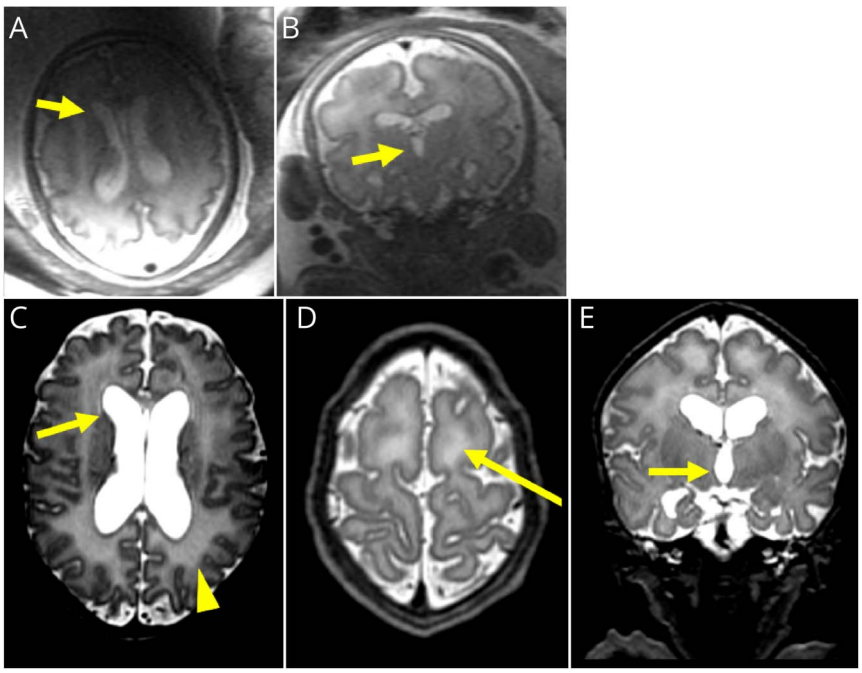
DM1 is caused by triplet CTG repeat expansions in the 3′ untranslated region of the *DMPK* gene. *DMPK* codes for myotonic dystrophy protein kinase, which maintains skeletal muscle structure and function.[11] Expansions from 5-34 are considered normal. Above 34 repeats, the expansion region becomes unstable and may expand further. Expansions from 50-150 CTG repeats is associated with mild DM1, 100–1,000 classic DM1, and >1,000 congenital DM1,[12] although cases of congenital DM1 have been reported in some individuals with repeat size between 730 and 1000.[12] DM1 is an autosomal dominant disorder. Most cases of CMD are caused by large DNA repeat expansions, whereby a parental premutation or pathogenic repeat allele undergoes expansion of CTG repeats during meiosis. While cases of paternal anticipation have been documented, expansion with transmission of the maternal allele is the most common mechanism of inheritance.[13] The exact molecular mechanisms of how CTG expansion leads to disease has not been fully defined. It is hypothesized that abnormal RNA transcripts with expanded CUG repeats exert a dominant-negative effect suppressing genetic expression across chromosome 19, sequestering specific transcription factors, inducing signaling pathways, or disrupting alternative splicing pathways, all of which lead to the diverse multiorgan phenotype.[14,15]

Cases

Case 1

Family 1 was referred at 32 weeks' gestation with fetal re-entrant supraventricular tachycardia (SVT), polyhydramnios, and equinovarus without frank talipes. Fetal MRI showed normal cardiac structure, and screening brain MR images showed moderate ventriculomegaly involving the frontal horns and third ventricle (Figure 1, A and B). Treatment with maternal digoxin was initiated. The patient declined prenatal genetic testing. All prenatal visits occurred during a period of mandatory mask-wearing because of the COVID-19 pandemic, obscuring maternal craniofacial assessment. The patient underwent induction of labor at 39 weeks' gestation, and cesarean delivery was performed for category II fetal heart tracing. Apgars were 7,8. Head circumference was consistent with macrocephaly, and metatarsus adductus, undescended left testis, and mild hypotonia were present. The infant required CPAP for 3 weeks and treatment with sotalol for cardiac rate control. A sacral tuft of hair was noted with limited spine MRI demonstrating borderline low-lying conus. Brain MRI showed stable ventricular enlargement and subtle T2 hyperintensity in the bilateral periventricular and parasagittal white matter (Figure 1, C–E). Microarray returned normal male. Exome sequencing (ES) was performed by next-generation sequencing using the Illumina NovaSeq 6000 at the University of California, San Francisco Genomic Medicine Laboratory, and showed no reportable variants. Methylation studies for Prader-Willi and Angelman syndrome were negative. Follow-up brain and spine MRI at 6 months showed persistent ventriculomegaly, increased conspicuity of areas of

Figure 1 Case 1



(A) Fetal MRI at 32 weeks: Axial T2 image demonstrates moderate dilation of the lateral ventricles also involving the frontal horns (arrow). (B) Fetal MRI at 32 weeks: Coronal T2 image demonstrates additional dilation of the third ventricle (arrow). (C) Neonatal MRI: Axial T2 image demonstrates persistent dilation of the lateral ventricles, including of the anterior lateral ventricles (arrow), and subtle increased signal in the periventricular and subcortical white matter (arrowhead). (D) Neonatal MRI: Axial T2 image at the vertex demonstrates hyperintensity in the white matter of the bilateral superior frontal gyri (arrow). (E) Neonatal MRI: Coronal T2 image demonstrates similar findings and persistent dilation of the third ventricle (arrow).

supratentorial white matter T2-hyperintensity, mild hypoplasia of the corpus callosum, and normal position of the conus. In clinical follow-up, targeted maternal examination revealed a gaunt-appearing lower face with facial weakness and grip myotonia. Specialized testing with repeat-primed PCR of the *DMPK* 3′ UTR (GeneDx, Gaithersburg, MD) demonstrated a heterozygous expanded allele >200 repeats, confirming the diagnosis of DM1 in the infant.

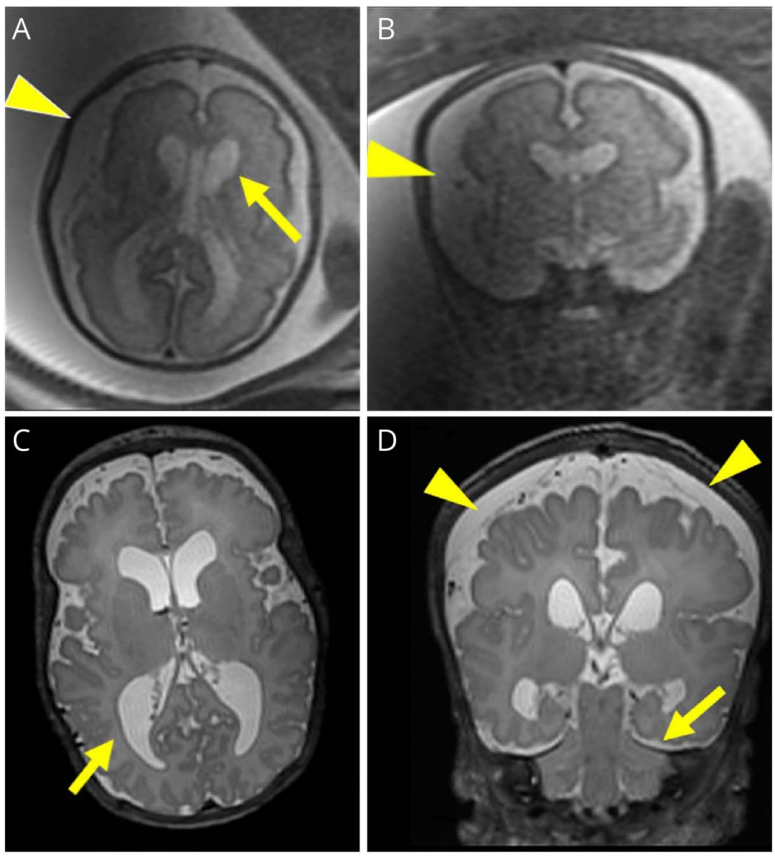
Case 2

Family 2 was referred at 29 weeks' gestation with bilateral clubbed feet, bilateral ventriculomegaly, polyhydramnios, mild right hydronephrosis, and left renal pelviectasis. Fetal MRI demonstrated mild ventriculomegaly with prominence of the frontal horns, dilated subarachnoid spaces, and mild frontal bossing (Figure 2, A and B). The patient declined prenatal genetic testing. The patient experienced premature prelabor rupture of membranes at 32 weeks' gestation and progressed into labor. Operative vaginal delivery was performed for category II fetal heart tracing with prolonged decelerations. The infant emerged limp and apneic with depressed Apgars and required intubation at 30 minutes. They had a prolonged hospital course requiring prolonged intubation with significant hypotonia and weakness. Postnatal MRI at term-equivalent age demonstrated ventriculomegaly, enlarged subarachnoid spaces, diminished white matter volume with hypoplasia of the corpus callosum, small bilateral subdural hygromas, small germinal matrix hemorrhage, and small posterior fossa with a low position of the tentorium (Figure 2, C and D). Maternal examination demonstrated myotonia, eye closure weakness, and distal extremity weakness. ES was nondiagnostic with no reportable variants. Specialized testing with repeat-primed PCR of the *DMPK* 3′ UTR demonstrated a heterozygous expanded allele >200 repeats in both the infant and the mother, confirming the diagnosis of DM1 in both.

Discussion

Prenatal recognition of DM1 enables a unique opportunity to better understand the phenotypic spectrum across the lifespan and potentially a unique opportunity for intervention when therapies become available. We report expansion of the prenatal phenotype of DM1 with fetal SVT and frontal bossing with dilated subarachnoid spaces. Both cases shared prenatal features of lateral ventricle dilation involving the anterior bodies and frontal horns on fetal MRI. Follow-up MRI additionally demonstrated new postnatal findings, including callosal hypoplasia and nonspecific white matter abnormalities, which have been described in neonatal reports of congenital DM1.[8] Whether ventriculomegaly and white matter abnormalities on fetal or neonatal imaging in DM1 are a marker of prognostic significance merits further study.

Figure 2 Case 2



(A) Fetal MRI at 29 weeks: Axial T2 image demonstrates mild dilation of the lateral ventricles including of the frontal horns (arrow), prominent subarachnoid spaces, and right subdural hygroma. (B) Fetal MRI at 29 weeks: Coronal T2 image demonstrates bilateral ventriculomegaly and right subdural hygroma (arrowhead). (C) Neonatal MRI: Axial T2 image demonstrates persistent mild dilation of the lateral ventricles (arrow), prominent subarachnoid spaces, and diffusely diminished white matter volume. (D) Postnatal MRI: Coronal T2 image demonstrates bilateral subdural hygromas (arrowheads) and inferior position of the tentorium with small posterior fossa (arrow).

There is broad agreement among pediatric neurologists and maternal-fetal medicine specialists to obtain fetal MRI for ventriculomegaly detected on prenatal ultrasound to assess for other brain malformations that may inform workup, counseling, and care.[16,17] Despite the inherent uncertainties that are often present at the time of fetal MRI, most pregnant women who receive a fetal brain MRI report a better understanding of their fetus's health and prognosis.[18] Fetal ventriculomegaly has been previously reported in a few cases of CMD.[6-8] A pooled analysis of ventriculomegaly in reported cases of CMD described 3 of 7 cases with prenatal ventriculomegaly and 43 of 97 with ventriculomegaly at birth.[7] A more recent series of MRI in CMD reported fetal MRI in 2 cases: one had bilateral ventriculomegaly at 36 weeks and one was normal.[8] In contrast to the pattern of ventriculomegaly observed in our cases, a different series[6] reported mild ventriculomegaly involving the occipital horns on prenatal ultrasound in 2 of 16 cases of CMD.

Parents of affected fetuses may have mild or subtle clinical findings, and initial symptoms can emerge during pregnancy.[5,6] Attention to maternal symptoms, physical examination, and family history can be helpful in suspected cases. Molecular diagnosis of DM1 requires specialized testing of the 3′ untranslated region of the *DMPK* gene to target the CTG repeat using a combination of Southern transfer and PCR. Owing to somatic mosaicism, even when a prenatal diagnosis is made through analysis of villous trophoblasts or amniocytes, it is not possible to precisely predict whether the fetus will have congenital, classic, or milder adult-onset DM1.[19] Postnatal examination and clinical trajectory are fundamentally important in the classification of disease severity.[9] Standard prenatal genetic testing methods such as karyotype, microarray, and exome sequencing will not reliably detect DM1. Exome sequencing may produce reliable results in some intronic and untranslated regions, but requires additional specialized probes and focused analysis that is not routinely included without special consultation of the laboratory. Genome sequencing, however, has the potential to detect DMPK expansion because the entire genome is amplified, including introns and 3′ UTRs. Accurate determination of the DMPK expansion using genome sequencing requires further specific platform validation and follow-up testing.

Prenatal testing and diagnosis of myotonic dystrophy requires a high clinical index of suspicion and can affect both obstetric and neonatal care. Assessment for maternal clinical features of DM1 should be prompted by the presence of ventriculomegaly, particularly when other features such as polyhydramnios, clubfoot, or fetal tachycardia are present.

Study Funding

The authors report no targeted funding.

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/NG for full disclosures.

Publication History

Received by *Neurology: Genetics* March 1, 2024. Accepted in final form July 8, 2024. Submitted and externally peer reviewed. The handling editor was Editor Stefan M. Pulst, MD, Dr med, FAAN.

Appendix Authors

Name	Location	Contribution
Matthew A. Shear, MD	Department of Obstetrics, Gynecology, and Reproductive Sciences; Division of Medical Genetics, Department of Pediatrics; Fetal Treatment Center, Division of Maternal-Fetal Medicine and Reproductive Genetics; Center for Maternal Fetal Precision Medicine, University of California, San Francisco	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Monica Penon-Portmann, MD	Division of Medical Genetics, Department of Pediatrics, University of California, San Francisco; Division of Genetic Medicine, Department of Pediatrics, University of Washington, Seattle	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
Joseph T. Shieh, MD, PhD	Division of Medical Genetics, Department of Pediatrics, University of California, San Francisco	Drafting/revision of the manuscript for content, including medical writing for content
Orit A. Glenn, MD	Departments of Neurology and Pediatrics; Department of Radiology and Biomedical Imaging, University of California, San Francisco	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Mari-Paule Thiet, MD	Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Francisco	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Shilpa Chetty, MD	Department of Obstetrics, Gynecology, and Reproductive Sciences; Fetal Treatment Center, Division of Maternal-Fetal Medicine and Reproductive Genetics, University of California, San Francisco	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Teresa N. Sparks, MD, MAS	Department of Obstetrics, Gynecology, and Reproductive Sciences; Fetal Treatment Center, Division of Maternal-Fetal Medicine and Reproductive Genetics, University of California, San Francisco	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Dawn Gano, MD, MAS	Center for Maternal Fetal Precision Medicine; Departments of Neurology & Pediatrics, University of California, San Francisco	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data

References

1. Thornton CA. Myotonic dystrophy. *Neurol Clin.* 2014;32(3):705-719, viii. doi: 10.1016/j.ncl.2014.04.011
2. Reardon W, Newcombe R, Fenton I, Sibert J, Harper PS. The natural history of congenital myotonic dystrophy: mortality and long term clinical aspects. *Arch Dis Child.* 1993;68(2):177-181. doi:10.1136/adc.68.2.177
3. Campbell C, Sherlock R, Jacob P, Blayney M. Congenital myotonic dystrophy: assisted ventilation duration and outcome. *Pediatrics.* 2004;113(4):811-816. doi: 10.1542/peds.113.4.811
4. Johnson NE, Aldana EZ, Angeard N, et al. Consensus-based care recommendations for congenital and childhood-onset myotonic dystrophy type 1. *Neurol Clin Pract.* 2019;9(5):443-454. doi:10.1212/CPJ.0000000000000646
5. Yee C, Choi SJ, Oh SY, Ki CS, Roh CR, Kim JH. Clinical characteristics of pregnancies complicated by congenital myotonic dystrophy. *Obstet Gynecol Sci.* 2017;60(4): 323-328. doi:10.5468/ogs.2017.60.4.323
6. Zaki M, Boyd PA, Impey L, Roberts A, Chamberlain P. Congenital myotonic dystrophy: prenatal ultrasound findings and pregnancy outcome. *Ultrasound Obstet Gynecol.* 2007;29(3):284-288. doi:10.1002/uog.3859
7. Mutchnick IS, Thatikunta MA, Gump WC, Stewart DL, Moriarty TM. Congenital myotonic dystrophy: ventriculomegaly and shunt considerations for the pediatric neurosurgeon. *Childs Nerv Syst.* 2016;32(4):609-616. doi:10.1007/s00381-015-2993-y
8. Peglar LM, Nagaraj UD, Tian C, Venkatesan C. White matter lesions detected by magnetic resonance imaging in neonates and children with congenital myotonic dystrophy. *Pediatr Neurol.* 2019;96:64-69. doi:10.1016/j.pediatrneurol.2019.03.004
9. Massalska D, Zimowski JG, Bijok J, et al. Prenatal diagnosis of congenital myopathies and muscular dystrophies. *Clin Genet.* 2016;90(3):199-210. doi:10.1111/cge.12801
10. Rudnik-Schöneborn S, Zerres K. Outcome in pregnancies complicated by myotonic dystrophy: a study of 31 patients and review of the literature. *Eur J Obstet Gynecol Reprod Biol.* 2004;114(1):44-53. doi:10.1016/j.ejogrb.2003.11.025
11. Stelzer G, Rosen N, Plaschkes I, et al. The GeneCards suite: from gene data mining to disease genome sequence analyses. *Curr Protoc Bioinformatics.* 2016;54:1.30.1-1.30.33. doi:10.1002/cpbi.5
12. Redman JB, Fenwick RG, Fu YH, Pizzuti A, Caskey CT. Relationship between parental trinucleotide GCT repeat length and severity of myotonic dystrophy in offspring. *JAMA.* 1993;269(15):1960-1965. 10.1001/jama.269.15.1960
13. Martorell L, Cobo AM, Baiget M, Naudó M, Poza JJ, Parra J. Prenatal diagnosis in myotonic dystrophy type 1. Thirteen years of experience: implications for reproductive counselling in DM1 families. *Prenat Diagn.* 2007;27(1):68-72. doi: 10.1002/pd.1627
14. Liu J, Guo ZN, Yan XL, Yang Y, Huang S. Brain pathogenesis and potential therapeutic strategies in myotonic dystrophy type 1. *Front Aging Neurosci.* 2021;13:755392. doi:10.3389/fnagi.2021.755392
15. Hasuike Y, Mochizuki H, Nakamori M. Expanded CUG repeat RNA induces premature senescence in myotonic dystrophy model cells. *Front Genet.* 2022;13:865811. doi:10.3389/fgene.2022.865811
16. Agarwal S, Venkatesan C, Vollmer B, et al. Fetal cerebral ventriculomegaly: a narrative review and practical recommendations for pediatric neurologists. *Pediatr Neurol.* 2024;156:119-127. doi:10.1016/j.pediatrneurol.2024.04.016
17. Society for Maternal-Fetal Medicine SMFM; Electronic address pubs@smfmorg, Fox NS, Monteagudo A, Kuller JA, Craigo S, Norton ME. Mild fetal ventriculomegaly: diagnosis, evaluation, and management. *Am J Obstet Gynecol.* 2018;219(1):B2-B9. doi: 10.1016/j.ajog.2018.04.039
18. Griffiths PD, Bradburn M, Campbell MJ, et al.; MERIDIAN collaborative groupUse of MRI in the diagnosis of fetal brain abnormalities in utero (MERIDIAN): a multicentre, prospective cohort study. *Lancet.* 2017;389(10068):538-546. doi:10.1016/S0140-6736(16)31723-8
19. Prior TW, American College of Medical Genetics ACMG Laboratory Quality Assurance Committee. Technical standards and guidelines for myotonic dystrophy type 1 testing. *Genet Med.* 2009;11(7):552-555. doi:10.1097/GIM.0b013e3181abce0f