American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2020; 21: e919867
DOI: 10.12659/AJCR.919867

Received: 2019.09.03
Accepted: 2019.11.11
Published: 2020.01.09

Congenital Myotonic Dystrophy and Brugada Syndrome: A Report of Two Cases

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABDEF 1 Kunal Gupta
CDEF 2 Marie R. Kennelly
ABDEF 1 Ashajyothi M. Siddappa

1 Division of Neonatology, Department of Pediatrics, Hennepin County Medical Center (HCMC), Minneapolis, MN, U.S.A.
2 Department of Maternal-Fetal Medicine, Hennepin County Medical Center (HCMC), Minneapolis, MN, U.S.A.

Corresponding Author: Kunal Gupta, e-mail: Kunal.gupta@hcmed.org
Conflict of interest: None declared

Case series
Patients: Female, 40 weeks GA • Male, 37 weeks GA
Final Diagnosis: Congenital myotonic dystrophy with family history of Brugada syndrome
Symptoms: Frog leg positioning • hypotonia • poor respiratory effort
Medication: —
Clinical Procedure: —
Specialty: Pediatrics and Neonatology

Objective: Rare co-existance of disease or pathology

Background: Congenital myotonic dystrophy is a subtype of type 1 myotonic dystrophy presenting in the neonatal period. Cardiac involvement is commonly seen in patients with type 1 myotonic dystrophy beyond the neonatal period. Brugada syndrome is a conduction abnormality associated with a mutation in the sodium voltage-gated channel alpha subunit 5 (SCN5A) gene and has been described in adult patients with type 1 myotonic dystrophy. Two cases are presented of type 1 myotonic dystrophy in neonates, one who had family members with a confirmed diagnosis of Brugada syndrome.

Case Reports: Case 1: A female infant at 40 weeks gestational age, birth weight of 3,395 grams was born to a 40-year-old gravida 4, para 3 (G4P3) mother. The mother had previously been diagnosed with Brugada syndrome. Multiple family members were identified and diagnosed with type 1 myotonic dystrophy and Brugada syndrome. The infant is being monitored closely with a plan to perform genetic testing for Brugada syndrome if she develops cardiac conduction abnormalities. Case 2: A male infant at 37 weeks gestational age, with a birth weight of 2,900 grams, was born to a 24-year-old gravida 2, para 1 (G2P1) mother. He was admitted to the neonatal intensive care unit (NICU) secondary to poor respiratory effort and generalized hypotonia. Severe polyhydramnios was diagnosed during pregnancy. The mother had previously been diagnosed with type 1 myotonic dystrophy.

Conclusions: Infants with congenital myotonic dystrophy should be carefully monitored for both structural and conduction abnormalities of the heart, supported by genetic testing.

MeSH Keywords: Brugada Syndrome • Myotonic Dystrophy • NAV1.5 Voltage-Gated Sodium Channel • Infant, Newborn • Mutation

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/919867

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Background

Myotonic dystrophy is an autosomal dominant disorder with variable penetrance and is a subtype of type 1 myotonic dystrophy that presents in the neonatal period [1]. The incidence of myotonic dystrophy in Caucasians is 1 in 8,000 and is considered to be rare in the non-Caucasian population [2]. Two types of myotonic dystrophy have been described, type 1 myotonic dystrophy and type 2 myotonic dystrophy. Cardiac involvement is commonly seen in patients with type 1 myotonic dystrophy beyond the neonatal period [1]. The genetic *loci* of type 1 myotonic dystrophy are in the myotonic type 1 myotonic dystrophy pyruvate kinase (DMPK) gene at 19q13.3 (OMIM 160900). The genetic loci of type 2 myotonic dystrophy are in the zinc finger protein 9 (ZNF9) gene at 3q21 (OMIM 602668). While type 2 myotonic dystrophy is almost exclusively limited to adults, type 1 myotonic dystrophy can present at any age [3]. Congenital myotonic dystrophy is a form of type 1 myotonic dystrophy which presents in the neonatal period [1,4].

Brugada syndrome is a conduction abnormality associated with a mutation in the sodium voltage-gated channel alpha subunit 5 (SCN5A) gene and has been described in adult patients with type 1 myotonic dystrophy, but it is unclear whether Brugada syndrome is associated with congenital myotonic dystrophy [5–7]. Brugada syndrome is inherited in an autosomal dominant pattern. More than 300 variants of Brugada syndrome and approximately 19 different genes have been reported. About 20–30% of patients with Brugada syndrome have a mutation in the SCN5A gene. Over 300 types of SCN5A mutations have been reported in association with Brugada syndrome. Other genes that have been implicated include but are not limited to other members of the SCN gene family, potassium and calcium channels, and chromosome [8,9]. Two cases are presented of type 1 myotonic dystrophy in neonates, one who had family members with a confirmed diagnosis of Brugada syndrome.

Case Reports

Case 1

A female infant at 40 weeks gestational age, birth weight of 3,395 grams, was born to a 40-year-old gravida 4, para 3 (G4P3) mother. The mother had previously been diagnosed with Brugada syndrome. The family history was significant for the sudden death of maternal uncle at 29 years of age. The older half-brother of the infant had experienced a myocardial infarction and cardiac arrest at the age of 11 years. A loss of functional mutation in the SCN5A gene was found during clinical work-up following myocardial infarction, which was associated with Brugada syndrome [7]. Similar SCN5A gene mutations were found in the mother and older half-sister of the infant.

In the neonatal intensive care unit (NICU), the infant required non-invasive respiratory support until the 14th day of life. The findings on physical examination included poor respiratory effort, hypotonia with 'frog-leg' positioning of the lower limbs, characteristic features of the facial muscles, and weakness, in keeping with a diagnosis of congenital myotonic dystrophy. Premature atrial contractions were diagnosed on electrocardiography (ECG).

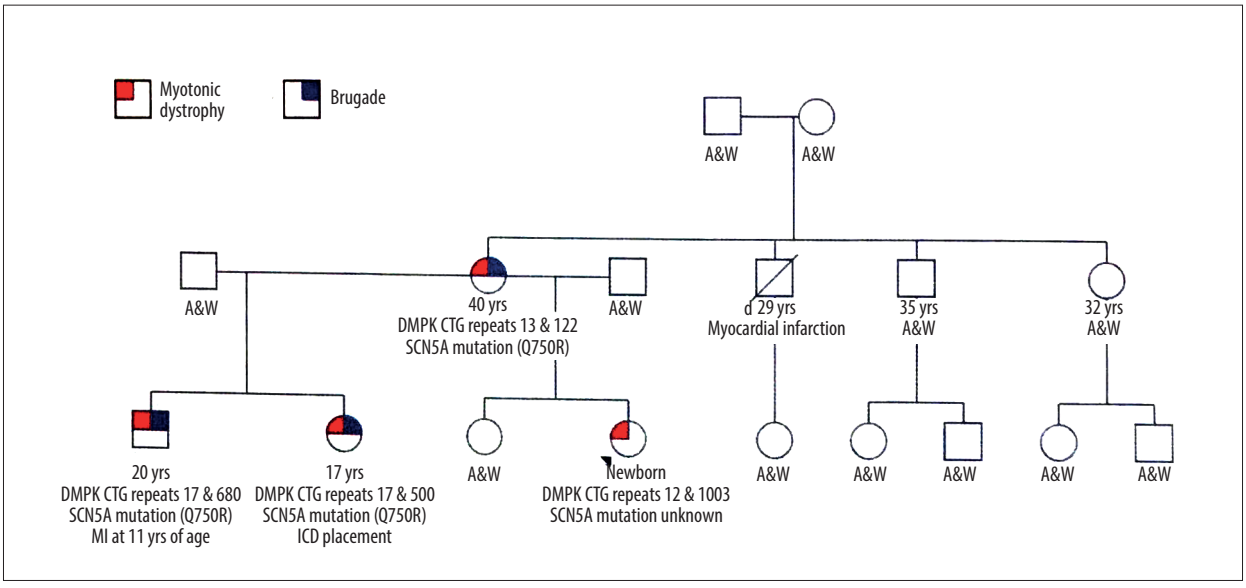

Figure 1. Case 1: The family pedigree.

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

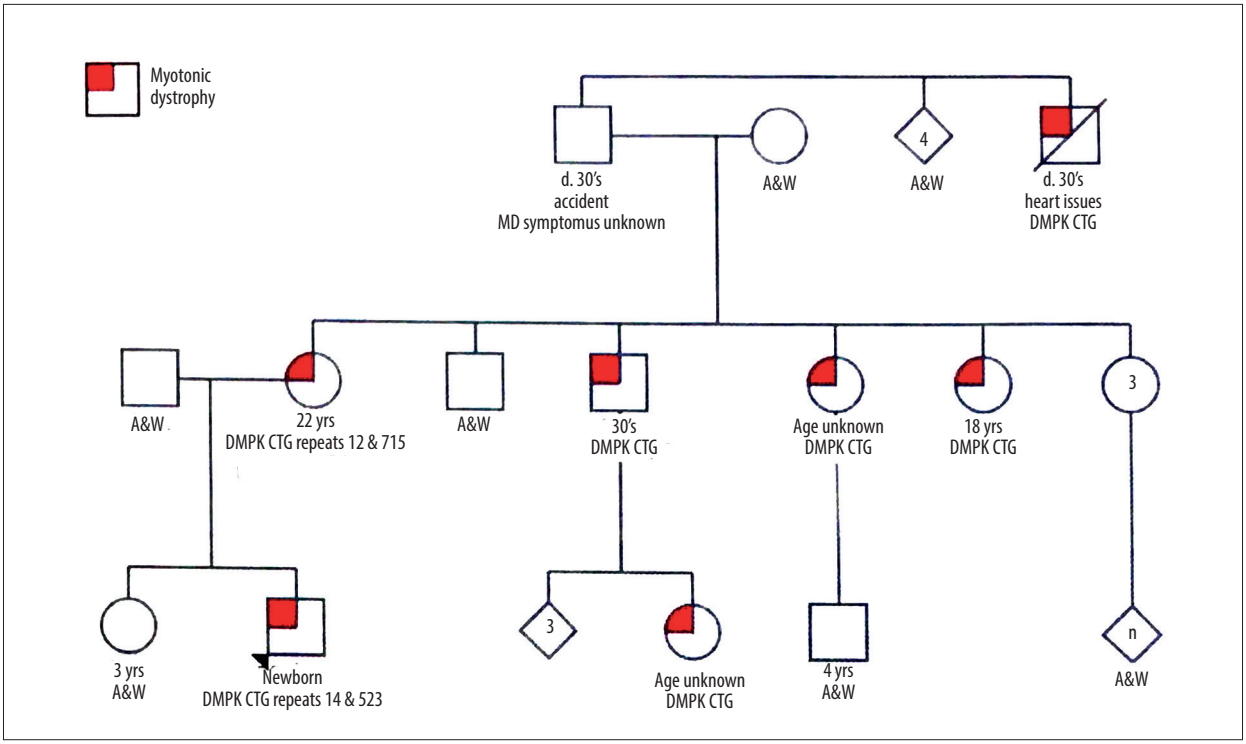

Figure 2. Case 2: The family pedigree.

The infant was discharged home on the 18th day of life. Genetic testing identified a DMPK gene with cytosine, thymine, guanine repeats that confirmed a diagnosis of congenital myotonic dystrophy. Her hypotonia improved with age, and her muscle tone and strength were found to be appropriate by 3 years of age. She has needed surgical correction for bilateral talipes equinovarus and congenital hip dysplasia. Currently, her cardiac assessment remains normal, and genetic testing, including SCN5A mutation testing, has not been performed. Following the diagnosis of congenital myotonic dystrophy in the index case, her mother and two older siblings were also diagnosed with type 1 myotonic dystrophy (Figure 1).

Case 2

A male infant at 37 weeks gestational age, with a birth weight of 2,900 grams, was born to a 24-year-old gravida 2, para 1 (G2P1) mother. He was admitted to the neonatal intensive care unit (NICU) with symptoms of poor respiratory effort and generalized hypotonia. Severe polyhydramnios was diagnosed during pregnancy. The mother had previously been diagnosed with type 1 myotonic dystrophy, and her family history was also significant for type 1 myotonic dystrophy in her two sisters, one brother, and a paternal uncle. The infant required invasive ventilation for six weeks, followed by two weeks of non-invasive respiratory support. A gastrostomy tube was cited for optimal nutrition due to his poor oral intake. The cardiac evaluation was normal. He was discharged at a postmenstrual age of 50 weeks. A diagnosis of congenital myotonic dystrophy was considered due to the strong family history, polyhydramnios during pregnancy, respiratory failure, generalized hypotonia and cryptorchidism. Genetic testing identified 1,523 cytosine, thymine, guanine repeats in the DMPK gene confirming the diagnosis of congenital myotonic dystrophy. Currently, at 3 years of age, his fine motor skills are at the 23-month developmental level (Figure 2).

Discussion

Congenital myotonic dystrophy is an autosomal dominant condition that is inherited from the maternal genome, although paternal transmission has been reported [10]. The incidence of congenital myotonic dystrophy varies from 0.8–2.1 per 100,000 live births [10,11]. Congenital myotonic dystrophy is associated with a 16–40% mortality rate in the neonatal period [10].

The molecular pathogenesis of congenital myotonic dystrophy includes the expansion of microsatellite cytosine, thymine, guanine repeats in the 3'DNA segment of the DMPK gene [6]. The usual number of cytosine, thymine, guanine repeats in this part of the genome is 4–37, but commonly exceeds 1,000 in patients with congenital myotonic dystrophy [12]. The expanded cytosine, thymine, and guanine repeat sequences cause disruptions in the normal processing of pre-mRNA, resulting in multisystem involvement [6]. Larger repeats are associated

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

with severe symptoms and an earlier age of onset, and when an infant is diagnosed with congenital myotonic dystrophy, they may represent the familial index case [10]. The phenomenon of 'genetic anticipation' occurs when there is an earlier and more severe presentation of type 1 myotonic dystrophy in offspring, and arises due to the unstable trinucleotide repeat mutation expansion in subsequent generations.

Pregnancy may be complicated by polyhydramnios, reduced fetal movement, and preterm delivery [4,10,13]. Polyhydramnios results from impaired pharyngo-esophageal motility in the affected fetus [14,15]. At birth, infants with congenital myotonic dystrophy may present with respiratory insufficiency, generalized hypotonia, tented upper lips ('carp mouth'), and arthrogryposis or club feet [1,16]. Infants who survive the neonatal period may experience an initial improvement followed by the development of adult symptoms myotonic dystrophy [17].

Type 1 myotonic dystrophy can involve involuntary muscles, including the gastrointestinal, genitourinary, cardiovascular, ophthalmic, and head and neck muscles. Respiratory difficulties are the main cause of mortality during the neonatal period [18]. A large epidemiological study, published in 2013 by Campbell et al. showed that approximately 71% of infants with congenital myotonic dystrophy required respiratory support [10]. Respiratory symptoms in children with congenital myotonic dystrophy can include weakness, cough, aspiration pneumonia, and recurrent chest infections [19]. Diaphragmatic hypoplasia may lead to unilateral or bilateral diaphragmatic eventration [20].

In neonates and infants with type 1 myotonic dystrophy, cardiac involvement is rare in the neonatal period. Beyond the neonatal period, the ECG abnormalities can be found in up to 80% of children with congenital myotonic dystrophy [4,10]. The presence of conduction disturbances has been correlated with the size of cytosine, thymine, guanine repeats in some adult studies and the condition is believed to progress more rapidly in patients with cytosine, thymine, guanine repeats >1,000 [21,22]. When compared with congenital myotonic dystrophy, both tachyarrhythmias and bradyarrhythmias may be seen in patients with type 1 myotonic dystrophy. Arrhythmias include atrial tachycardia, atrial flutter, and atrial fibrillation, ventricular tachycardia, ventricular fibrillation, premature ventricular contractions, bundle branch block, non-sustained ventricular tachycardia, and bradycardia-induced ventricular fibrillation [23].

Although risk factors in patients with Brugada syndrome have been identified but risk stratification in patients with asymptomatic Brugada syndrome remains controversial. Some of the common risk factors for sudden death in patients with Brugada syndrome include spontaneous type I ECG changes, a family history of sudden death, a history of syncope, sick sinus syndrome, and a history of sudden cardiac death. The use of implantable cardiac devices may be considered in such cases [8].

In Case 1 of this report, there was a strong family history of Brugada syndrome, which is an autosomal dominant disorder characterized by ST-segment elevation in leads V1 to V3 [24]. Brugada-type ECG patterns can be found in 7.7/1,000 patients with type 1 myotonic dystrophy, and is 50-times more common in type 1 myotonic dystrophy patients when compared with the general population, and is a major risk factor for ventricular arrhythmias and sudden cardiac death [6, 7]. Loss of functional mutations in the SCN5A gene, which are associated with the development of Brugada syndrome, have also been found in patients with type 1 myotonic dystrophy [6, 7]. It is possible that disrupted RNA splicing may disrupt the normal splicing of the SCN5A gene leading to a loss of function mutation in patients with type 1 myotonic dystrophy [5]. To the best of our knowledge, Case 1 is the first case report of an infant with congenital myotonic dystrophy and a significant family history of Brugada syndrome.

The infant described in Case 2 required a gastrostomy tube for optimal enteral feeding. This finding is supported by a previous clinical report from Canada, which showed that 80% of patients with congenital myotonic dystrophy experienced feeding difficulties, and 16% required placement of either a nasogastric tube or a gastric tube for feeding [10]. Also, a week neonatal sucking ability, impaired chewing, drooling, delayed gastric emptying, and reduced peristalsis may have been reported [25]. Cryptorchidism was diagnosed in the infant described in Case 2, which may result from hypogonadism or androgen insensitivity in infants with congenital myotonic dystrophy. Other manifestations of endocrine dysfunction include hypothyroidism, growth hormone imbalance, testicular atrophy, and infertility in men, and irregular periods, and prolonged episodes of amenorrhea in women [16,26].

Neurological outcome in patients of congenital myotonic dystrophy can include cognitive impairment and mental delay, sleep disturbances, autistic spectrum disorders, and other psychosocial dysfunction [27,28]. Brain imaging may show hydrocephalus, ventriculomegaly, cortical atrophy, and other periventricular white matter changes [29]. Infants with congenital myotonic dystrophy may require intensive physical therapy, braces, supports, and surgical correction for impaired motor function, as described in the infant in Case 1.

There is limited evidence for the use of medications for the treatment of myotonia in infants with congenital myotonic dystrophy. Management of myotonia is largely supportive, with the aim of optimizing function and reducing secondary complications. Early genetic testing is important in understanding the inheritance and to provide appropriate family counselling [4].

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Conclusions

Two cases are presented of type 1 myotonic dystrophy in neonates, one who had family members with a confirmed diagnosis of Brugada syndrome. Congenital forms of myotonic dystrophy and Brugada syndrome may share a common genetic and pathophysiological pathway. All infants with congenital myotonic dystrophy should be carefully monitored for both structural and conduction abnormalities of the heart. These cases reports have highlighted that genetic testing for mutations in sodium channel genes should be undertaken in infants with congenital myotonic dystrophy, even when cardiac conduction abnormalities have not yet developed.

Conflict of interest

None.

References:

1. Echenne B, Bassez G: Congenital and infantile myotonic dystrophy. Handb Clin Neurol, 2013; 113: 1387–93
2. Suominen T, Bachinski LL, Auvinen S et al: Population frequency of myotonic dystrophy: Higher than expected frequency of myotonic dystrophy type 2 (DM2) mutation in Finland. Eur J Hum Genet, 2011; 19(7): 776–82
3. Campbell C: Congenital myotonic dystrophy. J Neurol Neurophysiol, 2012; S7
4. Ho G, Cardamone M, Farrar M: Congenital and childhood myotonic dystrophy: Current aspects of disease and future directions. World J Clin Pediatr, 2015; 4(4): 66–80
5. Pambrun T, Mercier A, Chatelier A et al: Myotonic dystrophy type 1 mimics and exacerbates Brugada phenotype induced by Nav1.5 sodium channel loss-of-function mutation. Heart Rhythm, 2014; 11(8): 1393–400
6. Perez-Riera AR, Baranchuk A, Zhang L et al: Myotonic dystrophy and Brugada syndrome: A common pathophysiologic pathway? J Electrocardiol, 2017; 50(4): 513–17
7. Wahbi K, Algalarrondo V, Becane HM et al: Brugada syndrome and abnormal splicing of SCN5A in myotonic dystrophy type 1. Arch Cardiovasc Dis, 2013; 106(12): 635–43
8. Giuseppe C, Egle C, Antonio C et al: Update on Brugada syndrome 2019. Curr Probl Cardiol, 2019 [Epub ahead of print]
9. Horie M, Ohno S: Genetic basis of Brugada syndrome. J Arrhythm, 2013; 29: 71–76
10. Campbell C, Levin S, Siu VM et al: Congenital myotonic dystrophy: Canadian population-based surveillance study. J Pediatr, 2013; 163(1): 120–25.e1-3
11. Gonzalez de Dios J, Martinez Frias ML, Egues Jimeno J et al: [Epidemiological study of Steinert's congenital myotonic dystrophy: dysmorphological characteristics]. An Esp Pediatr, 1999; 51(4): 389–96 [in Spanish]
12. Firth HV, Hurst JA: Oxford desk reference: Clinical genetics. Oxford University Press, 2005
13. Zaki M, Boyd PA, Impey L et al: Congenital myotonic dystrophy: Prenatal ultrasound findings and pregnancy outcome. Ultrasound Obstet Gynecol, 2007; 29(3): 284–88
14. Leonard RJ, Kendall KA, Johnson R, McKenzie S: Swallowing in myotonic muscular dystrophy: A videofluoroscopic study. Arch Phys Med Rehabil, 2001; 82(7): 979–85
15. Modolell I, Mearin F, Baudet JS et al: Pharyngo-esophageal motility disturbances in patients with myotonic dystrophy. Scand J Gastroenterol, 1999; 34(9): 878–82
16. Echenne B, Rideau A, Roubertie A et al: Myotonic dystrophy type I in childhood Long-term evolution in patients surviving the neonatal period. Eur J Paediatr Neurol, 2008; 12(3): 210–23
17. Hageman AT, Gabreels FJ, Liem KD et al: Congenital myotonic dystrophy; A report on thirteen cases and a review of the literature. J Neurol Sci, 1993; 115(1): 95–101
18. Shahrizaila N, Kinnear WJ, Wills AJ: Respiratory involvement in inherited primary muscle conditions. J Neurol Neurosurg Psychiatry, 2006; 77(10): 1108–15
19. Harper P: Myotonic dystrophy. 3rd edition. London WB Saunders, 2001
20. Kapoor V, Wright IM: Congenital myotonic dystrophy with cardiac conduction defect and eventration of the diaphragm. Pediatr Int, 2010; 52(1): e6–8
21. Clarke NR, Kelion AD, Nixon J et al: Does cytosine-thymine-guanine (CTG) expansion size predict cardiac events and electrocardiographic progression in myotonic dystrophy? Heart, 2001; 86(4): 411–16
22. Mahadevan M, Tsilfidis C, Sabourin L et al: Myotonic dystrophy mutation: An unstable CTG repeat in the 3' untranslated region of the gene. Science, 1992; 255(5049): 1253–55
23. Thornton CA: Myotonic dystrophy. Neurol Clin, 2014; 32(3): 705–19
24. Brugada P, Brugada J: Right bundle branch block, persistent ST segment elevation and sudden cardiac death: A distinct clinical and electrocardiographic syndrome. A multicenter report. J Am Coll Cardiol, 1992; 20(6): 1391–96
25. Bodensteiner JB, Grunow JE: Gastroparesis in neonatal myotonic dystrophy. Muscle Nerve, 1984; 7(6): 486–87
26. O'Brien TA, Harper PS: Course, prognosis and complications of childhood-onset myotonic dystrophy. Dev Med Child Neurol, 1984; 26(1): 62–67
27. Ho G, Carey KA, Cardamone M, Farrar MA: Myotonic dystrophy type 1: Clinical manifestations in children and adolescents. Arch Dis Child, 2019; 104(1): 48–52
28. Ekstrom AB, Hakenas-Plate L, Samuelsson L et al: Autism spectrum conditions in myotonic dystrophy type 1: A study on 57 individuals with congenital and childhood forms. Am J Med Genet B Neuropsychiatr Genet, 2008; 147b(6): 918–26
29. Kuo HC, Hsiao KM, Chen CJ et al: Brain magnetic resonance image changes in a family with congenital and classic myotonic dystrophy. Brain Dev, 2005; 27(4): 291–96

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]