Child Neurology: Maternal Transmission of Congenital Myotonic Dystrophy Type 2

Case Report

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Abstract

Congenital manifestations in Myotonic Dystrophy type 2 (DM2) point to anticipation and have only rarely been described. We report a three-generation family with genetically confirmed DM2. The youngest family member presented with unilateral congenital pes planovalgus and equinus. Genetic analysis in four family members showed a CCTG repeat expansion in the *CNBP* gene. We highlight the association between foot deformities and congenital DM2. Remarkably, the transmission to the congenital form of DM2 has been exclusively maternal so far. If this association is confirmed in other families, clinical practice and genetic counseling in DM2 families need to be adapted.

Myotonic dystrophy type 2 (DM2) is a dominantly inherited multisystem disease caused by a cytosine-cytosine-thymine-guanine (CCTG) repeat expansion in intron 1 of the *CNBP* gene on chromosome 3q21.3.[1] The disease is characterized by progressive proximal muscle weakness, myotonia, early-onset cataracts, and multiorgan involvement. In contrast to myotonic dystrophy type 1 (DM1), congenital or childhood forms are very rare. Recently, 2 cases of presumed congenital DM2 have been reported.[2,3]

We report a family with 4 genetically confirmed DM2 patients, including an 8-year-old girl with DM2 and congenital pes planovalgus and equinus. We highlight the association of DM2 and congenital foot deformities and the possible anticipation with maternal transmission.

Case Summary

Family

The girl's mother and grandmother were diagnosed with DM2 at age 32 and 62 years, respectively, before the index case. They both had typical DM2 manifestations: proximal weakness, pain, and myotonia. The family history was negative for foot deformities, and the mother did neither smoke nor use selective serotonin reuptake inhibitors. The grandmother has had cataract surgery and cholecystectomy.

Index Patient

The girl was age 8 years at the time of last follow-up. Prenatal genetic testing (chorionic villi sampling) had confirmed DM2. Pregnancy and a term delivery were normal (1-minute Apgar score 9, birth weight 3,295 g). Two weeks after birth, the mother and baby girl visited the general practitioner because of the child's crying when her right leg was pulled during diaper changes. The symptoms were treated conservatively, and she started walking at 14 months. One month later, she was referred to an orthopedic surgeon because of persistent pain in the right foot and difference in foot size. Examination showed right pes planovalgus and equinus. The

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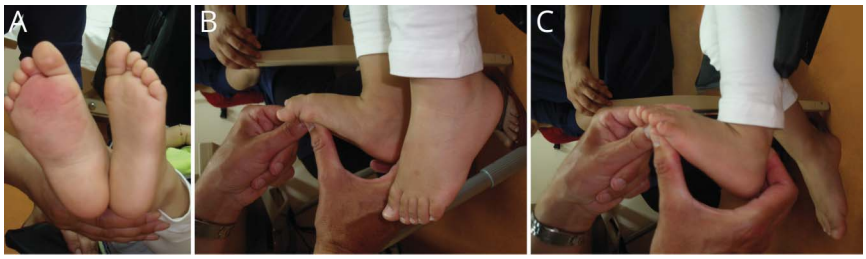
Figure 1 Foot Deformities in the 2-Year-Old Girl



(A) Pes planovalgus right. (B and C) Pes equinus right, a 15° reduction in dorsiflexion right compared with the left (healthy) side. The literature suggests that the normal range of motion (ROM) for ankle joint dorsiflexion is 0°–16.5° by standard non–weight-bearing method.[10] We used, however, the ROM of the opposite, healthy side as an indicator of normal ROM for ankle joint dorsiflexion, as also has been reported in the literature.[11]

right foot was larger and wider, and dorsiflexion was limited (Figure 1). A foot x-ray showed no osseous abnormalities. At the age of 24 months, quantitative muscle ultrasound showed normal echo intensity and muscle diameter and electromyography showed no abnormalities. Conservative treatment by semiorthopedic shoes with arch support was prescribed, and physical therapy was started. Six years after presentation, the girl shows normal motor development, except for difficulty with sports because of pain in the foot.

The CCTG repeat in intron 1 of the *CNBP* gene was analyzed by fragment length analysis of repeat-primed PCR and of long-range PCR with Southern blotting. The index patient, her mother, maternal uncle, and grandmother had a pathogenic CCTG expansion varying from 250 to over 2,000 repeats in each patient (Figure 2).

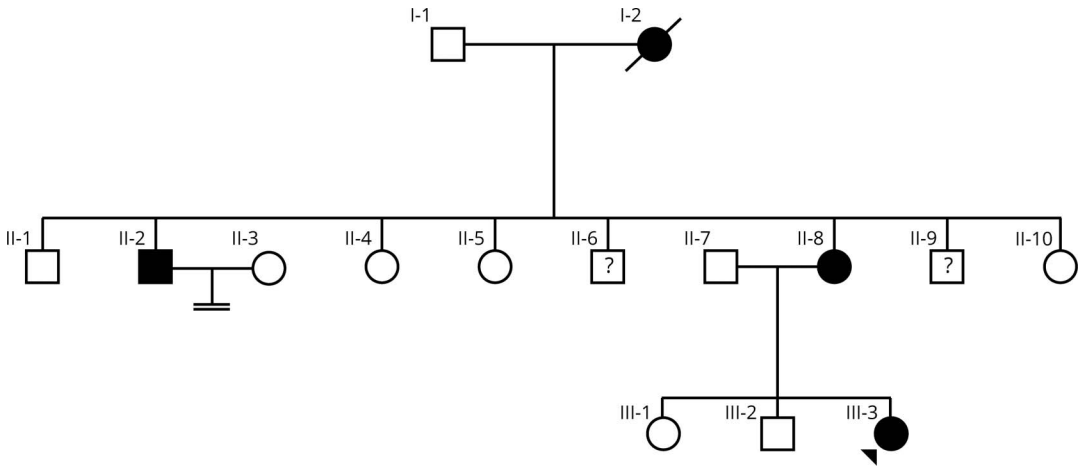
Discussion

We reported a girl with DM2 and unilateral congenital pes planovalgus and equinus. DM2 was confirmed by the detection of a CCTG expansion varying from 250 to over 2,000 repeats and inherited maternally.

Our observation is in line with 2 previously reported DM2 cases. Kruse et al.[2] reported a 2-year-old boy with unilateral congenital pes equinus, neonatal generalized hypotonia, and delayed motor and cognitive development. Molecular analysis revealed a CCTG repeat size of 2,500 repeats for the boy and the mother. Renard et al.[3] described a 2.5-year-old girl with DM2 and congenital bilateral talipes equinovarus (clubfoot), which were already detected by prenatal ultrasound. Corrective foot surgery was performed. Molecular analysis revealed a CCTG repeat size of 85 and 88 for the girl and the mother, respectively. A recent retrospective study on pregnancy in DM1/2 included 1 newborn with talipes equinovarus out of the first pregnancies in women with DM2 (n = 22).[4] This newborn was not genetically tested for DM2.[4]

These previous reports together with our case suggest a higher prevalence than expected based on the rarity of these foot deformities. Among Caucasians, the incidence of talipes equinovarus is approximately 1 per 1,000 live births.[5] In the, to date,

Figure 2 Pedigree



Individuals with DM2 are depicted by the black symbols. DM2 = myotonic dystrophy type 2.

worldwide number of 1,500 patients with DM2, the extrapolated incidence of talipes equinovarus would be 1.5.[6] The incidence of congenital pes equinus is, to our knowledge, unknown in the literature. Based on the above cases, a causal relation between congenital foot deformities and DM2 seems likely and would need a larger study. The phenotypic differences among the family members might also be explained by variable expressivity.

Foot deformities are also observed in DM1. In a retrospective study, 17 congenital and 4 adult-onset DM1 patients with orthopedic disorders were reported (n = 21).[7] In 20 patients, foot deformities were reported; the equines deformity was most common.

Clinical anticipation in DM2 was first mentioned by Schneider et al.[8] Congenital manifestations were not observed yet. In contrast to other repeat diseases, e.g., DM1[9] and Huntington disease, clinical anticipation was not associated with an increase of the repeat expansion in the DM2 cases described so far. Remarkably, transmission in all cases of congenital foot deformities was maternal.

We here suggest the existence of congenital DM2 because of anticipation on maternal transmission. The occurrence of a congenital form of DM2 would widen the spectrum of DM2 and has implications for clinical practice. Exclusive maternal origin in the transmission of DM2 to the congenital form needs further examination in a large number of families.

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