



Module 4

What clinical phenotypes are seen in myotonic dystrophy type 1 (DM1)?



Module summary



DM1 presents with varying disease phenotypes across the age continuum¹⁻³

Phenotypes can be categorized as congenital, childhood, adult, or mild/late-onset adult DM1^{1-3}*



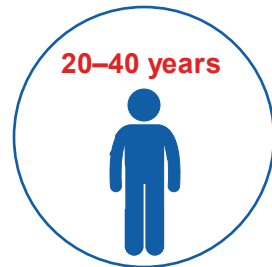
Congenital DM1 is the most severe form of DM1 and age at symptom onset is <1 month^{1,2,4,5}

Newborns typically have complications including hypotonia, immobility, weak cry, respiratory and cognitive difficulties, and EDS^{2,3,5,6}



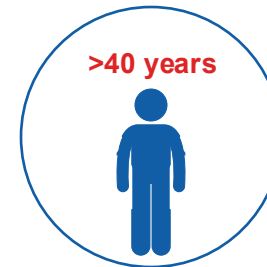
In childhood DM1, age at symptom onset is 1 month–20 years¹

Children present with subtle facial weakness, cognitive defects, intellectual impairment, psychosocial issues, and incontinence²



In adult DM1, age at symptom onset is 20–40 years¹

Around 75% of individuals develop symptoms in their 2nd–4th decade of life, presenting with highly variable features and multi-organ involvement^{4,7}



Mild/late-onset DM1 can occur anytime >40 years of age, and individuals may have fully active lives^{1,3}

Individuals often present with mild myotonia, muscle weakness, and cataracts^{1,2}

*There is currently no standard on the classifications of DM1.

DM1, myotonic dystrophy type 1; EDS, excessive daytime sleepiness.

1. De Antonio M, et al. *Rev Neurol (Paris)*. 2016;172:572–580; 2. Ho G, et al. *World J Clin Pediatr*. 2015;4:66–80; 3. Bird TD. Myotonic Dystrophy Type 1. 1999 Sep 17 [Updated 2021 Mar 25]. In: Adam MP, Eveman DB, Mirzaa GM, et al., editors. *GeneReviews*® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2022; 4. Wenninger S, et al. *Front Neurol*. 2018;9:303; 5. Barbe L, et al. *Am J Hum Genet*. 2017;100:488–505; 6. Lanni S, Pearson CE. *Neurobiol Dis*. 2019;132:104533; 7. Thornton CA. *Neurol Clin*. 2014;32:705–719.

How do clinical phenotypes vary within DM1?

Phenotype*	Age of onset	Clinical manifestations ^{1,2}	Life expectancy
Congenital DM1^{1,2}	<1 month ¹	• Hypotonia • Respiratory distress • Cognitive defects • Motor and developmental delays • Feeding difficulties	45 years [†] (30–40% mortality rate within neonatal period) ²
Childhood DM1¹	1 month–20 years ¹	• Facial weakness • Cognitive defects • Psychosocial issues • Incontinence	~60 years ^{2†}
Adult DM1^{1–3}	20–40 years ¹	• Myotonia • Muscle weakness • Cognitive defects • Cataracts • Conduction defects • Insulin resistance • Respiratory failure	Up to 55 years ³
Late-onset DM1^{1–3}	>40 years ¹	• Mild myotonia • Cataracts	60 years to normal ³

DM1 presents with varying disease phenotypes across the age continuum^{1–3}

*There is currently no standard on the classifications of DM1. †Mean.

DM1, myotonic dystrophy type 1.

1. De Antonio M, et al. *Rev Neurol (Paris)*. 2016;172:572–580; 2. Ho G, et al. *World J Clin Pediatr*. 2015;4:66–80; 3. Bird TD. Myotonic Dystrophy Type 1. 1999 Sep 17 [Updated 2021 Mar 25]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. *GeneReviews*® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2022.

What are the key features of **congenital DM1**?

Molecular pathology	Clinical presentation	Morbidity	Mortality
 <i>DMPK</i> CTG repeat expansion size $\geq 1,000$ almost always due to maternal transmission^{1–3} - Triphasic disease course: severe, global spliceopathy at birth, followed by period of improvement despite large CTG expansions. In adolescence, some maintain improved spliceopathy and others revert to severe spliceopathy⁴	 - Prenatal symptoms include polyhydramnios and reduced fetal movement⁵ - Neonates are often born preterm with the following distinct complications: hypotonia, immobility, bilateral talipes, contractures, arthrogryposis, facial dysmorphism, hyporeflexia, weak cry, sucking, respiratory and cognitive difficulties, and EDS^{2,3,5,6} - Neonatal symptoms may improve and stabilize, then progress during young adulthood^{3,4} - Intensive intervention at birth is commonly required⁷	 - Surviving infants can initially experience gradual improvements in motor function and reach motor and cognitive milestones with some delay; strength typically remains stable until adolescence, when deterioration becomes evident^{1,3} - In young adults, rapid, increasing muscle weakness may occur³	 30–40% mortality rate within the neonatal period³ - The average life expectancy is 45 years³ - Mortality from respiratory failure is common⁶

Congenital DM1 is the most severe form of DM1 and age at symptom onset is <1 month.^{1–3,8}
Neonates are often born preterm with distinct neuromuscular, respiratory, and cognitive complications^{2,3,5,6}

CTG, cytosine–thymine–guanine; DM1, myotonic dystrophy type 1; DMPK, dystrophin myotonia protein kinase; EDS, excessive daytime sleepiness.

1. Wenninger S, et al. *Front Neurol*. 2018;9:303; 2. Barbe L, et al. *Am J Hum Genet*. 2017;100:488–505; 3. Ho G, et al. *World J Clin Pediatr*. 2015;4:66–80; 4. Hale MA, et al. *Hum Mol Genet*. 2023;32:1413–1428; 5. Lanni S, Pearson CE. *Neurobiol Dis*. 2019;132:104533; 6. Bird TD. Myotonic Dystrophy Type 1. 1999 Sep 17 [Updated 2021 Mar 25]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2022; 7. Johnson NE, et al. *Neurol Clin Pract*. 2019;9:443–454; 8. De Antonio M, et al. *Rev Neurol (Paris)*. 2016;172:572–580.

What are the key features of **childhood DM1**?

Molecular pathology	Clinical presentation	Morbidity	Mortality
 • <i>DMPK</i> CTG repeat expansion size of >800^{1,2}	 • Children present with subtle facial weakness, cognitive defects, intellectual impairment, psychosocial issues, and incontinence² • Neurocognitive symptoms typically present prominently at around the age 10, and may be recognized earlier than muscular symptoms¹ • Juveniles may show typical muscular and non-muscular symptoms of adult-onset DM1 (distal weakness, clinical myotonia, cardiac or GI symptoms)¹	 • Children (aged 1–10 years) may have relatively normal motor development early on, and the age of occurrence of the first clinical signs is variable^{1,2} • Juveniles (aged 10–20 years) gradually progress to the adult phenotype, with individuals developing muscular and non-muscular symptoms such as muscle weakness and myotonia, GI symptoms, and cardiac involvement, while retaining the neurocognitive symptoms developed in childhood^{1,2}	 • Average life expectancy of ~60 years²

In childhood DM1, age at symptom onset is 1 month–20 years, and individuals present with subtle facial weakness, cognitive defects, intellectual impairment, psychosocial issues, and incontinence^{2,3}

What are the key features of adult DM1?

Molecular pathology	Clinical presentation	Morbidity	Mortality
 <i>DMPK</i> CTG repeat expansion size of 50–1,000^{1–3}	 - Around 75% of individuals develop symptoms in their 2nd–4th decade of life,⁴ presenting with highly variable features and multi-organ involvement³ - Adult-onset DM1 is often characterized by a combination of symptoms, including facial weakness, ptosis, grip myotonia, and distal muscle weakness with atrophy, cognitive impairment, cataracts, diabetes mellitus, fatigue, EDS, GI disturbances, and cardiac conduction symptoms^{1–3}	 - Muscle weakness is reported by >45% of individuals with the adult DM1 phenotype³ - Chronic respiratory impairment is the primary cause of morbidity⁵	 - Death typically occurs by 65 years of age^{6,7} - Chronic respiratory impairment is the primary cause of mortality⁵

In adult DM1, age of symptom onset is 20–40 years, and presentation is highly variable^{1,3}

CTG, cytosine–thymine–guanine; DM1, myotonic dystrophy type 1; *DMPK*, dystrophin myotonia protein kinase; EDS, excessive daytime sleepiness; GI, gastrointestinal.
1. De Antonio M, et al. *Rev Neurol (Paris)*. 2016;172:572–580; 2. Ho G, et al. *World J Clin Pediatr*. 2015;4:66–80; 3. Wenninger S, et al. *Front Neurol*. 2018;9:303; 4. Thornton CA. *Neurol Clin*. 2014;32:705–719; 5. MDF. Consensus-based Care Recommendations for Adults with Myotonic Dystrophy Type 1. Accessed February 14, 2025. https://www.myotonic.org/sites/default/files/pages/files/MDF_Consensus-basedCareRecsAdultsDM1_1_21.pdf; 6. de Die-Smulders CE, et al. *Brain*. 1998;121:1557–1563; 7. Bird TD. Myotonic Dystrophy Type 1. 1999 Sep 17 [Updated 2021 Mar 25]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. *GeneReviews*® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2022.

What are the key features of mild/late-onset DM1?

Molecular pathology	Clinical presentation	Morbidity	Mortality
 • <i>DMPK</i> CTG repeat expansion size of 50–150^{2,3}	 • Symptoms generally include mild myotonia, muscle weakness, and cataracts^{1,2}	 • May have fully active lives⁴	 • Life expectancy for mild DM1 is 60 years to a normal life span⁴

Mild/late-onset DM1 can occur anytime >40 years of age, usually presenting with mild myotonia, muscle weakness, and cataracts^{1,2}

CTG, cytosine–thymine–guanine; DM1, myotonic dystrophy type 1; *DMPK*, dystrophin myotonia protein kinase.

1. De Antonio M, et al. *Rev Neurol (Paris)*. 2016;172:572–580; 2. Ho G, et al. *World J Clin Pediatr*. 2015;4:66–80; 3. Wenninger S, et al. *Front Neurol*. 2018;9:303;

4. Bird TD. Myotonic Dystrophy Type 1. 1999 Sep 17 [Updated 2021 Mar 25]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. *GeneReviews*® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2022.