Nemaline Myopathy: A Clinical Study of 143 Cases

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We report 143 Australian and North American cases of primary nemaline myopathy. As classified by the European Neuromuscular Centre guidelines, 23 patients had severe congenital, 29 intermediate congenital, 66 typical congenital, 19 childhood-onset, and 6 adult-onset nemaline myopathy. Inheritance was autosomal recessive in 29 patients, autosomal dominant in 41, sporadic in 72, and indeterminate in 1. Twenty-two patients had skeletal muscle actin mutations and 4 had mutations in the α-tropomyosin$_{SLOW}$ gene. Obstetric complications occurred in 49 cases. Seventy-five patients had significant respiratory disease during the first year of life, and 79 had feeding difficulties. Atypical features in a minority of cases included arthrogryposis, central nervous system involvement, and congenital fractures. Progressive distal weakness developed in a minority of patients. Thirty patients died, the majority during the first 12 months of life. All deaths were due to respiratory insufficiency, which was frequently underrecognized in older patients. Arthrogryposis, neonatal respiratory failure, and failure to achieve early motor milestones were associated with early mortality. Morbidity from respiratory tract infections and feeding difficulties frequently diminished with increasing age. Aggressive early management is warranted in most cases of congenital nemaline myopathy.

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Nemaline myopathy (NM) is an uncommon disorder defined by the presence in muscle fibres of inclusions known as nemaline bodies or rods (Greek *nema* = thread). In most cases, muscle weakness and hypotonia are apparent from the neonatal period or infancy; but fetal, childhood-onset, and adult-onset forms are also recognized.[1] The existing classification defines severe, intermediate, and typical congenital subtypes and forms with onset in childhood and adulthood.[2,3] Previous series have included no more than 22 patients with NM and do not reflect clinical heterogeneity in this disorder.

Mutations in five genes have been identified in NM: α-tropomyosin$_{SLOW}$ *(TPM3)*,[4] nebulin *(NEB)*,[5] α-actin *(ACTA1)*,[6] β-tropomyosin *(TPM2)*,[7] and troponin T1 *(TNNT1)*.[8] These genes encode for protein components of muscle thin filaments. The relative frequency of these causative mutations is unknown. Inheritance is variable. Both autosomal dominant and autosomal recessive families have been identified with mutations in *TPM3*,[9,10] and *ACTA1*.[6] Mutations in *TPM2* have been described only in autosomal dominant families.[7] All mutations identified in *NEB* and *TNNT1* are inherited in an autosomal recessive fashion.[5,8]

We report clinical findings in 143 cases of NM identified by two research centers, in Australia and North America. Clinical phenotypes and inheritance patterns are defined. We also include genotypic characterization of the series, prognostic indicators for outcome and survival, and a review of the current classification.

Patients and Methods

NM was defined by the European Neuromuscular Centre criteria.[1] Australian cases were identified through hospitals and pathology services in New South Wales, Victoria, Queensland, South Australia, Western Australia, and Australian Capital Territory. Consent for access to medical records and pathology specimens was obtained from all patients'

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physicians. The study was approved by the Research Ethics Committees of all involved hospitals.

North American cases were identified through a research laboratory at Children's Hospital (Boston, MA) using the HELIX online directory (www.genetests.org) and referrals from North American neuromuscular clinics. Informed consent was obtained from patients or their parents in all cases.

Clinical data were obtained from medical records. Patients were grouped according to the existing classification system (Table 1), with the following exceptions: neonates with joint contractures were not classified as having severe congenital disease unless other inclusion criteria were met; we did not exclude patients with cardiac disease, foot drop, or intranuclear nemaline bodies; and facial weakness was not regarded as an exclusion criterion for childhood-onset NM.

Inheritance was defined as likely autosomal recessive in families with 2 or more affected siblings and clinically normal parents, even where parents had not undergone electromyography and/or muscle biopsy. Cases were classified as likely autosomal dominant when there was a suggestive parental phenotype with or without biopsy-proven disease. Where there was no family history of neuromuscular disease, no consanguinity, and no clinically affected first-degree relatives, cases were classified as sporadic.

Where possible mRNA was extracted from muscle biopsies or DNA from blood samples, and patients were analyzed for α-tropomyosin$_{SLOW}$ *(TPM3)* mutations using single-strand conformational polymorphism analysis or direct sequencing of polymerase chain reaction (PCR) products (methodology of Laing et al[4]). Patients were screened for mutations in α-actin *(ACTA1)* by sequencing of PCR products from exon 2 to 7 of genomic DNA (methodology of Nowak et al[6]). DNA isolated from over 100 individuals served as controls. Where available, parental DNA samples were also screened.

Results

We identified 162 cases (71 Australian, 91 North American). Thirteen were excluded because of insufficient clinical data or failure to obtain consent for inclusion. Six were excluded because the biopsy finding of nemaline bodies was felt to be a secondary phenomenon. The primary diagnoses in these cases were glycogen storage disease type IV (2 patients), polymyositis, facioscapulohumeral dystrophy, poststreptococcal vasculitis, and human immunodeficiency virus myopathy. This series therefore includes 143 cases, 3 previously reported by Laing and colleagues[10] and 7 by Nowak and colleagues.[6]

Clinical Presentation

CONGENITAL ONSET. Sixty-nine patients presented in the neonatal period. Obstetric complications occurred in 35 cases (51%), including polyhydramnios (29%), decreased foetal movements (39%), and abnormal presentation or foetal distress (49%). Fourteen infants were delivered prematurely.

Table 1. Clinical Classification: Nemaline Myopathy

	Inclusion Criteria	Exclusion Criteria
Severe congenital NM	No spontaneous movements neonatally No spontaneous respiration neonatally Contractures at birth Fractures at birth	Cardiomyopathy Ophthalmoplegia
Intermediate congenital NM	Infantile onset Breathing and moving at birth Inability to maintain respiratory independence after early childhood Failure to sit or walk independently Use of wheelchair before 11 years Contractures developing in early childhood	Cardiomyopathy Ophthalmoplegia
Typical congenital NM	Onset in infancy or early childhood Weakness most pronounced in facial, bulbar, and respiratory muscles and neck flexors Weakness initially primarily proximal Late distal involvement Milestones delayed but reached Slowly progressive/nonprogressive course	Contractures or fractures at birth Failure to sit or walk independently Use of wheelchair before 11 years Cardiomyopathy Ophthalmoplegia Unusual distribution of weakness
Childhood-onset NM	Childhood or juvenile onset No facial weakness	Cardiomyopathy Ophthalmoplegia
Adult-onset NM	Adult onset	
Other forms	Cardiomyopathy Ophthalmoplegia	

Modified from Wallgren-Pettersson and colleagues, 1999[2], and Wallgren-Pettersson and Laing, 1999.[3]

Most infants (91%) were hypotonic at birth, with generalized muscle weakness; 26% had no spontaneous antigravity movement, and 52% were areflexic. Facial weakness was apparent in all but 3 patients. None had ophthalmoplegia.

ONSET AFTER THE NEONATAL PERIOD. Sixty-five cases presented in childhood (28 days to 18 years) and 9 in adulthood. Diagnosis was frequently delayed for years after disease onset. Younger patients most commonly presented with delayed motor milestones, whilst older children complained of gait abnormalities and poor exercise tolerance. A small number of children presented with dysarthria, scoliosis, or acquired contractures. Four parents were diagnosed after the identification of NM in their more severely affected offspring.

Muscle weakness in this group was most commonly proximal. Eight patients, including 3 from the kindred previously described by Laing and colleagues,[10] had distal involvement at presentation. All but 9 patients (5 of whom had childhood-onset NM) had facial diplegia. None had ophthalmoplegia. Deep tendon reflexes were lost or depressed in all but 2 cases.

Six patients had adult-onset NM, presenting at 41 to 59 years of age. Four were symptomatic for up to 20 years prior to diagnosis. Two presented with weakness and fatigability and 4 with myalgia. All had mild facial and proximal weakness.

Clinical findings are summarized in Table 2. In some cases, classification was made retrospectively, based on achievement of motor milestones in the second 6 months of life.

Clinical Course

RESPIRATORY INVOLVEMENT. Seventeen of 23 infants from the severe congenital group died of respiratory insufficiency (Table 3). Twelve were ventilator-dependent from delivery until death. Two of the 6 surviving infants required mechanical ventilation from the first few months of life.

Eight of 29 patients from the intermediate congenital group died, 6 of chronic respiratory failure, 1 child having received ventilatory support from the age of 2 weeks. Two children died after aspiration despite previously mild pulmonary disease.

Of 21 surviving patients, 11 were ventilator-dependent for up to 14 years. Nine required 24-hour ventilatory support, 2 receiving only nocturnal ventilation. Eight children had recurrent pneumonia early in life, with a diminution in the frequency and severity of infections after 12 months of age. Two patients had minimal respiratory involvement.

Sleep studies were abnormal in all 4 children, 3 having central hypoventilation and 1 mixed central and obstructive apnea.

Forty-two of 66 patients with typical congenital NM had no or minimal respiratory involvement. Fifteen patients had recurrent pneumonia or abnormal pulmonary function tests [forced vital capacity (FVC) and/or forced expiratory volume in 1 second (FEV_1) <60% predicted]. In 11 cases, the frequency of chest infections decreased with increasing age; in some instances, this could be correlated with discontinuation of oral feeding.

Nine patients had severe lung disease. Three died of progressive respiratory failure. One died after acute re-

Table 2. Clinical Findings in Nemaline Myopathy

	Severe Congenital (n = 23)	Intermediate Congenital (n = 29)	Typical Congenital (n = 66)	Childhood-Onset (n = 19)	Adult-Onset (n = 6)
Presentation <28 days of age	23	27	19	0	0
Presentation after 28 days of age	0	2	47	19	6
Obstetric complications	12	18	17	2	0
AMC	8	1	0	0	0
Neonatal hypotonia	23	22	18	0	0
Delayed motor milestones	23	26	27	0	0
Incoordinate swallow	23	25	31	1	0
Significant respiratory symptoms	23	28	25	0	0
Outcome	17 died (1d–1.3y), 6 alive (1m–5.9 y)	8 died (2w–2.9 y), 21 alive (8m–17y)	4 died (6–19y), 62 alive (0.8–68y)	1 died (46y), 18 alive (8–62y)	6 alive (42–74y)

AMC = arthrogryposis multiplex congenita (congenital contractures of 3 or more joints); d = day; w = week; m = month; y = year.

Table 3. Respiratory Disease in Congenital Nemaline Myopathy

	n	Early Respiratory Distress[a]	Ventilated				
			<4w of Age	4w–1y of Age	>1y of Age	Only for LRTIs	Never
Severe congenital							
Deceased	17	17	12 (1d–4w)			2 (0.6–1.1y)	3 (0.5–1.3y)
Surviving	6	6	1 (12m)	1 (1.7y)			4 (1–5.9y)
Intermediate congenital							
Deceased	8	5	1 (2m)			2 (0.6–0.8y)	5 (0.2–2.9y)
Surviving	21	9	1 (4m)	3 (12–14y)	8 (2.5–17y)	1 (0.7y)	8 (3.2–13y)
Typical congenital							
Deceased	4	1			1 (19y)	1 (13y)	2 (6–16y)
Surviving	62	19	1 (5.5y)	1 (1.3y)	2 (2.3–2.5y)	1 (1.3y)	57 (0.8–68y)

[a]Oxygen requirement, persistent tachypnea, or recurrent apnea during first 4 weeks of life. In parentheses, age at death or when last seen.
LRTIs = lower respiratory tract infections.

spiratory decompensation following scoliosis repair. Three of the 5 surviving patients required nocturnal ventilation.

Pulmonary function tests were abnormal in 11 of 12 patients studied. Progressive deterioration occurred in 5 of the 7 patients tested serially. In 5 cases, there were significant abnormalities (FVC and/or FEV_1 <60%) in patients with no symptoms of respiratory disease. Sleep studies revealed obstructive sleep apnea in 3 of 5 patients studied.

Sixteen of 19 patients in the childhood-onset group had no respiratory disease. In adulthood, 1 developed restrictive lung disease, 1 asthma, and 1 died of adult respiratory distress syndrome following multiple strokes.

One of 6 patients in the adult-onset group had longstanding asthma which remained stable after development of her myopathy.

GASTROINTESTINAL INVOLVEMENT. Food intolerance necessitated gavage feeds and gastrostomy with or without fundoplication in 26% of patients, all of whom had congenital NM. Gastroesophageal reflux was proven in a minority of those investigated with pH probe or barium studies. Two infants with congenital NM required surgery for pyloric stenosis. A single patient with childhood-onset NM developed achalasia and chronic upper gastrointestinal tract pseudoobstruction in adulthood.[10]

Few details regarding growth were recorded in most cases, but failure to thrive (height and weight under the third percentiles for age) occurred in 16 cases. It was unclear whether this was related to poor intake or chronic illness.

BULBAR DYSFUNCTION. Bulbar dysfunction was common in congenital NM and resulted in significant speech delay and dysarthria, excessive drooling, and aspiration of oral secretions.

CARDIAC DISEASE. Six neonates developed transient congestive cardiac failure: 1 with severe congenital NM, 4 with intermediate congenital disease, and 1 with typical congenital NM and valvular pulmonary stenosis.

Symptomatic cardiac disease after the neonatal period was seen in only 2 cases. An infant with congenital long QT syndrome developed progressive ventricular dysfunction after recurrent episodes of torsades de pointes, and an adolescent with severe respiratory disease developed cor pulmonale months before his death. Both patients had typical congenital NM.

Electrocardiographic abnormalities were identified in 22 of 50 patients (44%) from all subgroups and included increased right atrial and ventricular voltages and right bundle branch block. Structural abnormalities included patent ductus arterioses (4 patients) and pulmonary stenosis (1 patient). Three patients had pulmonary hypertension and 4 decreased cardiac contractility.

CENTRAL NERVOUS SYSTEM INVOLVEMENT. Five infants (3 with severe congenital and 2 with intermediate congenital NM) were unresponsive to the external environment during the neonatal period. Two had neonatal seizures. Neuroimaging was abnormal in 1 child with cerebral dysgenesis. No cause was identified in 4 cases.

Eight patients had seizures after the neonatal period. Computed tomography and magnetic resonance imaging of the brain were normal in these and 27 other cases. Neuroimaging was abnormal in 4 children: global cerebral atrophy, patchy white matter signal abnormalities, and delayed myelination were each seen in 1 and another had pachygyria and diffuse leukomala-

cia. On autopsy of the latter case, there was cortical thickening with neuronal necrosis, white matter degeneration and calcification, and abnormal myelination of the peripheral nerves with vacuolated periaxonal regions.

Electroencephalograms were normal in 12 of 22 children. Cognitive deficits were apparent in 12 patients.

ORTHOPEDIC INVOLVEMENT. Congenital fractures occurred in 7 infants with severe congenital NM, 3 of whom had generalized hypomineralization on skeletal survey. Another patient who, in all other respects, fitted into the typical congenital subgroup, had multiple congenital fractures. Fractures in later life occurred in 13 cases, often after minor trauma.

Nine infants presented at delivery with symmetrical contractures of three or more large joints. Seven infants had isolated hip dislocation and 8 had fixed varus deformities at the ankles. Scoliosis, most commonly at the thoracolumbar junction, developed in 33 children.

Anesthetics

One hundred and thirty patients underwent 1 or more surgical procedure. None developed malignant hyperthermia, but 5 developed unexpected postoperative respiratory failure (following scoliosis repair in 4 and fundoplication in 1), necessitating prolonged ventilation in 3 patients and resulting in the death of another.

Atypical Features

Developmental anomalies occurred in isolated cases: hemifacial microsomia, bifid tongue, cleft palate, contraction band necrosis of the gut and genitourinary tract, and cerebral dysgenesis.

Other Investigations

Serum creatine kinase levels were elevated in only 4 of 50 patients tested. Nerve conduction studies were performed in 46 patients. Three neonates had nonspecific abnormalities. One child with distal weakness and pes cavus had findings consistent with a demyelinating polyneuropathy. She was adopted and no family history was available. Nerve biopsy revealed segmental demyelination and loss of myelinated fibres, whilst muscle biopsy demonstrated typical NM. Three adults had late-onset neuropathies, attributed in 2 cases to diabetes mellitus.

Electromyography was abnormal in 42 of 64 patients. Abnormal parameters (polyphasia, shortened action potential duration, and low amplitudes) were seen at similar frequency in proximal and distal muscle groups in all age groups. Only 2 patients had electromygraphic changes suggestive of denervation.

Outcome

Only 1 child with severe congenital NM walked (Table 4). In the intermediate congenital subgroup, no patients who died or required ventilation before 1 year of age achieved ambulation. Ten children demonstrated stable or improving motor function with increasing age. Three developed progressive distal weakness between 5 and 10 years of age.

In contrast, most patients with typical congenital NM walked, including those with fatal respiratory disease. Progressive distal weakness developed in 13 children late in the first decade and in 2 patients in adulthood.

All but 1 patient with childhood-onset NM remained ambulant. Slowly progressive weakness was seen in 9 cases and was predominantly distal in 6 pa-

Table 4. Motor Milestones

	n	Mean Age when Last Seen (Range)	Sat <9m	Sat >9m	Crawled <12m	Total Crawled	Walked <18m	Total Walked
Severe congenital								
Deceased	17	3m (1d–1.3y)	0	0	0	0	0	0
Surviving	6	2.8y (1m–5.9y)	0	1	0	1	0	1 (19m)
Intermediate congenital								
Deceased	8	12m (2w–2.9y)	0	3	0	0	0	0
Surviving	21	6.6y (0.3–17y)	3	12	2	13	2	13 (13–50m)
Typical congenital								
Deceased	4	13.5y (6–19y)	0	4	0	4	0	4 (30–42m)
Surviving	62	16.9y (0.8–68y)	19	42	13	49	24	48 (11–48m)
Childhood-onset								
Deceased	1	46y	1	0	1	1	1	1 (<18m)
Surviving	18	22.1y (8–62y)	18	0	18	18	18	18 (9–15m)
Adult-onset								
Surviving	6	54.3y (42–74y)	6	0	6	6	6	6 (<18m)

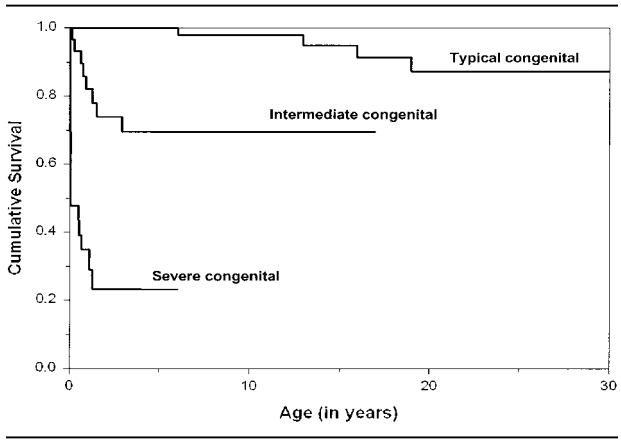

Fig. Analysis of cumulative survival probabilities graphed using the Kaplan-Meier method. Significant differences in survival between patients with severe, intermediate, and typical congenital nemaline myopathy ($p < 0.0001$ *in each instance*) *were identified by* χ^2 *analysis using the log-rank test.*

tients. All patients with adult-onset NM remained ambulant.

Analysis of cumulative survival probabilities (Fig) revealed significant differences in survival between patients with severe, intermediate, and typical congenital NM ($p < 0.0001$ in each instance).

Inheritance

Twenty-nine patients from 15 kindreds had autosomal recessive NM (Table 5). There was substantial variation in disease severity within 8 kindreds, despite presumed genotypic homogeneity.

Autosomal dominant inheritance was apparent in 41 patients from 22 kindreds, 1 of whom was previously described by Laing and colleagues.[10] In 2 families, asymptomatic parents had pathological changes of NM on muscle biopsy. Neither parent was included in this series. Marked intrafamilial phenotypic variability was again seen in autosomal dominant NM.

In 1 case of severe congenital NM, both clinically normal, unrelated parents had occasional nemaline bodies on muscle biopsy. It was unclear whether both were manifesting heterozygotes or whether one had subclinical dominant NM.

Four of 46 patients tested had mutations in the α-tropomyosin$_{SLOW}$ *(TPM3)* gene. One had sporadic typical congenital NM, whilst 3 were from the autosomal dominant family with childhood-onset NM described by Laing and colleagues.[10]

Twenty-two of 71 patients tested had mutations in the skeletal muscle α-actin gene *(ACTA1).*[6] Clinical presentation and course varied widely in these cases (Table 6), 7 of whom were reported by Nowak and colleagues.[6] Four autosomal dominant kindreds were identified. In 2 families, all affected members had typical congenital NM. In 2 others, 1 of which was previously described,[6] patients were variably affected with typical congenital and childhood-onset NM. The remaining 12 patients were sporadic cases with new dominant mutations in *ACTA1.*

No patient in this series has, as yet, been fully screened for nebulin or troponin T1 mutations. None of 16 patients screened had *TPM2* mutations.

Discussion

Previous clinical descriptions of NM are summarized in Table 7. Direct comparison with our series was hampered by variability in classification and patient ascertainment. Nevertheless, our results confirm trends identified in smaller series.

Prenatal expression of NM is reflected in its association with the foetal akinesia sequence[26] and the frequency of obstetric complications. Arthrogryposis multiplex congenita (9 patients) and congenital fractures (8 patients) have rarely been reported in NM.[23,27–31] Both probably reflect paucity of fetal movement.

In this series, mortality was invariably due to respiratory insufficiency. Ventilatory failure at delivery was associated with early death. Patients requiring respiratory support later in the first year of life survived but remained ventilator-dependent. Several patients with progressive respiratory failure who were not afforded respiratory support also died. Survival in congenital NM was therefore predicated on the severity of neonatal respiratory disease and, to a lesser extent, the provision of ventilatory support.

Motor outcome paralleled respiratory involvement. Patients requiring ongoing ventilatory support in the

Table 5. Nemaline Myopathy: Inheritance

	n	Sex	Sporadic	AR	AD	Indeterminate
Severe congenital	23	14M, 9F	16	6	1	
Intermediate congenital	29	16M, 13F	16	7	5	1
Typical congenital	66	34M, 32F	29	14	23	
Childhood-onset	19	6M, 13F	7	2	10	
Adult-onset	6	4M, 2F	4		2	
Total	143	74M, 69F	72	29	41	1

AR = autosomal recessive; AD = autosomal dominant.

Table 6. Nemaline Myopathy: Genetic Characterization

Phenotype	n Tested for *ACTA1* Mutations	*ACTA1* Mutations	n Tested for *TPM3* Mutations	*TPM3* Mutations
Severe congenital	17	4	11	—
Intermediate congenital	14	3	8	—
Typical congenital	31	12	19	1
Childhood-onset	9	3	8	3
Adult-onset	—	—	—	—
Total	71	22	46	4

first year did not walk, but 8 of 11 patients ventilated after 12 months of age were ambulant. In most children surviving the neonatal period, muscle weakness and pulmonary function remained stable or improved with increasing age. In a minority, however, subclinical respiratory disease was unmasked by aspiration, pneumonia, or anesthesia. Pulmonary function tests and sleep studies frequently revealed underestimated respiratory disease.

In a review of 14 patients and 85 cases from the literature, Martinez and Lake[17] identified neonatal hypotonia as the most important prognostic sign in NM. In our series, hypotonia and severe weakness were not predictive of early mortality. Ventilatory failure at delivery and arthrogryposis multiplex congenita were associated with death in the first year of life in all but one instance. In patients with these findings, provision of ongoing ventilatory support should be weighed against the poor prognosis.

Beyond the neonatal period, respiratory failure requiring ventilatory assistance did not predict mortality. Independent ambulation before 18 months of age was predictive of survival. In many patients, a stormy early course with frequent respiratory tract infections was followed by clinical stabilization. Aggressive management of pulmonary infections and feeding difficulties is warranted in most children with NM. Recurrent aspiration may be alleviated by the early institution of gastrostomy feeds. Baseline and follow-up pulmonary function testing should be performed where possible. Preoperative assessment of pulmonary function is essential, to ensure optimal timing of elective procedures.

Cardiac and central nervous system involvement occur rarely in NM.[28,30–37] In this series, cardiac failure

Table 7. Previously Reported Cases of Nemaline Myopathy (Including all English-language series of 3 or more patients)[a]

	Severe Congenital (n = 15)	Severe/ Intermediate Congenital (n = 17)	Intermediate Congenital (n = 11)	Intermediate/ Typical Congenital (n = 4)	Typical Congenital (n = 66)	Childhood-Onset (n = 14)	Adult-Onset (n = 4)
Obstetric complications	5	1	3	0	3	0	0
AMC[b]	11	0	0	0	2	0	0
Neonatal hypotonia	15	11	10	4	40	0	1
Delayed motor milestones	5	6	10	4	51	0	0
Incoordinate swallow	5	8	5	4	7	1	1
Significant respiratory symptoms	6	7	9	4	16	2	0
Ventilated	7	5	7	1	3	0	0
Outcome	13 died (1d–4m), 2 alive (9m–2y)	5 died (6w–22m), 6 alive (13m–9y), 6 NS	4 died (2d–11m), 7 alive (18m–16y)	2 died (<1y), 2 alive (>1y)	3 died (7m–15y), 50 alive (1.1–55y), 13 NS	1 died (46y), 13 alive (9–55y)	1 alive (26y), 3 NS

[a]Includes references 10 (10 patients, 3 included in the present study), 11 (5), 12 (4), 13 (3), 14 (3), 15 (10), 16 (4), 17 (14), 18 (3), 19 (13), 20 (12), 21 (22), 22 (4), 23 (8), 24 (4), 25 (3), and 26 (9).

[b]AMC = arthrogryposis multiplex congenita (congenital contractures of three or more joints). Patients with AMC otherwise meeting diagnostic criteria for typical congenital nemaline myopathy have been classified as typical congenital.

NS = not stated.

was probably secondary to respiratory disease and pulmonary hypertension. NM has not previously been associated with the long QT syndrome, although other arrhythmias have been attributed to conducting system infiltration by nemaline bodies.[37] Neonatal encephalopathy, as seen in 5 patients in this series, has been described previously in NM[30] and may be related to unrecognized hypoxic–ischemic injury in infants with respiratory failure. The combination of cerebral dysgenesis and NM in one infant is likely secondary to an unidentified primary condition.

Classification of Nemaline Myopathy

Clinical classification of NM is predicated on respiratory function, severity and distribution of weakness, and achievement of motor milestones. We found patients with severe congenital disease to represent a definable subgroup with poor outcome. However the distinction between intermediate and typical forms of NM could often be made only in retrospect. No single parameter separated these subsets in infancy, although survival differed significantly between the 2 groups. Children could be predicted to have typical congenital disease if they crawled before 12 months and walked before 18 months of age. Congenital contractures occurred in several forms of NM. In some patients with childhood-onset NM, undetected mild motor delay may have caused misclassification of typical congenital disease, but similarities in course in the 2 groups render the distinction of dubious significance. Facial weakness and late evolution of distal weakness occurred in both groups. There was also marked overlap between the childhood- and adult-onset forms of NM.

Genetics of Nemaline Myopathy

Neonatal presentation of NM has been reported in autosomal recessive cases related to mutations in nebulin[2,5] and tropomyosin[9] and to dominantly inherited actin mutations.[6] Childhood-onset disease has been seen with both dominant tropomyosin and actin mutations.[6,10] Families with autosomal recessive and autosomal dominant disease were identified in all but the adult-onset subgroups in this study. Considerable intrafamilial variation in course and outcome was apparent. Disease severity cannot be used to predict mode of inheritance in NM. The frequencies of new mutations and of germline mosaicism in this disease are unknown, although new dominant mutations appear to be common in *ACTA1*.[6] The 72 sporadic cases in this series likely represent instances of autosomal recessive inheritance and new dominant mutations.

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