Pediatric Neuromuscular Disorders: Clinical Assessment

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Definition

- Neuromuscular disorders are characterized by the **anatomic localization of the pathology within the motor unit.**

- The motor unit consists of the:

  1) **Motor neuron** within the ventral horn of the spinal cord and brainstem motor nuclei (**Neuronopathy**)

  2) **Peripheral nerve (Neuropathy)**

  3) **Neuromuscular junction (N.M.J disorders)**

  4) **Muscle (Myopathy)**

Disorders of muscle are subdivided into **six categories** based upon histopathology features on muscle biopsy:

- **1. Dystrophies** (degenerative disorders of the muscle fiber)
- **2. Congenital myopathies** (structural abnormality of the muscle fiber or extracellular collagen matrix)

- **3. Metabolic disorders** affecting muscle (storage diseases, energy processing disorders)

  4. Mitochondrial diseases (energy generation or utilization)

  5. Inflammatory myopathies (idiopathic)

  6. Infectious myositis (bacterial, viral, protozoan)

Epidemiology

- The point prevalence was 1 in 1600 children overall, and **1 in 1900 for genetically based disorders.** This indicates that about 84% of neuromuscular disorders in this cohort had a **genetic basis**, and only about 16% had an acquired etiology
- The **most commonly** encountered pediatric neuromuscular disorders, in descending order of prevalence, are **DMD, CMT disease, congenital myopathies, myotonic dystrophy, SMA,…**

Classification of Pediatric Neuromuscular Disorders

Acquired Etiology	*Disorder*	*Features*	*Gene*	*Protein*
			Genetic Etiology	
Motor Neuron				
Infection: Polio West Nile virus Enterovirus	SMA SMA with respiratory distress (SMARD) SMA, X-linked SMA, lower extremity predominant		*SMN1* *IGHMBP2* *UBA1* *TRPV4*	Survival of motor neuron 1 Immunoglobulin mu binding protein 2 Ubiquitin-activating enzyme 1 Transient receptor potential cation channel, subfamily V, member 4
Peripheral Nerve				
AIDP (Guillain-Barre syndrome)	CMT type 1, AD, demyelinating	6 main types e.g. CMT1A	13 genes e.g. *PMP22*	Peripheral myelin protein 22
CIDP	CMT type 2, AD, axonal	22 subtypes e.g. CMT 2A	22 genes e.g. MFN2	Mitofusin 2
Infection: Tick paralysis Lyme disease	CMT type 4, AR CMT, X-linked	6 types e.g. CMTX1	13 genes *GJB1*	Gap junction protein beta 1

Acquired Etiology	*Disorder*	*Features*	*Gene*	*Protein*
		Genetic Etiology		
Neuromuscular Junction				
Infantile botulism	CMS, slow channel	4 subtypes 3 subtypes	4 genes 3 genes	
Myasthenia gravis	CMS, fast channel			
Neonatal myasthenia gravis	CMS, acetylcholine receptor deficiency	3 subtypes	3 genes	
	Other specific phenotypes	17 subtypes	*RAPSYN, CHAT, CHRNE, DOK7, COLQ, MUSK, AGRN,* others	

Acquired Etiology	Disorder	Features	Gene	Protein
			Genetic Etiology	
Muscle				
	Muscular Dystrophy	DMD/BMD	*DMD*	Dystrophin
		EDD	*EMD*	Emerin
			FHL1	4½ LIM domain 1 lamin A/C
			LMNA	
		FSHD	*DUX4*	Double homeobox 4
		LGMDs	22AR and 8 AD forms	
	Congenital Muscular Dystrophy	Merosin deficient	*LAMA2*	Laminin alpha 2 chain of merosin
		Ullrich/Bethlem	*COL6A1, A2* and *A3*	Collagen type VI A1, A2, A3
		Rigid spine	*SEPN1*	Selenoprotein N1
			ACTA1	Alpha actin
		Defective glycosylation disorders	18 genes	e.g. FKRP
	Congenital Myopathy	Nemaline	10 genes	
		Congenital fiber type disproportion	5 genes	
		Myotubular	*MTM1*	Myotubularin
		Centronuclear	5 genes	
		Central core	RYR1 (also malignant hyperthermia gene)	Ryanodine receptor 1
		Distal Myopathy e.g. Miyoshi	*DYSF*	Dysferlin
	Myotonic Disorders	Myotonic dystrophy type 1	*DMPK*	Myotonic dystrophy protein kinase
		Myotonic dystrophy type 2	*CNBP*	Cellular nucleic acid binding protein
		Myotonia congenita	*CLCN1* (Thompson = AD, Becker = AR)	Chloride channel 1
		Paramyotonia congenita	*SCN4A* (also periodic paralysis)	Sodium channel, voltage-gated, type IV, alpha
		Schwartz-Jampel syndrome	*HSPG2*	Perlecan

	Disorder	*Features*	*Gene*	*Protein*
Acquired Etiology			**Genetic Etiology**	

	Disorder	*Features*	*Gene*	*Protein*
Acquired Etiology			**Genetic Etiology**	

	Metabolic Myopathy	Glycogen storage	10 genes	
		e.g. GSD type II (Pompe disease)	*GAA*	Alpha-glucosidase
		Glycolytic pathway	4 genes	
		e.g. GSD type V (McArdle disease)	*PYGM*	Muscle phosphorylase
		Lipid metabolism	12 genes	
		e.g. CPT type 2	*CPT2*	Carnitine palmitoyl-transferase II
Idiopathic Inflammatory Myopathy				
Dermatomyositis Polymyositis				
Infectious Myositis				

EVALUATION OF THE CHILD WITH A SUSPECTED NMD

- **Diagnosis is obvious** and needs only confirmation with a **definitive test**, for example, the classic infant with SMA or the boy with DMD.
- More often a **structured approach** is taken by the clinician to work through the diagnostic process.

- **Key Points:**
  - Presenting symptoms
  - gender
  - family history
  - age at symptom onset
  - rate of progression
  - other organ system involvement

- These clinical features will enable the clinician to:
- - **Localize the lesion within the neuroaxis**
- - **Develop a differential diagnosis**
- - **Strategize a plan for further evaluation**
- - **Consider treatment options**

TABLE 137-3 Localizing Clinical Features of Pediatric Neuromuscular Disorders

(Typical Features Are Listed, With an Example of a More Common Genetic and Acquired Disorder for Each Category)

Localization	Distribution and Features of Weakness	DTRs	Sensory Deficit	CNS	Other
Anterior Horn Cell	SMA: P > D	0	0	0	Fasciculations
	Polio: S or G	0	0	0	M pain
Peripheral Nerve	CMT: D > P	0	D > P	0	DA, pes cavus
	GBS: ascending	D:0 then G	D ±	0	Autonomic
Neuromuscular Junction	MG: F, G; fluctuates	+	0	0	M fatigue
	Botulism: G	+ or 0	0	0	Mydriasis
Muscle	MD: P > D; LE > UE, ±F	P = 0; D ±	0	±	H and/or A, C
	Myositis: P > *D*	P = 0; D ±	0	0	M tenderness

P: proximal
D: Distal
S: Segmental
G: Generalized
F: Focal (ptosis, facial, bulbar)
LE: Lower extremity
UE: Upper extremity
H: Hypertrophy
A: Atrophy
M: Muscle
C: Joint contractures
DTRs: deep tendon (muscle stretch) reflexes; 0: absent; +: reduced; ++: normal;, +++: brisk; ++++: hyperactive; +/–: marginally present
CNS: central nervous system component—seizures, intellectual disability, brain and eye malformation

- **Distinctive features and varied influence in different age**, reflects **age-related differences in psychomotor development.**
- **Weakness may not be the initial or predominant symptom**.
- **Fixed weakness** need to be distinguished from **fluctuating or intermittent** weakness.

- **Acquired disorders** generally present with an **acute or su-bacute onset and may progress rapidly.**
- **Genetically based** disorders tend to present with a **more indolent onset and subtle influence on motor function**.
- **Exceptions certainly occur: SMA type 1 can present acutely similar to infantile botulism, and CIDP may present in a chronic manner similar to CMT neuropathies**

History

- **Onset of symptoms and signs, tempo of progression, effect on motor development, muscle pain or cramp, sensory symptoms, and coordination/balance issues**
- **Related respiratory, cardiac, feeding/growth, and musculoskeletal issue, patient's independent functioning at home, at school, and in the community**.
- **A careful family history**
- **The review of systems**: for features of a systemic or genetic disease

Fetal/Neonatal onset

- **reduced fetal activity**
- **abnormal fetal ultrasound** (decreased fetal activity or contractures)
- **Abnormal Non-stress test** (decreased activity, reactivity, or abnormal posture)
- **Increased or decreased amniotic fluid volume**
- **Breech presentation**
- **Neonatal torticollis, scoliosis, multiple joint contractures or UDT**
- Characteristic facies and ophthalmoplegia in **congenital myopathies** and a characteristic facial appearance with atrophy of the temporalis muscles in **myotonic dystrophy**

Signs and symptoms in the infant

- Hypotonia (“floppy baby”)
- Delayed acquisition of motor milestones
- Dysphagia
- Failure to thrive
- Hypoventilation
- Cardiomyopathy

- **Childhood onset**: a plateau or slowing of progression in motor development
- **Adolescent onset**: muscle fatigue and activity-related myalgias more prominent than weakness
- **frank pain is not a typical symptom in most MNDs**. **Exceptions** include myotonic dystrophy type 2 and GBS
- **Fluctuating or intermittent weakness** is characteristic of NMJ, CMS, and different subtypes of periodic paralysis

Examination

- Inspection
- Muscle bulk and quality
- Joint mobility and tone
- Muscle strength and weakness
- Motor function testing
- Muscle stretch reflexes (DTR)
- Sensory testing

Figure 146-3. The Gowers maneurver in a 5-year old boy with Duchenne muscular dystrophy. The patient is asked to stand up from a supine position. Note that he rolls to the side, then into prone position, followed by widening the base of support, arising first with his buttocks then using his hands on his thighs to "climb up his legs" to gain an upright posture.

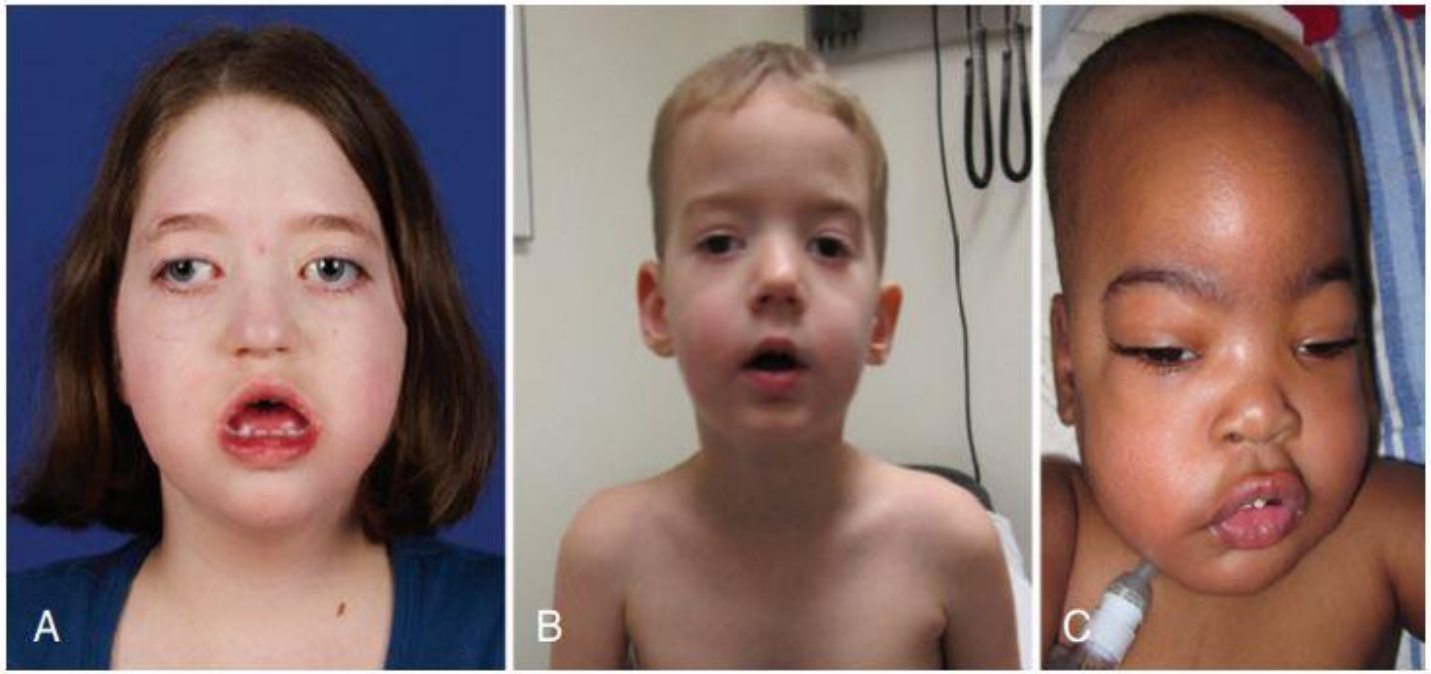

Figure 148-1. The "myopathic" facies. One of the characteristic clinical observations in many children with congenital myopathies is the so-called "myopathic" facial appearance. This can include both upper and lower facial weakness, as illustrated in these photomicrographs. *Left panel:* The patient depicted demonstrates ptosis, ocular misalignment caused by ophthalmoparesis, an inverted C-shape to her upper lip, and prominent lower facial weakness resulting in an open mouth appearance. The ultimate diagnosis in this case was nemaline myopathy caused by recessive mutation in the *LMOD3* gene. Patients with nemaline myopathy often have particularly striking lower facial weakness. *Middle panel:* This individual has ptosis, ophthalmoparesis, and moderate lower facial weakness. He has DNM2-related centronuclear myopathy. Note also the muscle atrophy present in his chest and shoulders. *Right panel:* Photograph of a young boy with myotubular myopathy caused by MTM1 mutation. He has the characteristic long face with bilateral ptosis and ophthalmoparesis.

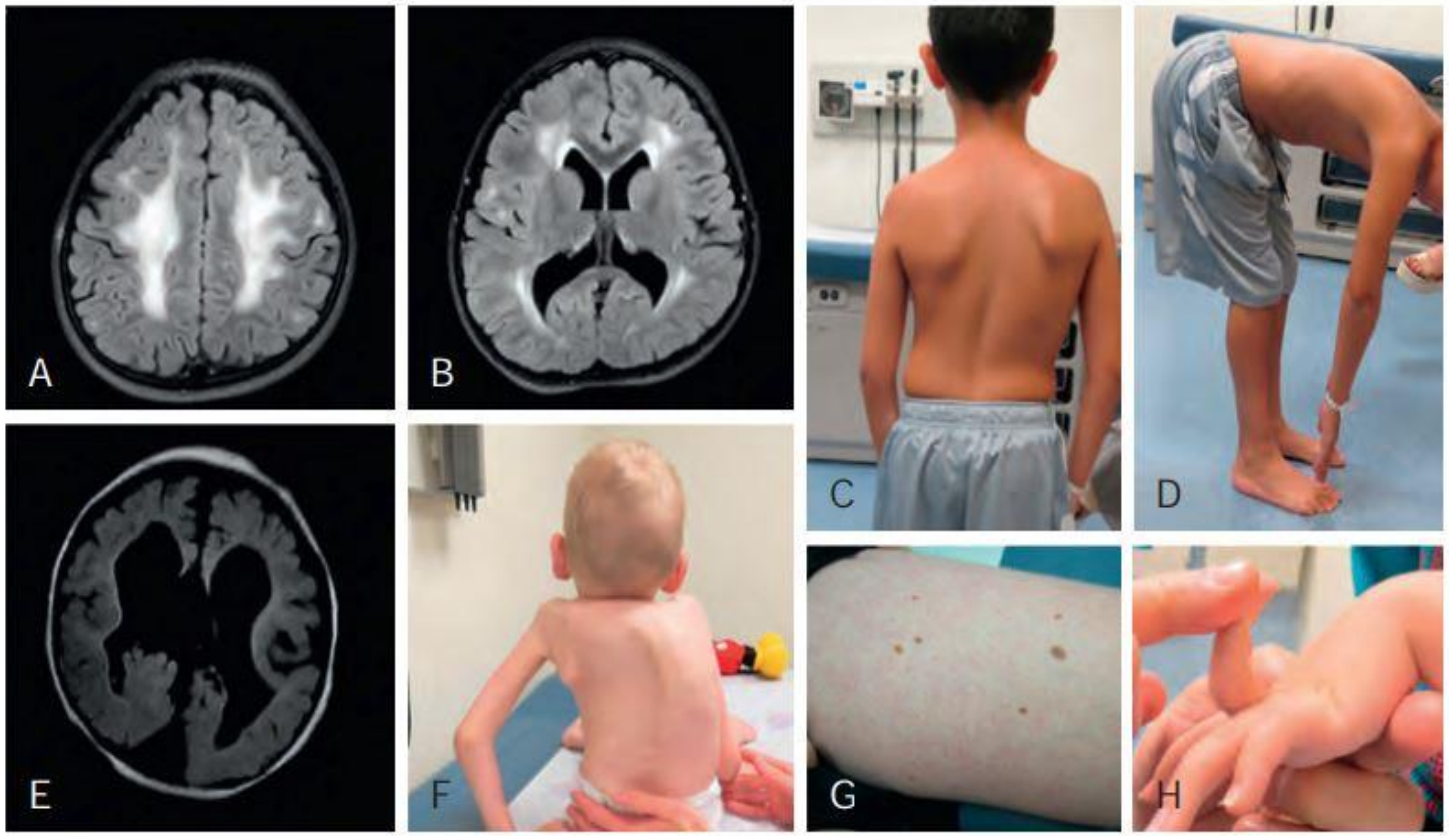

Fig. 627.7 Findings in congenital muscular dystrophies. **A** and **B,** Axial FLAIR brain MRI images showing the increased T2 hyperintensity seen within the white matter in patients with LAMA2 CMD. **C,** Scapular winging and scoliosis in patient with SEPN1 muscular dystrophy. **D,** Rigid spine noted in forward flexion in patient with SEPN1 muscular dystrophy. **E,** Brain MRI in patient with muscle–eye–brain disease with absent corpus callosum, Dandy-Walker malformation, subependymal cysts. **F,** Early and severe kyphoscoliosis in a child with Ullrich congenital muscular dystrophy. **G,** Keratosis pilaris, a common skin finding in patients with collagen VI–related CMDs. **H,** Distal hyperlaxity seen in patients with collagen VI–related CMDs. *(Courtesy Drs. Carsten Bönnemann and Reghan Foley, Neuromuscular and Neurogenetics Disorders of Childhood Section, NINDS/NIH.)*

Floppy Infant

Fig. 630.1 Type I spinal muscular atrophy (Werdnig-Hoffmann disease): clinical manifestations of weakness of limb and axial musculature in a 4–mo old infant with severe weakness and hypotonia. With vertical suspension **(A),** note the dangling lower limbs with lack of hip flexion, tendency of the upper limbs to slip through the examiner's hands, and lack of neck flexion with resulting head lag. When subject is supine, note the *frog-leg* positioning of the legs and the lack of traction response **(B)** and the lag of head **(C),** with attempts by the examiner to pull the infant to a sitting position. *(From Oskoui M, Darras BT, De Vivo DC: Spinal muscular atrophy: 125 years later and on the verge of a cure. In Sumner CJ, Paushkin S, Ko C-P, eds: Spinal muscular atrophy: disease mechanisms and therapy. San Diego, 2017, Academic Press, Chapters 1 and 3–19.)*

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A novel mutation in *SEPN1* causing rigid spine muscular dystrophy 1: a Case report

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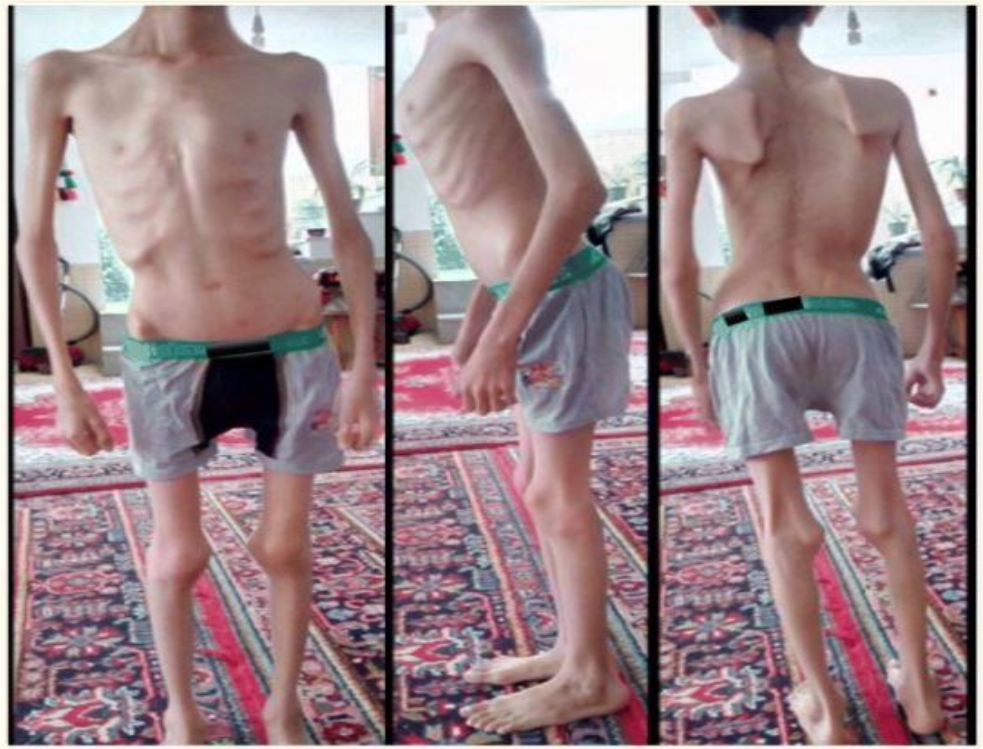


Fig. 1

Generalized muscular atrophy, kyphoscoliosis, and flexion contracture of the knees and elbows in our patient

Myotonic Muscular Dystrophy

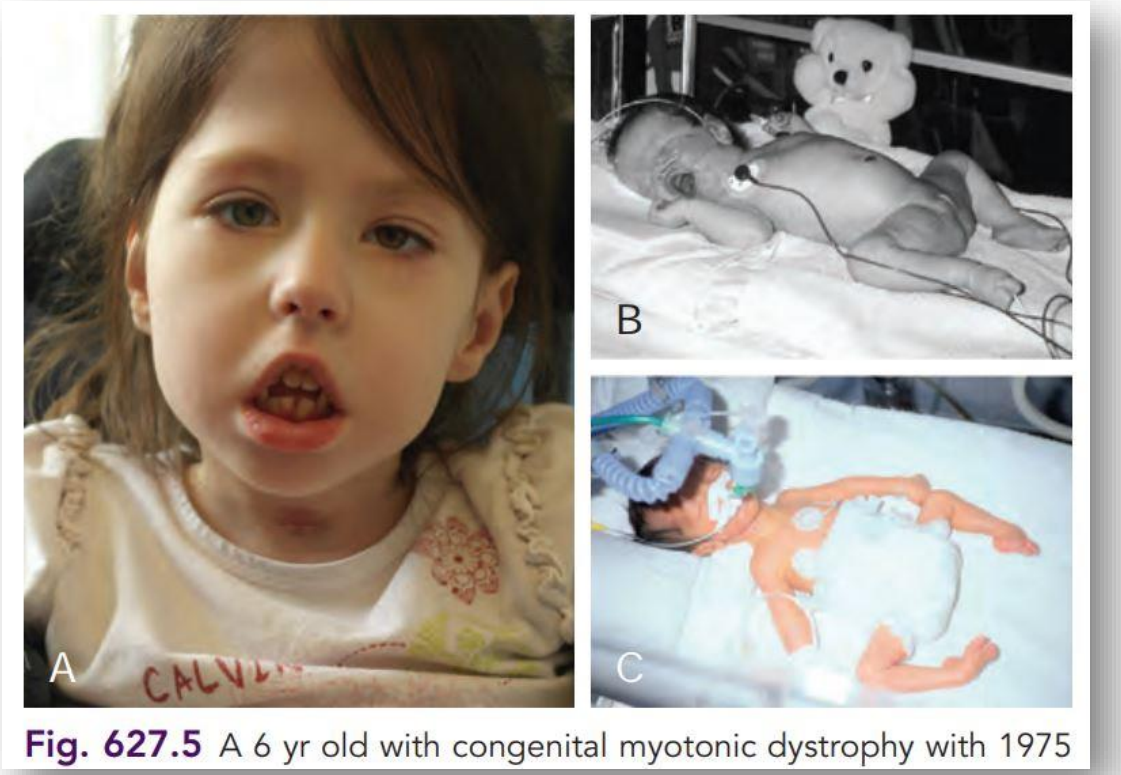
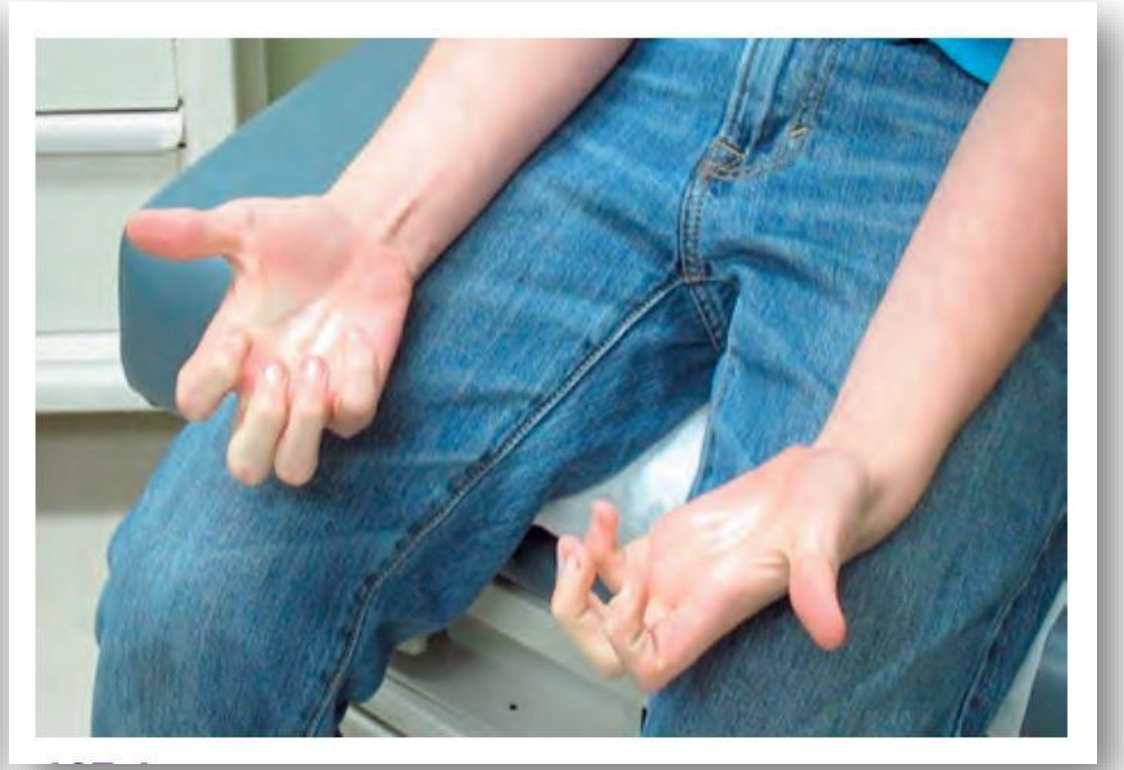
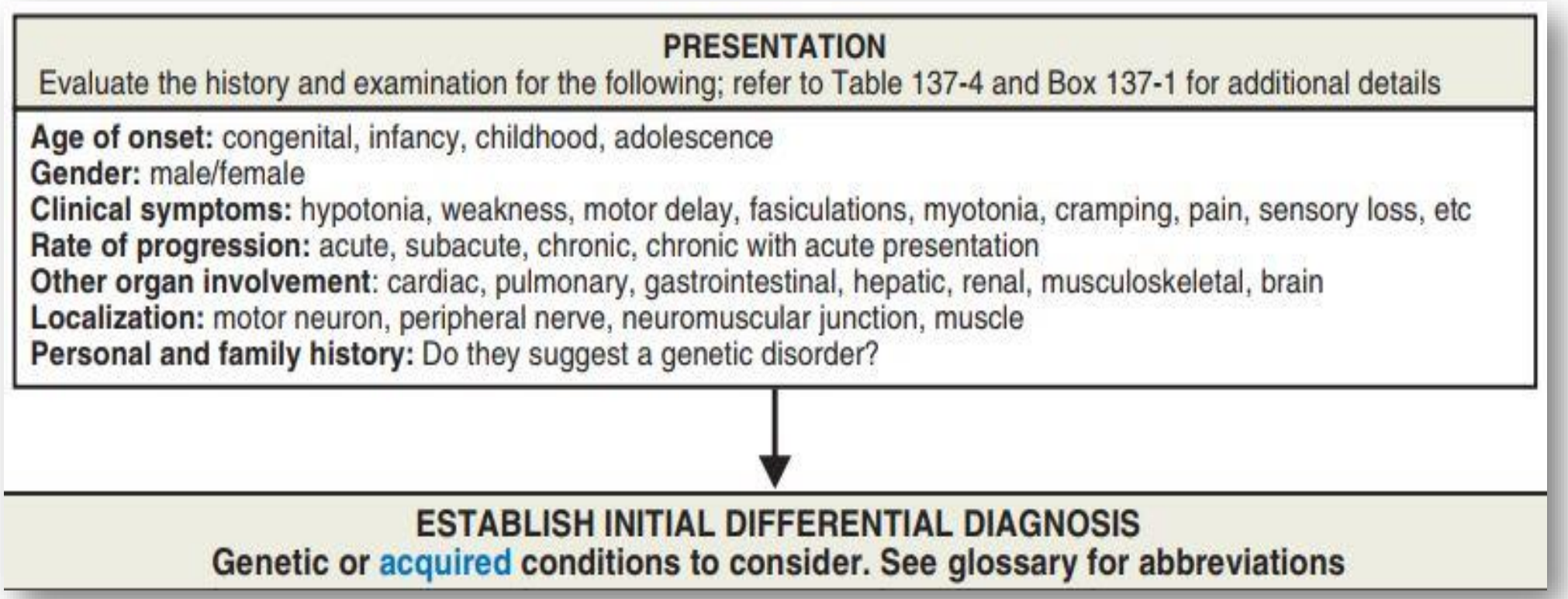


Fig. 627.5 A 6 yr old with congenital myotonic dystrophy with 1975



Suggested algorithm for the assessment of the child with a suspected NMD



Algorithm. . cont

ESTABLISH INITIAL DIFFERENTIAL DIAGNOSIS
Genetic or acquired conditions to consider. See glossary for abbreviations

	Motor Neuron	Peripheral nerve	NM junction	Muscle
Congenital	SMA type 0 *In utero toxin, HIE*	CMT variants *In utero toxin*	CMS *Neonatal MG*	Congenital DM1, CM, CMD
Infancy	SMA types 1 and 2 *Enterovirus/polio, WNV*	CMT variants *GBS, toxic, MN*	CMS *Botulism, MG*	CM, DM1, CMD, MM, MiM, DMD, LGMD *EM, IM*
Childhood	SMA type 3 *Enterovirus/polio, WNV*	CMT variants *GBS/CIDP,tick, toxic, IN, MN*	CMS *MG, toxin*	DMD/BMD, CM, LGMD, DM1, CMD, MM, MiM *DM/PM, IM, EM*
Adolescence	Juvenile ALS *Enterovirus/polio, WNV*	CMT variants *GBS/CIDP, tick, toxic, IN, MN*	CMS *MG, toxin*	BMD, LGMD, DM1, DM2, MM, MiM *DM/PM, IM, EM*

PERFORM NON-INVASIVE FIRST-TIER AND, IF NEEDED, INVASIVE SECOND-TIER TESTING TO DETERMINE IF:

Algorithm. . cont

PERFORM NON-INVASIVE FIRST-TIER AND, IF NEEDED, INVASIVE SECOND-TIER TESTING TO DETERMINE IF:
1. **Neuropathic (motor neuron or peripheral nerve), neuromuscular junction or muscle disorder**
2. **Genetic or acquired condition**

	Motor Neuron and Peripheral Neuropathy	Neuromuscular Junction	Myopathy
FIRST TIER			
Muscle Enzyme (Creatinine Kinase)	Normal or slightly elevated	Normal	Normal to marked elevation
Other blood tests	*Viral and antiganglioside antibody studies for acquired neuropathy *Heavy metal screen	Acetylcholine receptor antibody titer	Lactate/pyruvate, carnitine, acylcarnitine; K+ for periodic paralysis; aldolase, LDH, ESR and ANA for DM/PM
Muscle imaging	Muscle ultrasound	normal	*Ultrasound for CM and MD *MRI for MD, DM/PM
Brain or other organ imaging	MRI brain for leukodystrophy or mitochondrial features MRI for nerve root enhancement in GBS	Mediastinal MRI or CT for MG associated thymoma	MRI for CMD
SECOND TIER			
Electrophysiology Nerve conduction velocity and electromyography	*NCV: for axonal and demyelinating motor/sensory neuropathy – genetic and acquired *EMG: for motor neuron and axonal motor neuropathy	Repetitive nerve stimulation testing for MG, botulism, or NMJ poisoning	EMG for myopathic features and to exclude a neuropathy
Muscle and Nerve pathology	Nerve biopsy for inflammation or storage, EM for mitochondrial changes	EM of NMJ	Define disease specific myopathology (Chapter 135)
Lumbar Puncture	CSF profile for GBS/CIDP or metabolic neuropathy	N/A	N/A

1. **Create 'final' differential diagnosis and if acquired condition complete diagnostic evaluation.**
2. **If genetic, do disease specific testing, gene panel for neuromuscular disorder subtype or whole genome or exome sequencing (Chapter 136 and elsewhere in this section). The www.genetests.org**

Take Home Message

- Pediatric neuromuscular conditions may **present from prenatal through adolescent development**
- **Physical impairment and morbidity** are often substantial, and, in the most severe forms, there is reduced survival
- **Consider the early symptoms detection and physical examination** of pediatric NMD, and **how to evaluate patients** using structured functional measures
- **Determine change over time**, which can then be used to predict the future course and demonstrate a response to an intervention