APPROACH TO MYOPATHY

INTRODUCTION

- Myopathy : simply refers to an abnormality of the muscle and has no other connotation.

- Muscular dystrophies are genetic myopathies usually caused by a disturbance of a structural protein or enzyme, resulting in necrosis of muscle fibres and replacement by adipose and connective tissue.

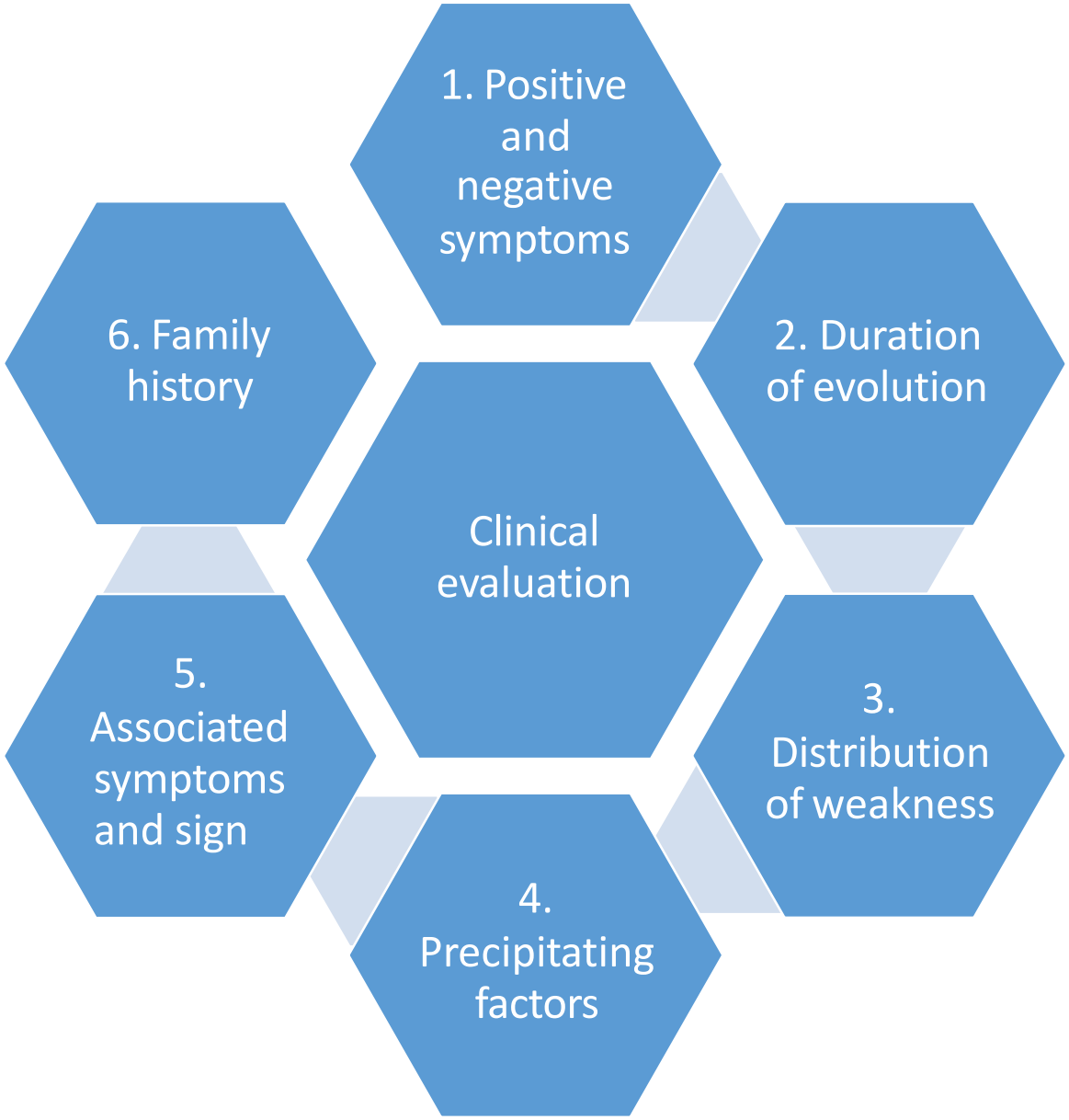
- Myositis implies an autoimmune or infectious disorder in which the muscle histology shows an inflammatory response.

- Myotonia are diseases in which the occurrence of involuntary persistent muscle activity accompanied by abnormal repetitive electrical discharges distorts the normal contractile process. This occurs after percussion or voluntary contraction.

1. The first goal in approaching a patient with a suspected muscle disease is to determine the correct site of the lesion.

2. The second goal is to determine the cause of the myopathy.

3. The third goal is to determine whether a specific treatment is available and if not, to optimally manage the patient’s symptoms to maximize his or her functional abilities and enhance quality of life.


1. Positive and negative symptoms
2. Duration of evolution
3. Distribution of weakness
4. Precipitating factors
5. Associated symptoms and sign
6. Family history
Clinical evaluation

Which negative and/or positive symptoms and signs does the patient demonstrate?

- Negative
  - Weakness
  - Fatigue
  - Exercise intolerance
  - Muscle atrophy
- Positive
  - Myalgia
  - Cramps
  - Contractures
  - myotonia

1. Weakness: MOST COMMON
   a) Proximal lower extremities:
      - difficulty climbing stairs, arising from a low chair or toilet, or getting up from a squatted position.
   b) Proximal upper extremities:
      - trouble lifting objects over their head and brushing their hair.
   c) Distal upper extremities:
      - difficulty opening jars, inability to turn a key in the ignition.
   d) Distal lower extremities:
      - tripping due to foot-drop.
   e) Cranial muscle weakness,
      - dysarthria, dysphagia, or ptosis.

2. Fatigue

- less useful negative symptom
- Nonspecific
- abnormal fatigability after exercise can result from certain metabolic and mitochondrial myopathies, and it is important to define the duration and intensity of exercise that provokes the fatigue.

3. Myalgia, like fatigue, is another nonspecific symptom
   - episodic (metabolic myopathies)
   - constant (inflammatory muscle disorders)
   - more likely to be due to orthopedic or rheumatological disorders

MUSCLE DISEASES ASSOCIATED WITH MYALGIAS

- Toxic/drug-induced myopathies (statins and others)
- Eosinophilia-myalgia syndrome
- Hypothyroid myopathy
- **Inflammatory myopathies (dermatomyositis, polymyositis)**
- Myotonic disorders
- Mitochondrial myopathies
- **Muscular dystrophies, examples:**

  X-linked myalgia and cramps/Becker's dystrophy variant
- Infectious myositis (especially viral)

4. Muscle cramp

- ❑ They are typically benign, occurring frequently in normal individuals, and are seldom a feature of a primary myopathy
- ❑ Cramps can occur with:
  - dehydration,
  - hyponatremia,
  - azotemia,
  - myxedema
  - disorders of the nerve or motor neuron (especially amyotrophic lateral sclerosis).

5. Muscle contractures

- uncommon
- They are typically provoked by exercise in patients with glycolytic enzyme defects.
- Contractures differ from cramps in that they usually last longer and are electrically silent with needle EMG.
- Cramps are characterized by rapidly firing motor unit discharge om needle EMG.

MYOPATHIES ASSOCIATED WITH MUSCLE CONTRACTURES

- Glycolytic/glycogenolytic enzyme defects
  - Myophosphorylase deficiency (McArdle's disease)
  - Phosphofructokinase deficiency
  - Phosphoglycerate kinase deficiency
  - Phosphoglycerate mutase deficiency
  - Lactate dehydrogenase deficiency
  - Debrancher enzyme deficiency
- Hypothyroid myopathy
- Rippling muscle disease
- Brody's disease

6. Myotonia **: phenomenon of impaired relaxation of muscle after forceful voluntary contraction.**
   - due to repetitive depolarization of the muscle membrane.
   - Patients may complain of muscle stiffness or tightness resulting in difficulty releasing their handgrip after a handshake, unscrewing a bottle top, or opening their eyelids if they forcefully shut their eyes.
   - Most commonly involves the hands and eyelids.
   - Myotonia classically improves with repeated exercise.

6. paramyotonia congenita:

- ‘‘paradoxical myotonia’’ in that symptoms are typically worsened by exercise or repeated muscle contractions.

- Exposure to cold results in worsening of both myotonia and paramyotonia.

Myopathies associated with muscle stiffness:

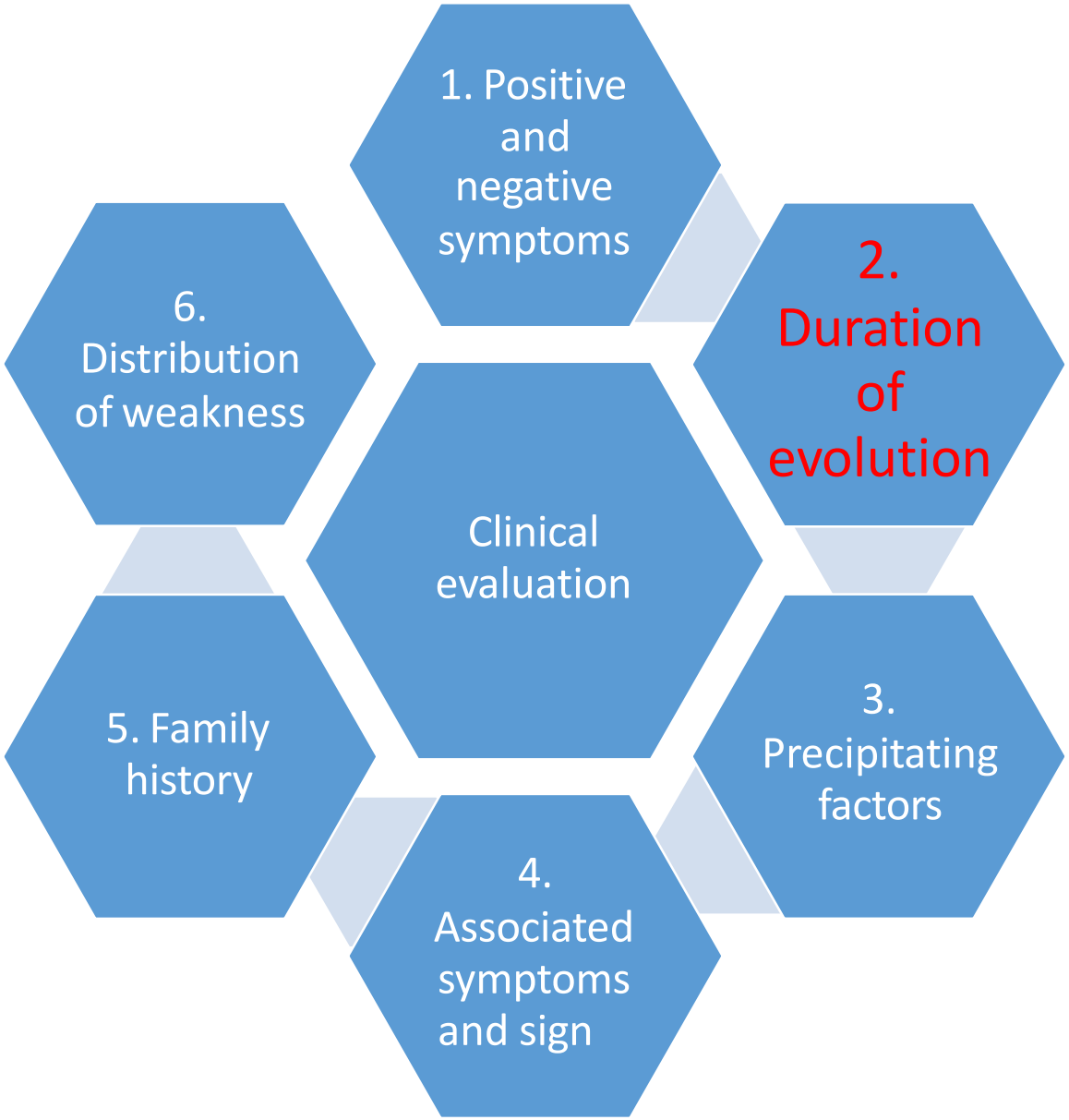
- Myotonic dystrophy
- Proximal myotonic dystrophy
- Myotonia congenita
- Paramyotonia congenita
- Hyperkalemic periodic paralysis
- Hypothyroid myopathy

7. Red/cola-colored urine

- uncommon manifestation of muscle disease
- caused by the excessive release of myoglobin from muscle during periods of rapid muscle destruction (rhabdomyolysis).
- If patients complain of exercise-induced weakness and myalgias, they should be asked if their urine has ever turned cola-colored or red during or after these episodes.
- Recurrent myoglobinuria is usually due to an underlying metabolic myopathy
- isolated episodes, particularly occurring after unaccustomed strenuous exercise, are frequently idiopathic.

CAUSES OF MYOGLOBINURIA

- Prolonged, intensive exercise
- Drugs and toxin
- Metabolic myopathies
  - Glycogenoses (myophosphorylase deficiency)
  - Lipid disorders (carnitine palmitoyltransferase deficiency)
  - Malignant hyperthermia (Central core myopathy, Duchenne MD)
- Heat stroke
- Some muscular dystrophies
- Neuroleptic malignant syndrome
- Severe metabolic disturbances, including prolonged fever
- Trauma (crush injuries)
- Viral and bacterial infections (rare)
- Inflammatory myopathies (rare)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Clinical evaluation

What is the temporal evolution?

- onset,
- duration, and
- evolution of the patient’s symptoms

Evolution and duration

- episodic periods of weakness with normal strength interictally
    - (periodic paralysis, metabolic myopathies due to certain glycolytic pathway disorders).

- constant weakness

Constant weakness

- acute or subacute progression
  - inflammatory myopathies (dermatomyositis and polymyositis);
- chronic slow progression over years
  - most muscular dystrophies
  - IBM
- Non-progressive weakness with little change over decades
  - congenital myopathies

Monophasic or relapsing

- polymyositis can occasionally have an acute monophasic course with complete resolution of strength within weeks or months.

- a patient with acute rhabdomyolysis due to cocaine may have a single episode.

- Patients with periodic paralysis or metabolic myopathies can have recurrent attacks of weakness over many years,

Myopathies Presenting at Birth

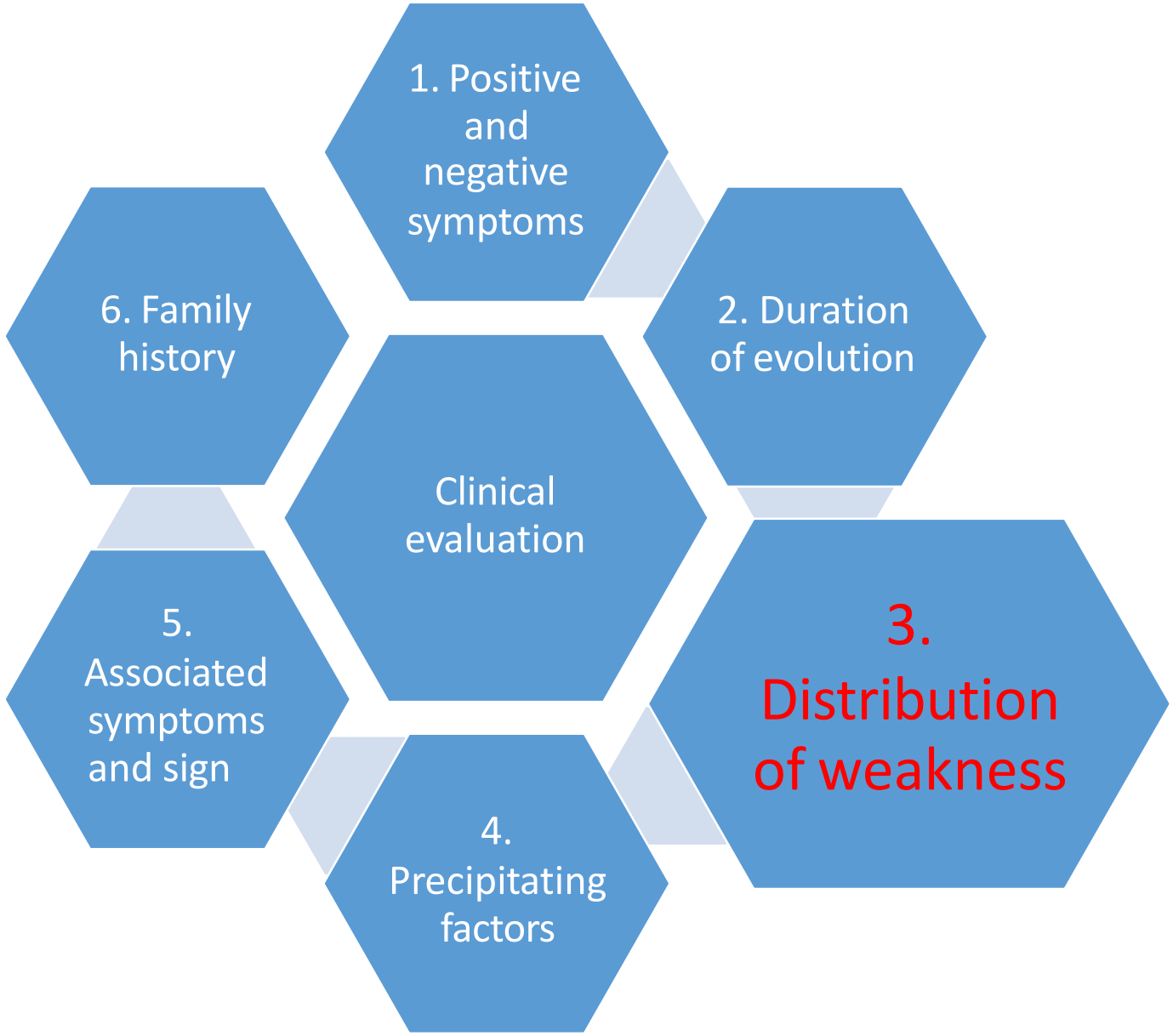
- Congenital myotonic dystrophy
- Centronuclear (myotubular) myopathy
- Congenital fiber-type disproportion
- Central core disease
- Nemaline (rod) myopathy
- Congenital muscular dystrophy
- Lipid storage diseases (carnitine deficiency)
- Glycogen storage diseases (acid maltase and phosphorylase deficiencies)

Myopathies Presenting in Childhood

- Muscular dystrophies
  - Duchenne
  - Becker
  - Emery-Dreifuss
  - Facioscapulohumeral
  - Limb-girdle
  - Congenital
- Inflammatory myopathies
  - Dermatomyositis
  - Polymyositis (rarely)
- Congenital myopathies
  - Nemaline
  - Centronuclear
  - Central core
- Lipid storage disease (carnitine def.)
- Glycogen storage disease (acid maltase deficiency)
- Mitochondrial myopathies
- Endocrine-metabolic disorders
  - Hypokalemia
  - Hypocalcemia
  - Hypercalcemia

Myopathies Presenting in Adulthood

- Muscular dystrophies
  - Limb-girdle
  - Facioscapulohumeral
  - Becker
  - Emery-Dreifuss
- Inflammatory myopathies
  - Polymyositis
  - Dermatomyositis
  - Inclusion body myositis
  - Viral [HIV]
- Metabolic myopathies
  - Acid maltase deficiency
  - Lipid storage diseases
  - Debrancher deficiency
  - Phosphorylase b kinase deficiency
  - Mitochondrial myopathies
- Endocrine myopathies
  - Thyroid
  - Parathyroid
  - Adrenal
  - Pituitary disorders
- Toxic myopathies
  - Alcohol
  - Corticosteroids
  - Local injections of narcotics
  - Colchicine
  - Chloroquine
  - Statins
- Myotonic dystrophy
- Distal myopathies
- Nemaline myopathy
- Centronuclear myopathy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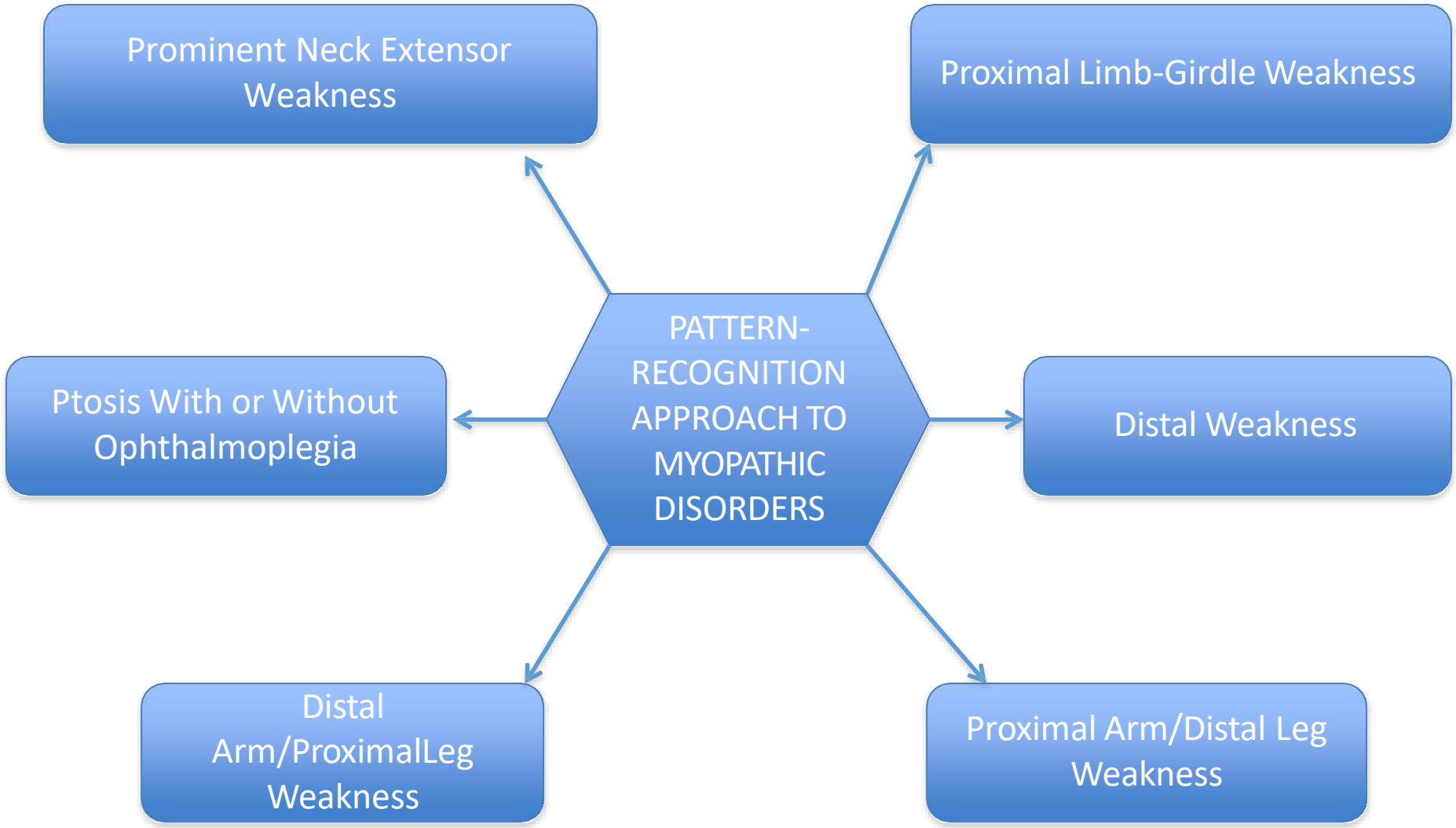

PATTERN-RECOGNITION APPROACH TO MYOPATHIC DISORDERS
Prominent Neck Extensor Weakness
Proximal Limb-Girdle Weakness
Ptosis With or Without Ophthalmoplegia
Distal Weakness
Distal Arm/ProximalLeg Weakness
Proximal Arm/Distal Leg Weakness

Pattern 1: Proximal Limb-Girdle Weakness

- The most common pattern of muscle weakness in myopathies
- symmetrical weakness affecting predominantly the proximal muscles of the legs and arms
- The distal muscles are usually involved, but to a much lesser extent.
- Neck extensor and flexor muscles are also frequently affected.
- This pattern of weakness is seen in most hereditary and acquired myopathies and therefore is the least specific in arriving at a particular diagnosis

Pattern 2: Distal Weakness

- This pattern of weakness predominantly involves the distal muscles of the upper or lower extremities (anterior or posterior compartment muscle groups)
- The involvement is usually, although not invariably, symmetrical.
- more commonly a feature of neuropathies

Myopathies Characterized by Predominantly Distal Weakness

- Distal Myopathies
  - Late adult-onset distalmyopathy type 1 (Welander)
  - Late adult-onset distal myopathy type 2 (Markesbery/Udd)
  - Early adult-onset distal myopathy type 1 (Nonaka)
  - Early adult-onset distal myopathy type 2 (Miyoshi)
  - Early adult-onset distal myopathy type 3 (Laing)
  - Desmin myopathy
  - Childhood-onset distal myopathy
- Myotonic Dystrophy
- Inflammatory Myopathies
- Inclusion Body Myositis
- Metabolic Myopathies
  - Debrancher deficiency
  - Acid-maltase deficiency
- Congenital Myopathies
  - Nemaline myopathy
  - Central core myopathy
  - Centronuclear myopathy

Pattern 3: Proximal Arm/Distal Leg Weakness

- This pattern of weakness affects the periscapular muscles of the proximal arm and the anterior compartment muscles of the distal lower extremity (scapuloperoneal distribution)
- The scapular muscle weakness is usually characterized by scapular winging.
- Weakness can be very asymmetrical.

Myopathies with proximal arm/distal leg involvement (scapuloperoneal)

- Scapuloperoneal dystrophy,
- Emery-Dreifuss dystrophy,
- LGMD1B, LGMD2A, LGMD2C–2F,
- Congenital myopathies,
  - Nemaline myopathy
  - Central core myopathy
- acid maltase deficiency.
- When this pattern is associated with facial weakness->(FSHD)

Pattern 4: Distal Arm/Proximal Leg Weakness

- This pattern is associated with distal arm weakness involving the distal forearm muscles (wrist and finger flexors) and proximal leg weakness involving the knee extensors (quadriceps).
- The facial muscles are usually spared.
- Involvement of other muscles is extremely variable.
- The weakness is often asymmetrical between the two sides, which is uncommon in most myopathies.
- This pattern is essentially pathognomonic for inclusion body myositis.
- This pattern may also represent an uncommon presentation of myotonic dystrophy; however, unlike IBM, muscle weakness is usually symmetrical

Pattern 5: Ptosis With or Without Ophthalmoplegia

- usually, although not always, occurs without symptoms of diplopia.
- Facial weakness is not uncommon,
- extremity weakness is extremely variable, depending on the diagnosis.

- The combination of ptosis, ophthalmoplegia (without diplopia), and dysphagia should suggest the diagnosis of oculopharyngeal dystrophy, especially if the onset is in middle age or later.

- Ptosis and ophthalmoplegia without prominent pharyngeal involvement is a hallmark of many of the mitochondrial myopathies.

- Ptosis and facial weakness without ophthalmoplegia is a common feature of myotonic dystrophy.

Myopathies With Ptosis or Ophthalmoplegia

- Ptosis Without Ophthalmoplegia
- Myotonic dystrophy
- Congenital myopathies
  - Centronuclear myopathy
  - Nemaline myopathy
  - Central core myopathy
- Desmin (myofibrillary) myopathy

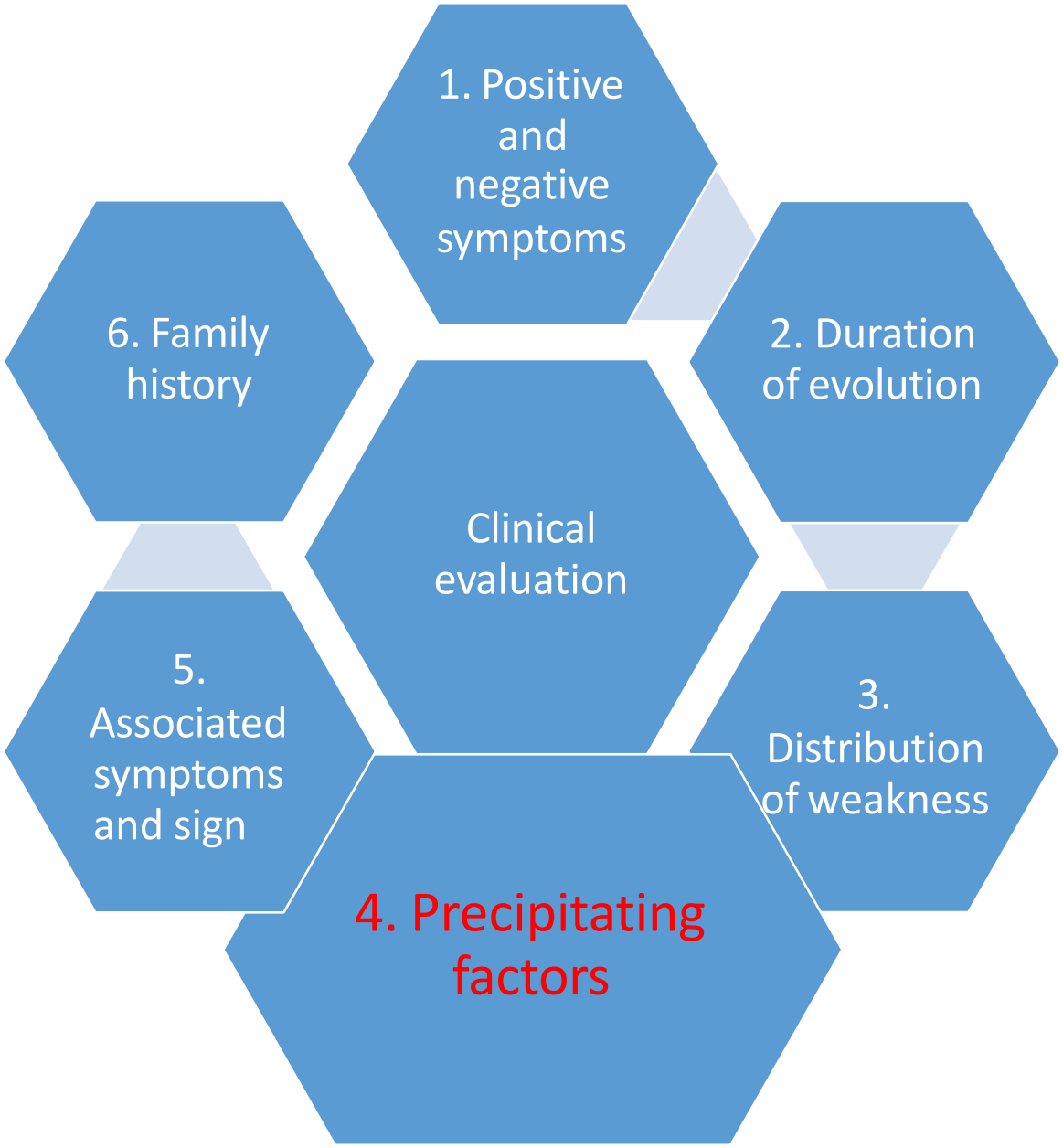
- Ptosis With Ophthalmoplegia
- Oculopharyngeal muscular dystrophy
- Oculopharyngodistal myopathy
- Chronic progressive external ophthalmoplegia (mitochondrial myopathy)
- Neuromuscular junction disease (myasthenia gravis, Lambert-Eaton, botulism)

Pattern 6: Prominent Neck Extensor Weakness

- ‘‘dropped head syndrome’’
- Involvement of the neck flexors is variable.
- Isolated neck extension weakness represents a distinct muscle disorder called isolated neck extensor myopathy.
- Prominent neck extensor weakness:
  - amyotrophic lateral sclerosis and
  - myasthenia gravis.

Myopathies With Prominent Neck Extensor Weakness

- Isolated neck extensor myopathy"
- Polymyositis "
- Dermatomyositis "
- Inclusion body myositis "
- Carnitine deficiency "
- Facioscapulohumeral dystrophy "
- Myotonic dystrophy "
- Congenital myopathy "
- Hyperparathyroidism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Precipitating factors

- Toxic myopathy : drug or prescription medication
- weakness, pain, and/or myoglobinuria provoked by exercise
  - a glycolytic pathway defect.
- Episodes of weakness with a fever
  - carnitine palmityl transferase deficiency.
- Patients with paramyotonia congenita frequently report that cold exposure may precipitate their symptoms of muscle stiffness.

DRUGS THAT CAN CAUSE TOXIC MYOPATHIES

Non-inflammatory Necrotizing or Vacuolar:

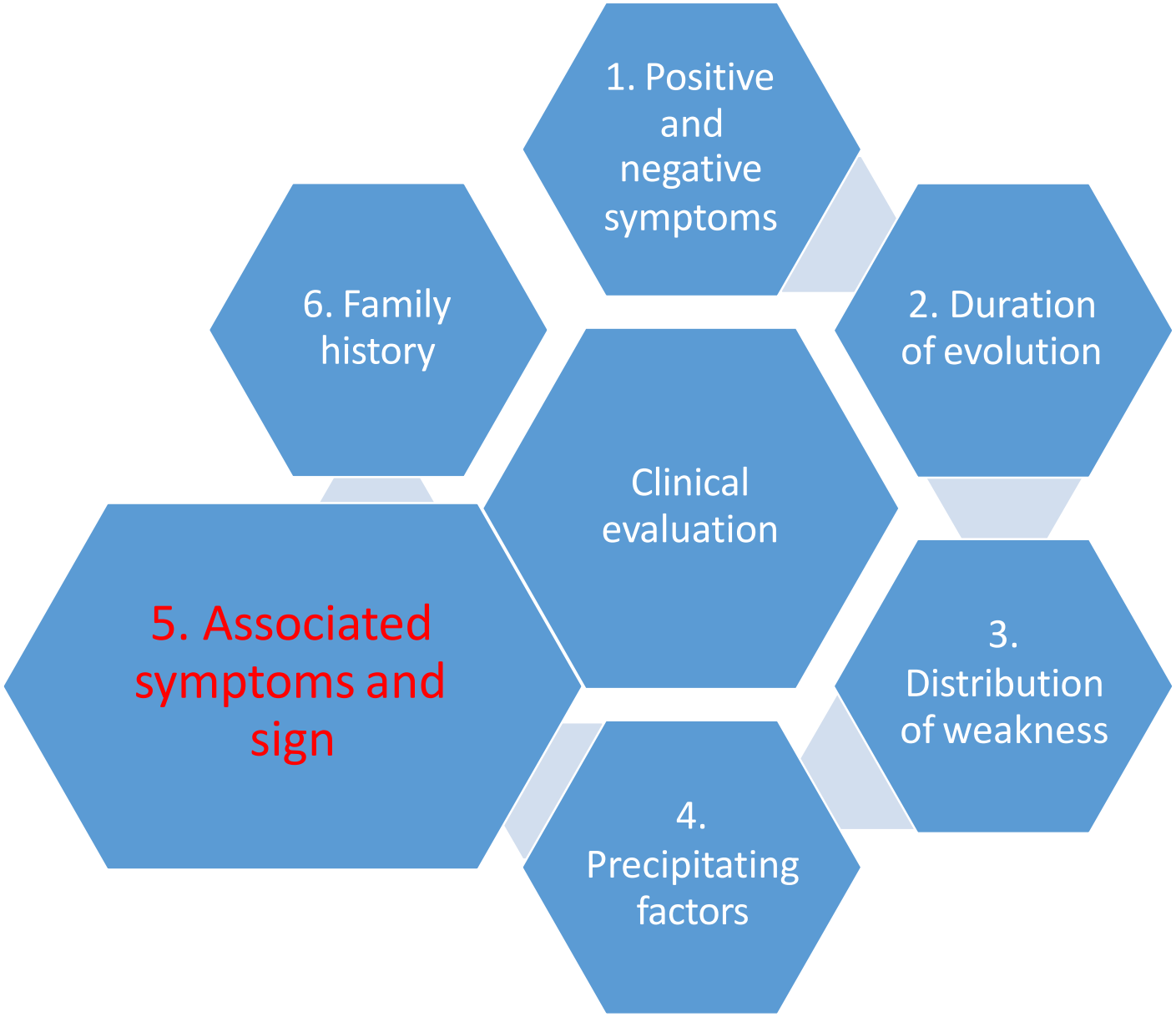
- Alcohol
- Cholesterol lowering agents
- Chloroquine
- Colchicine
- Cyclosporine and tacrolimus
- Emetine
- ε-aminocaproic acid
- Isoretinoic acid (vitamin A analogue)
- Labetalol
- Vincristine

Inflammatory:

- Cimetidine
- D-penicillamine
- Procainamide
- L-tryptophan
- L-dopa

DRUGS THAT CAN CAUSE TOXIC MYOPATHIES

- **Rhabdomyolysis and Myoglobinuria:**
  - Alcohol
  - Amphetamine
  - Cholesterol lowering drugs
  - Cocaine
  - Heroin
  - Toluene
  - ε-aminocaproic acid
- **Myosin Loss**
  - Non-depolarizing neuromuscular blocking agents
  - Steroids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Symptoms or signs associated with cardiac disease

- Arrhythmias
  - Kearns-Sayre syndrome
  - Andersen's syndrome
  - Polymyositis
  - Muscular dystrophies
    - Myotonic
    - Limb-girdle 1B, 2C-2F, 2G
    - Emery-Dreifuss"
- Congestive Heart Failure
  - Muscular dystrophies
    - Duchenne
    - Becker
    - Emery-Dreifuss
    - Myotonic
    - Limb-girdle 1B, 2C-2F, 2G
  - Nemaline myopathy
  - Acid maltase deficiency
  - Carnitine deficiency
  - Polymyositis

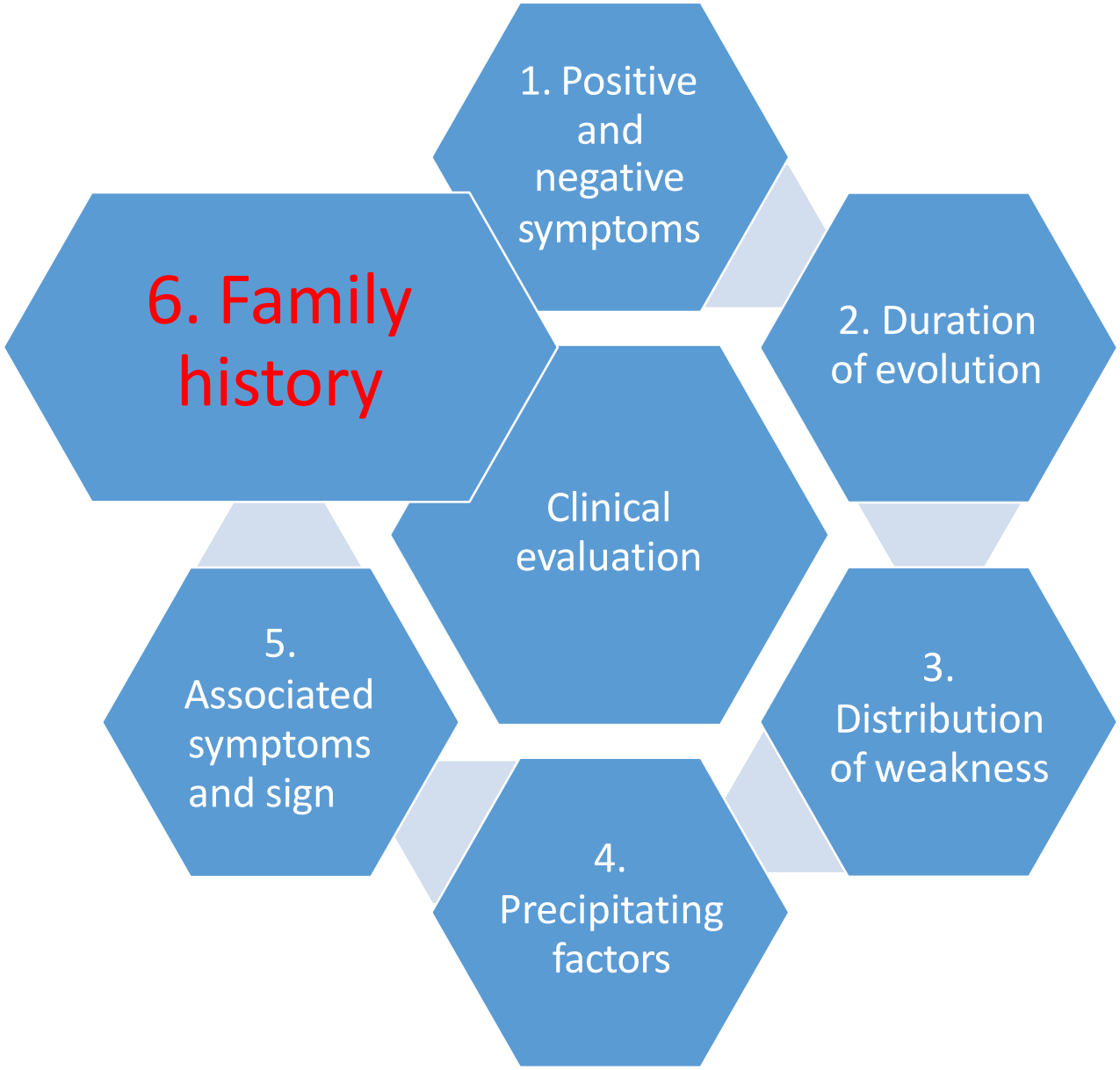
Respiaratory Insufficiency

- Muscular Dystrophies
  - Duchenne
  - Becker
  - Emery-Dreifuss
  - Limb-girdle
  - Myotonic
  - Congenital
- Metabolic Myopathies
  - Acid maltase deficiency
  - Carnitine deficiency
- Mitochondrial Myopathies
- Congenital Myopathies
  - Nemaline
  - Centronuclear
- Inflammatory Myopathies
  - Polymyositis

- Hepatomegaly
  - may be seen in myopathies associated with deficiencies in acid maltase, debranching enzyme,
  - infectious disease.
  - mitochondrial disorder.

- Cataract, frontal balding and mental retardation strongly s/o myotonic dystrophy.

- Rash is extremely helpful in confirming the diagnosis of dermatomyositis.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Family history

- A thorough family history is clearly of great importance in making a correct diagnosis.

- Questions regarding family members use of wheelchairs, skeletal deformities, or functional limitations are usually more informative than questions such as, ‘‘Does any member of your family have a muscle disease?’’

Diagnosis of Myopathy based on Inheritance

- X-Linked
  - Duchenne
  - Becker
  - Emery-Dreifuss
- Autosomal Dominant
  - Facioscapulohumeral
  - Limb-girdle
  - Oculopharyngeal muscular dystrophy
  - Myotonic dystrophy
  - Periodic paralysis
  - Paramyotonia congenita
  - Thomsen disease
  - Central core myopathy"
- Autosomal Recessive
  - Limb-girdle
  - Metabolic myopathies
  - Becker myotonia
- Maternal Transmission
  - Mitochondrial myopathies

Investigations

CK	EMG/NCV	Muscle Biopsy	Genetics

Creatine Kinase

- The CK is elevated in the majority of myopathies but may be normal in slowly progressive myopathies.
- Duchenne dystrophy, the CK level is invariably at least 10 times (and often up to 100 times) normal.
- CK may also be markedly elevated:
  - LGMD1C (caveolinopathy),
  - LGMD2A (calpainopathy), and
  - LGMD2B (dysferlinopathy),
- The CK level may not be elevated in
  - corticosteroid administration,
  - collagen diseases,
  - alcoholism
  - hyperthyroidism
  - profound muscle wasting

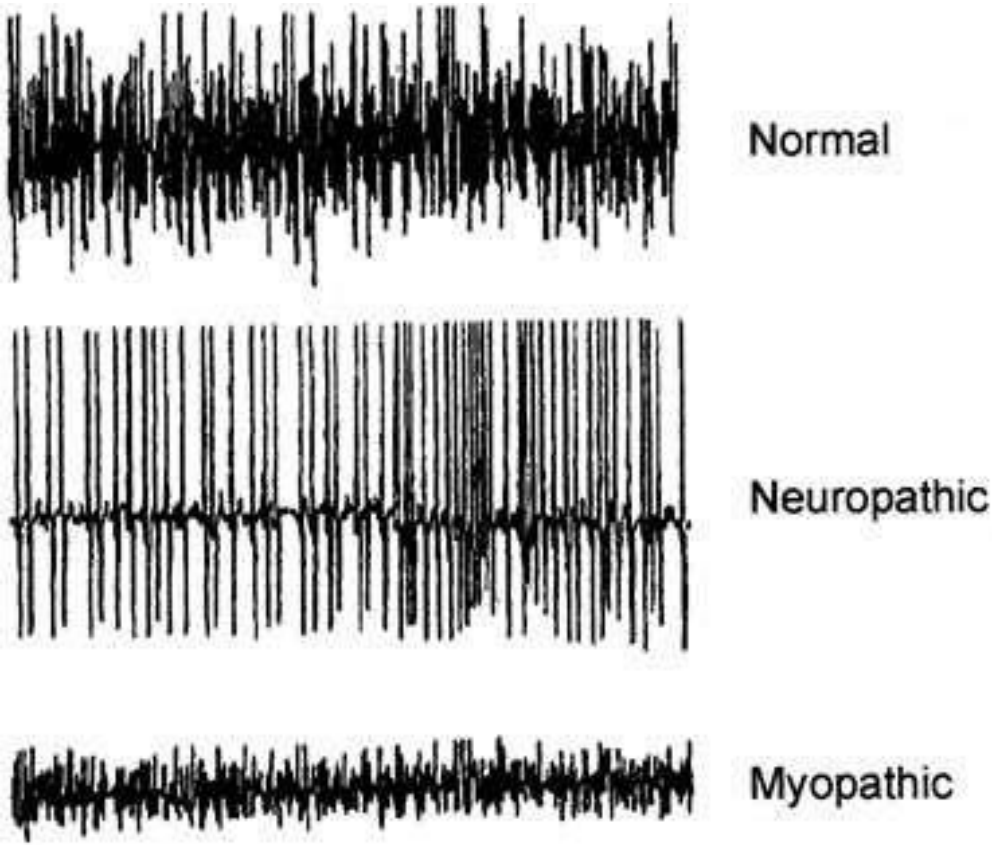
Differential Diagnosis of Creatine Kinase Elevation

- Myopathies
  - Muscular dystrophies
  - Congenital myopathies
  - Metabolic myopathies
  - Inflammatory myopathies
  - Drug/toxin-induced
  - Carrier state (dystrophinopathies)
- Channelopathies
- Motor Neuron Diseases
  - ALS
  - SMA
  - Postpolio syndrome
- Neuropathies
  - GBS
  - CIDP
- Viral Illness
- Medications
- Hypothyroidism/ Hypoparathyroidism
- SurgeryTrauma (electromyography studies, intramuscular or subcutaneous injections)
- Strenuous Exercise
- Increased Muscle Mass
- Race
- Sex
- ‘‘Idiopathic HyperCKemia’’

Electrophysiological Studies

- Confirm localization
- can be a guide as to which muscle to biopsy.
- r/o neuropathy, NMG disease, MND.
- NCS are typically normal in patients with myopathy.
- Needle EMG examination: motor units
  - Brief duration,
  - small-amplitude
  - Early recruitment

EMG findings



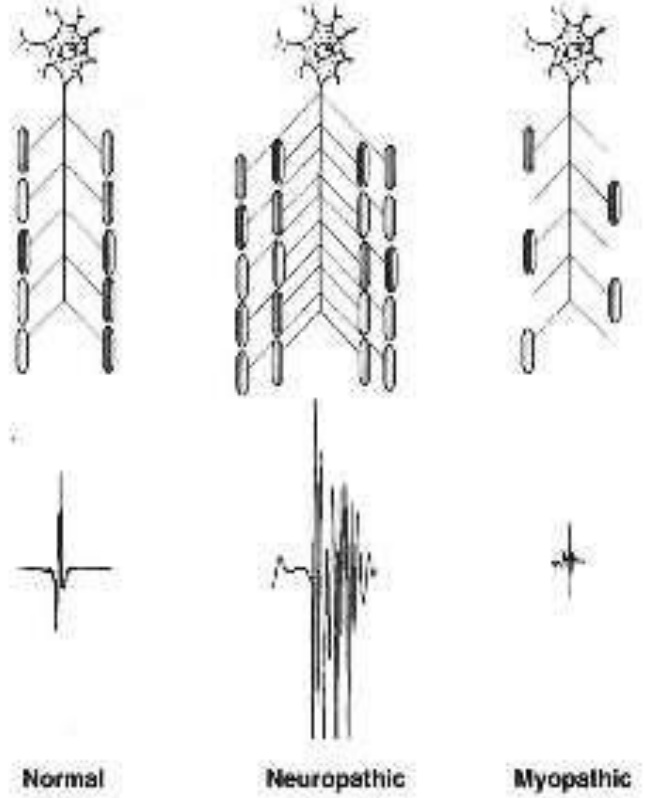


FIGURE 15–13
Motor unit action potential (MUAP) morphologies. *Normal MUAPs have two to four phases. In chronic neuropathic lesions that occur after reinnervation, the number of muscle fibers per motor unit increases, resulting in long-duration, high-amplitude, and polyphasic MUAPs. In myopathies or in neuromuscular junction disorders with block, the number of functional muscle fibers in the motor unit decreases. This leads to short-duration, small-amplitude, and polyphasic MUAPs.*

Muscle biopsy

- Selection of the appropriate muscle to biopsy is critical.

- Muscles that are severely weak (MRC grade 3 or less) should not be biopsied, since the results are likely to show only evidence of end stage muscle disease

- muscles that have recently been studied by needle EMG should be avoided because of the possibility of artifacts created by needle insertion.

- Biopsies should generally be taken from muscles that demonstrate MRC grade 4 strength.

- The muscle of choice:
  - biceps.
  - vastus lateralis.

- The gastrocnemius should be avoided, since its tendon insertion extends throughout the muscle and inadvertent sampling of a myotendinous junction may cause difficulty with interpretation.

- Typical myopathic abnormalities include:
  - central nuclei,
  - both small and large hypertrophic round fibers,
  - split fibers, and
  - degenerating and regenerating fiers.
  - Chronic myopathies frequently show evidence of increased connective tissue and fat.

Molecular Genetic Studies

- Disorders With Commercially Available Molecular Genetic Studies Performed With Peripheral Blood Samples
  - Duchenne and Becker muscular dystrophies ”
  - FSHD
  - MD (types 1 and 2) "
  - OPMD
  - LGMD1B, 2A, 2C–2F, and 2I "
  - Congenital muscular dystrophy (FKRP, FCMD, MEB, and POMT1 mutations) "
  - Nonaka myopathy/inclusion body myopathy type 2 "
  - Nemaline myopathy (ACTA1 mutations) "
  - Myotubular myopathy (MTM1 mutations) "
  - MERRF
  - MELAS

Take Home Message

- The initial key to the diagnosis of myopathies is recognition of a clinical pattern.
- There are six key questions the clinician should consider in arriving at the pattern that fits the patient
- After arriving at the pattern that fits best, then the clinician can better determine the most appropriate diagnostic tests and management.