Neurological disorders -V

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Neuromuscular Disorders

Definition

- Neuromuscular disease refers to disorders of the motor unit (specifically excluding cerebral palsy).

Components of the motor unit

- 1-Motor neuron; in the brain stem or anterior horn cell of the spinal cord.
- 2-Axons of the motor neuron forming the peripheral nerve.
- 3-Neuromuscular junction.
- 4- Muscle fibers.

General features of neuromuscular disorders

1-Muscle hypertrophy, muscle atrophy or wasting.

2-Generalized hypotonia, developmental delay (floppy infant).

3-Muscle pain or myalgias.

General features of neuromuscular disorders

4-Muscle contractures and skeletal deformities

5-Funnel shaped chest.

6-muscle fasciculation, fatigable weakness.

Diagnostic Investigations

- Serum creatine kinase (CK).
- Nerve conduction velocities(NCV)
- Electromyography(EMG)
- Muscle biopsy.

Diagnostic Investigations

- Nerve biopsy.
- Electrocardiography (ECG).
- Pulmonary function tests.
- Muscles imaging by ultrasound, CT, or MRI.

Spinal Muscular Atrophies

Werdnig-Hoffmann disease

Definition

- Degenerative diseases of lower motor neuron in the anterior horn of the spinal cord and brain stem.
- The disease begins in the fetal life and continue to progress in infancy and childhood.
- It is the second most common neuromuscular disease.

Etiology

- The SMAs are a group of relatively common diseases occurring in infancy or early childhood,
- transmitted by an autosomal recessive gene.
- The disease is caused by mutations in a gene, the telomeric survival motor neuron gene (SMN1).

Clinical manifestations

1-Weakness, hypotonia, hyporeflexia;

the infant appear flaccid, has little movements, weakness of the face, tongue, jaw, limbs, intercostals and bulbar muscles muscles.

2-Fasciculations of the tongue.

3-Congenital contractures.

Diagnostic Investigations

1-Genetic studies;

The definitive diagnosis may now be made by the marker in blood of the SMN gene that usually shows deletions of exons 7 and 8

2-Serum creatine kinase (CK):

Normal or mildly elevated.

3-EMG:

fibrillation potentials.

4-Muscle biopsy:

diagnostic, showing pattern of perinatal denervation.

Treatment

1-Physiotherapy and respiratory support, mechanical ventilation.

2-Orthopedic care for scoliosis and joint contracture.

- Gene replacement and protein replacement therapies remain theoretical and experimental. Potential therapeutic genetic
- strategies in SMA include upregulation of *SMN2* gene expression, preventing exon 7 skipping of SMN2 transcripts and improving the stability of the protein lacking the amino acid sequence encoded by exon 7.

Disorders of the Peripheral Nerves

Guillian Barre Syndrome (postinfectious polyneuropathy)

Definition

- Post-infectious polyneuropathy leading to demyelination mainly in motor nerves, sometimes sensory and autonomic nerves are affected, affecting all ages.

Etiology

- Flaccid paralysis follows respiratory or gastrointestinal tract infection.
- Sensitized lymphocytes to a protein component of myelin will lead to demyelination of peripheral nerves.

Clinical manifestation

1- The course is progressive over days or weeks.

2-Sensory features;

tenderness, muscles pain, sometimes paresthesia.

3-Autonomic features;

transient urinary incontinence or retention, postural hypotension or hypertension.

4-Motor features;

- Weakness usually begins in the lower limbs; progressively involve the trunk, then upper limbs, finally the bulbar muscles due to cranial nerves affection leading to dysphagia, diaphragmatic paralysis.

- The weakness is symmetrical, bilateral, associated with hypotonia and hyporeflexia or absent tendon reflexes.

Prognosis

1-Progressive course; bulbar involvement leading to dysphagia, aspiration pneumonia while respiratory muscles affection results in respiratory failure.

2-Regressive course; spontaneous recovery starting within 2-3 weeks in 90 % of patients.

Diagnostic Investigations

1-Cerebrospinal fluid (CSF) studies;

showing protein elevation with normal CSF cells count and glucose level.

2-Motor & sensory nerve conduction velocities;

marked reduction.

Treatment

1-Supportive management including hospitalization,

observation,

nutritional support,

cardiovascular monitoring,

ventillatory support if needed.

2-Care of the bladder, bowel and skin.

3-Intravenous immunoglobulin (IVIG); used for 5 days.

4- Other treatment includes plasmapharesis or steroids if IVIM is ineffective.

Muscles Disorders

Muscular dystrophies

Definition

- The muscular dystrophies are a group of diseases that are distinguished from other neuromuscular disorders by four obligatory criteria:

(a) Primary myopathies, not neurogenic

(b) Genetically determined

(C)Progressive diseases, some slowly progressive and compatible with normal longevity and others more rapidly progressive and leading to early death

(d) Myofiber degeneration at some stage in the disease.

Duchenne Muscular dystrophy

Incidence:

- It is a relatively common condition with a prevalence of 1 in 25,000.
- Clinically, it is the most clearly defined of the muscular dystrophies.
- The disease becomes apparent in early childhood.

Genetics &Pathogenesis;

- Transmitted in a sex-linked recessive manner.
- The gene for Duchenne and Becker muscular dystrophy is localized on Xq21.2. Its product has been named dystrophin, a protein with a molecular weight of 427,000.
- The most common gene mutation in both Duchenne and Becker muscular dystrophies is a deletion which affects the process of dystrophin synthesis in different manners.

Clinical Manifestations

1-The onset;

- At first, these are often confined to difficulty in climbing stairs,
- in arising from the floor, or
- in performing other activities that involve the pelvic muscles.

2-Gowers' sign;

- An early indication of pelvic weakness is the manner by which patients arise from the floor, he first rolls to the prone position, kneels and then raises himself to standing by pushing with his hands against shins, knees, and then thighs.

3-**Waddling gait**:

due to weakness of the gluteus medius and minimus muscles.

4-Lordosis;

commonly appears with progression of the disease due to weakness of the extensors of the trunk.

5- Hypotonia & Hyporeflexia.

6-Muscular wasting & Pseudohypertrophy of the calves and, less commonly, of the deltoids and infraspinati.

7-Contractures are common and occur chiefly at the hamstrings.

8-Cardiomyopathy, enlargement of the heart, persistent tachycardia, and myocardial failure, significant electrocardiographic abnormalities.

9-Smooth muscle dysfunction like

- gastric hypomotility can result in sudden episodes of vomiting,
- abdominal pain, and distention.
- In a small number of patients, there is a history of diarrhea, malabsorption, or megacolon.

- **10-Constipation, fecal retention, and distention of the bowel** may result not only from smooth muscle involvement, but also from weakness of the striated rectus abdominus muscles.

- **11- Defective intellectual development;** The mean IQ of children with Duchenne muscular dystrophy is approximately 85.

12-The course of the illness; steadily downhill. Death usually occurs in adolescence and results from secondary infections or intractable congestive heart failure.

13-The female carrier for muscular dystrophy is usually asymptomatic, but occasionally demonstrates pseudohypertrophy and mild weakness of the pelvic musculature.

Diagnostic Investigations

1-Muscle biopsy:

diagnostic with histological features revealed

- connective tissues proliferation,
- scattered degenerating and regenerating myofibers.
- Dystrophin protein assessment showed absent dystrophin.

2-Muscles enzymes evaluation;

- The serum level of many soluble enzymes normally present in muscle tissue is increased.
- These include

1-aspartate aminotransferase,

2-alanine aminotransferase,

3-lactic dehydrogenase,

4-aldolase, and

5-CK- MM isozyme is the most sensitive and specific for the presence of a dystrophic process.

3-Molecular genetic studies:

DNA markers derived from within the dystrophin gene locus have been used in the prenatal diagnosis of Duchenne muscular dystrophy using amniocytes or chorionic villus cells.

4-EMG:

- characteristic myopathic pattern.

5-Motor and sensory nerve conduction velocities:

- normal

Treatment

At present, no treatment is effective for any of the muscular dystrophies.

- **1-Corticosteriods;**A variety of corticosteroids slow the progression of the disease,

- One protocol gives prednisone
- (0.75 mg/kg/day) for the 1st 10 days of each month to avoid
- chronic complications. Deflazacort, administered as 0.9 mg/kg/day,
- may be more effective than prednisone.

- however long-term treatment with corticosteroids may actually make the patient weaker
- by the added weight of additional subcutaneous adipose tissue that the weakened muscles must overcome and because of other

- complications of chronic corticosteroid therapy in any patient.

- **2-Myoblast transfer;**

Other potential therapeutic approaches include gene replacement, myoblast transplantation, or replacement of dystrophin by other, dystrophin-related proteins.

3-Physiotherapy;

- can be helpful in preventing contractures of the ankles and hips in particular.
- But if physiotherapy is too vigorous, it may actually accelerate the rate of degeneration of the fragile myofibers with abnormal sarcolemmal membranes.

4- Using of braces and avoidance of major surgery & orthopedic measures.

- Another potential treatment still under investigation is intravenous or subcutaneous injection of antisense oligonucleotide drugs that induce exon skipping during mRNA splicing in patients with susceptible mutations (~15% of patients) to restore the open reading frame in the DMD gene.

- Drisapersen and eteplirsen are exon 51 skipping antisense oligonucleotides that bind RNA and skip (bridge) over the defective exon, thus producing a shorter but potentially functional dystrophin protein.
- The shortened protein has been demonstrated to appear in muscle biopsies after treatment with these agents


Thank you