Spinal muscular atrophy (pediatrics)

Spinal muscular atrophy (SMA) is a clinically heterogeneous group of hereditary degenerative diseases affecting the anterior horns of the spinal cord and often the motor nuclei of the cranial nerves. Peripheral nerves and cerebrospinal pathways are not affected. SMA is the second most common neuromuscular disease after Duchenne muscular dystrophy, it is also the second most common cause of infant mortality in autosomal recessive disease. They are mainly manifested by marked muscle hypotonia with hyporeflexia of the limbs, muscle hypotrophy to atrophy and fasciculations of the tongue. The pathogenesis and causal therapy of SMA are still unknown, diagnosis is based on molecular-genetic examination. In 95% of proximal forms of SMA, causality has already been demonstrated mutation in the SMN gene on chromosome 5q.[1]

Classification

Classification of SMA according to the age of onset of difficulties, motor maximum and an average age of life:

SMA type I. (*Werdnig-Hoffmann*)

- Difficulties until the 6th month of age, inability to sit independently

SMA type II.

- Difficulties until 18 months of age, inability to walk independently

SMA type III. (*The Kugelberg-Welanders*)

- Difficulties after 18 months of age, able to walk independently

SMA type IV.

- Difficulties after 30 years of age, able to walk independently[1]

Clinical forms

SMA type I – *Werdnig-Hoffmann disease*

- Severe clinical form; "acute infantile form“
- Accounts for 35% of all SMA cases.
- **The beginning of difficulties** is already at birth, or they develop up to 6 months of age. In 35% of cases, mothers report reduced foetal movements.[2]
- **Clinical picture**: severe, rapidly progressing muscle weakness with mainly proximal localisation, hypotonia with hyporeflexia. Fasciculations of the tongue are common. Children are never able to sit independently. The occurrence of a bulbar syndrome (disappearance of the gag reflex) is an unfavourable prognostic sign that reduces the average life expectancy to 6 months.[1]
- **Prognosis**: 95% of children die before 18 months of age from respiratory failure.[2]

SMA type II – *Werdnig-Hoffmann disease II*

- Moderately severe clinical form; "chronic infantile or intermediate form"
- A most common form of all SMAs, up to 45% reported.[2]
- **The onset of difficulties** is usually before the 18th month of age. Difficulties can be apparent even before 6 months of age, and in these initial stages, we are not able to determine the clinical form of SMA.
- **Clinical picture**: peripheral hypotonic syndrome, symmetrical muscle weakness, more pronounced in the lower limbs. Muscle contractures often develop, and pseudohypertrophy of the calves can also be seen. Children are never able to stand or walk independently.
- **Prognosis**: difficulties progress slowly, and life expectancy is reduced to 20-30 years.[2] The cause of death is again respiratory insufficiency.[1]

SMA type III – *Wohlfart-Kugelberg-Welander disease*

- Mild clinical form; "juvenile form"
- 8% of all SMAs.[2]
- **The onset of difficulties** is 95% between 1st and 3rd years. Again, the age of onset of symptoms does not allow for predicting the course of the disease.
- **Clinical picture**: The first symptom is a walking disorder, which is caused by a weakening of the proximal muscles of the lower limbs. Weakness is symmetrical with slow progression, it also spreads to the distal muscles of the lower and later also the upper limbs. At the beginning of the disease, and pseudohypertrophy of the calves is evident. Later, dysphagia and dysarthria may also be present.
- **Prognosis**: Children usually live to adulthood.[1]

SMA type IV

- "Adult form".
- **The onset of difficulties is** usually only after the age of 35. Progression can be rapid, so amyotrophic lateral sclerosis (ALS) must also be considered, but it is usually very slow.
- '*Clinical picture*: Several types are distinguished according to the predilection of difficulties. *Distal SMA* is manifested by symmetrical distal weakness of the upper or lower limbs, so the possibility of hereditary motor-sensitive neuropathy must also be considered in the differential diagnosis (HMSN 1, 2). *Segmental SMA* is often asymmetric with a predilection for either proximal or distal involvement (peroneal type of SMA). Bulbar involvement is absent.[3]

Kennedy's disease (bulbospinal muscular atrophy)

- A rare recessively inherited disease linked to the X chromosome. It occurs in men, women are asymptomatic carriers, and the incidence is 1:40 000 men.
- **The onset of difficulties** is usually in middle age (3rd to 5th decade).
- **Clinical picture**: increased fatigue and cramps, later weakness of the root muscles. As the disease progresses, proximal weakness with muscle atrophy progresses, generalised fasciculations appear, especially on the tongue and around the mouth, hand tremors, bulbar symptomatology increases, and difficulty swallowing and speech (dysarthria, nasolalia). In addition to signs of motor neuron involvement, symptoms of androgen deficiency - gynaecomastia and sometimes also testicular atrophy. In the laboratory, there is an increased level of estradiol, often also creatine kinase.
- '*Prognosis*: the course of the disease is variable, but it is usually a very slowly progressive disease, developing over years to decades.[3]

Pathogenesis

The pathogenesis of the disease is unclear. It is not proven whether this is primary damage to the motoneuron body or axon damage that would lead to this damage secondarily.[1]

Childhood SMA is in most cases AR hereditary. AD inheritance is described in approximately 2% of cases (in contrast to adults, where up to 30%), and cases of XR inheritance are also described very rarely.[4]

Diagnostics

- Objective finding;
- Laboratory examination – creatine kinase may be slightly elevated (maximum five times normal);
- EMG examination – typical findings of fibrillation and fasciculations, action potentials have high amplitude and prolonged duration, are often polyphasic, interference is reduced;
- Molecular genetic examination of the deletion of exon 7.8 of the SMN 1 gene (*survival motor neuron gene*) – the SMN 1 gene is mutated in 95% of proximal SMAs;
- If the genetic examination is negative, a muscle biopsy must be performed.[1]

Differential diagnosis

- Metabolic defects (e.g. glycogenosis), congenital myopathy or muscular dystrophy;
- Polymyositis and polyneuropathies.[1]

Therapy

- The new drug Spinraza - antisense oligonucleotide nusinersen, which is applied intrathecally
- Symptomatic therapy with the aim of preventing joint contractures, spine deformities and respiratory infections - intensive rehabilitation (including spa care), orthopedic care (splints, orthoses and corsets), respiratory rehabilitation and non-invasive ventilation.
- In the Czech Republic, there is an option for prenatal diagnostics.[1]

Links

External links

- Medical journal - Spinal muscular atrophy (https://zdravi.euro.cz/clanek/postgradualni-medicina/spinalni-svalove-atrofie-271481)
- Neurology for practice - Spinal muscular atrophy in childhood (https://www.neurologiepropraxi.cz/artkey/neu-200204-0003_Spinalni_svalove_atrofie_v_detskem_veku.php)
- Association of muscular dystrophies in the Czech Republic (http://www.amd-mda.cz/)

Reference

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3. Univerzita Karlova v Praze, 1. LF a VFN, Neurologická klinika. Spinální svalové atrofie. *Postgraduální medicína* [online]. 2006, y. 5, p. -, Available from <https://zdravi.euro.cz/clanek/postgradualni-medicina/spinalni-svalove-atrofie-271481>.
4. Kobayashi H, Baumbach L, Matise TC. A gene for severe lethal form of X-linked arthrogryposis (X-linked infantile spinal muscular atrophy) maps to human chromosome Xp11.3-q11.2, HumMolGenet 1995; 4 (7), 1213–1216.