6.23 Neuromuscular diseases

This is a large group of diseases, that are manifested with **disturbances of skeletal muscle functions**. The cause of which lies in the injury to a part of **neuromuscular unit**. The region of the primary lesion is the determinant factor for the clinical symptomatology, and this is why we devide these diseases into 4 groups:

1. myopathies (muscular dystrophy)
2. neural atrophies (primary affection of the peripheral nerves, secondary muscular atrophy)
3. atrophy of the ganglionic cells (affection of the neuromuscular cells)
4. diseases of the neuromuscular plate (muscular dysfunction).

Most of the diseases of this group have genetic and heriditary basis. Some role might be related to the effected external environment and metabolic abnormalities.

6.23.1 Myasthenia gravis

Myasthenia gravis (MG) is a disease that affects the neuromuscular junction. It is manifested by **a chronic tiredness**. When repeating the movement the limb becomes weak and tired as paralysed. This disease might spread to the surrounding segments (**iradiation of the tiredness**). MG mostly affects the facial muscles to form what is called **myasthenic facies** as well as affecting the language. The patient loses the ability to talk after few words. But after a short rest he is able to talk again. Generally patients having MG are more vital after rest and sleep e.g. in the morning if compared to the evining (they are tired). The gradual fade of activity, that returns back after a short rest is known as **the myasthenic reaction**. The disease might occur in any age, yet it usually appears after 20 years of age and it is more common in women than men.

In our books of neurology they only mention the disturbance of the presynaptic area, despite that it is clear that the postsynapotic lesion is present as well. There is a shortening and smoothening of the postsynaptic membrane and widening of the synoptic grove. Commonly there is arborization of the nerve endings, that leave the failing synaptic junctions, and search for a new contact along the muscle fibers.

The pathomechanism of the disease is connected to **the motor end plate – the transmission of nervous stimuli into the skeletal muscle**. The transmission of nervous stimuli is disturbed due to the abnormalities of ACH in the neuromuscular junction. The release of ACH from the vesicules of the presynoptic neuronal endings depends on the depolarisation of the presynoptic membrane by the effect of action potential, due to which Ca^{2+} influx activates the presynaptic vesicules. Those vesicules will difuse into the synaptic space and ACH will be released into this space. After the depolarisation ends, the Ca^{2+} is released fast into the terminal ending, or it might be absorbed by the mitochondria. The destiny of the released ACH is either:

1. Acetylcholin esterase (ACHE) is present in the grove and hydrolyses ACH into acetate and cholin, and those products return back to the nerve ending.
2. Acelylcholin will pass via the junctional space and reaches the ACH-receptors on the postsynoptic membrane.

The interaction of ACH and the receptor leads to a higher permeability via the postsynaptic membrane for Na^+, K^+, Ca^{2+}, and Mg^{2+} along their electrochemical gradient. These changes are proportional to the amount of released ACH, and the number of ACH – R interaction. For an adequate number of interactions there will be depolarisation of the post synoptic membrane, transmission of impulses, and muscular contraction. The whole event normally lasts for 10–20 ms. For the proper function of the neuromuscular junction we need to renew the passage which means the removal of ACH from the synaptic area. This is performed by ACHE, that is present in an amount of 5 – folds its needed quantity. This means that abnormalities of ACH removal and hence abnormalities in preparing the neuromuscular junction for the transmission of stimuli will happen when the level of ACHE drops to 20 % of its normal amount.

The mechanism, that disturbs those smoothly going on procedures on the neuromuscular junction is related to many physiological, pharmacological and

viral interactions. Recently **the pathomechanism of MG is related to immunological mechanism**.

Because MG is known from the year 1672 when the disease was described by T. Willis (the doctor of Charles the 2nd in England), we have a quantity of clinical observations, that reflect the development of openion about the pathogenesis of this disease. The first theory, the deficiency of the living energy was replaced with openions about the microbial origin of the disease. After the year 1900 MG was related to diseases of **thymus**. **Thymectomy** that is used up to date really improves the patientd̈s situation. In 1932 Loewi described ACH as a transmitter in the neuromuscular junction and two years later a symptomatic treatment with physostigmin was used. From the 60s long acting blockers of ACHE were used. It was shown that serum of patients with MG had a depressive effect on the transmission of impulses in the neuromuscular apparatus of the frogs. A positive therapeutic effect of the corticosteroids confirmed the immunological pathogenesis of MG that was pointed to by the clinical experience with thymectomy. The proven immunological alteration of the post synaptic part of the neuromuscular junction and the common association of MG with other autoagresive diseases but mainly the experimentally evoked autoimmune MG, lead to the present opinion about the pathogenesis of this discase.

From the neuromuscular junction functional point of view in cases of MG many authors wrongly thought that there was an altered function of the presynaptic part and hence the synaps contained low amount of ACH. Some precise calculations could prove that the production of ACH on the neuromuscular junction in patients with MG is similar to normal individuals. Some marked changes were found in the sensitivity of postsynaptic membrane and hence the acetylcholin receptors for the acetylcholin. In patients with MG this decrease was up to 80 % compared with the normal value. The lower postsynaptic sensitivity can be caused by many factors:

- lower number of the ACH – receptors
- an abnormal acetylcholin-receptor binding
- disturbed function of the ion channels, that provide the occurance and the continuation of the stimulation on the muscle.

The last possibility was not proven yet. On the other side many clinical and experimental studies showed that, the postsynaptic membrane is the target of the autoimmune reaction in cases of the experimental autoimmune MG in animals and the functional as well as the morphological changes are markedly similar to the human MG The result of both cases is a lower number of functioning acetylcholin receptors, which is most probably the most important factor of the disturbed neuromuscular transmission.

The role of thymus in the pathogenesis of MG is yet not much understood. The hypothesis, claiming, that thymopoetin, that has got a role in the transformation of lymphoid cells into T-lymphocytes, at the same time has an inhibitory effect on the neuromuscular junction was left nowadays. A new concept about the initiation of autoimmune aggressive process in MG came upon the exploration of the thymic myoid cells. These cells compose acetylcholin receptors on their surface and we assume that exactly here the reaction between ACH-receptor proteins with T-lymphocytes can occur for the first time (e.g. during a viral infection) and this could initiate the formation of antibodies. This hypothesis says that thymus is the primary site of autoimmunization, where the T-lymphocytes after sensitization by the ectopic acetylcholin receptors, the myoid cells act as inductors for the production of pathological IgG in the B-lymphocytes. The T-lymphocytes at the same time act as helpers to maintain the pathological process.

If we want to understand the pathogenesis of the disease completely, we have to know which pathophysiological moment is the most important in the course of the disease: whether it is the autoaggressive immunity pathway itself, or it is an immunity defect that released those autoimmune processes from the controlling effects.

6.24 Autonomous (vegetative) nervous system

Most pathologic conditions do not represent a simple change of some organ function. They mostly evoke a secondary alteration of activity in the autonomous nervous system. A non-causal therapy of diseases often represents an intervention into the autonomous nervous system. Thus, from the pharmacological point of view it is often not the pathologically altered organ that is influenced but the autonomous nerves that control its activity.