

same substance all the time. Many of these antigenically active substances do not have encephalitis generating effect. Finally it was found out that the determinant protein is localized in the myelin.

Injection of the prepared antigen will provoke an immune reaction, the consequence of which are histological changes in the brain of the experimental animals. The clinical picture is apathy, paresis, paralysis, loss of weight, incontinence, spasms and death. The immunological etiopathogenesis of the EAE is supported by evidences since the 60 yrs:

1. The experimental animals will have signs of sensitisation after administrating the nervous tissue extract.
2. The disease will appear after 10 days of the day of antigen administration.
3. Upon reimmunisation the latent period is shortened
4. The reaction is very specific. The disease process occurs only after the administration of the antigen that is present in the white mater of the brain and medullary myelin.

**The immunological reaction is the delayed hypersensitivity type.** This reaction is manifested by the cytotoxic effect of lymphocytes on the antigen containing cells.

We conclude from the mentioned facts that EAE is an **autoimmune disease**, in which the hypersensitivity is experimentally induced by an encephalitogenic component of the nervous tissue (myelin).

The pathogenesis of EAE can hence be the sum of the following:

1. **Lymph node cells sensitization** after the transition of antigen-adjuvans complex via the lymphatic system from the infected site.
2. **Circulation (possibly recirculation) of the immune competent lymphatic cells** via blood and lymph.
3. **The entrance** of the specifically sensitized cells **into the nerve tissue** via the cerebral circulation.
4. The formation of **contact with the target tissue** (oligodendroglia, and myelin).

5. **The release of chemotactic factors**, that attack other non sensitized leukocytes (a great secondary inflammatory reaction).

EAE can hence occur when antibodies against the administered antigen also react with the same (similar) CNS tissue antigens.

The possibility to transfer the EAE from an animal with an induced EAE to another healthy animal via a passive transfer of the sensitized lymphocytes has got a great value in the research of the demyelination diseases.

EAE serves as a model to discover the etiopathogenesis of demyelination diseases. By this way it would be necessary to produce EAE that comes in attacks, similar to the MS for example. Following the formerly explained method this is not possible yet. EAE also helped in the classification of encephalomyelitis into primary (infectious) and secondary (neuroimmunological).

### 6.10.5 Dysmyelination diseases

In this group of **leukodystrophies**, the molecular structure of the myelin is disturbed or namely different from the normal. Most of the cases has some genetic basis, that manifest from the childhood and is very progressive. The abnormal or the disturbed enzyme structure leads to the accumulation of different metabolites in the macrophages, glia, or neurons. An example of this might be **metachromic leukodystrophy** with the accumulation of sulfatids, or **Karbbes disease** with the deposition of cerebroside in the so called globoid cells (polynuclear histiocytes).

We often use the term diffuse cerebral sclerosis in those cases where the absence of myelin is accompanied with a prominent gliosis.

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## 6.11 Degenerative diseases of the CNS

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A large group of diseases belong here. The common sign is the gradual degeneration of neurones and

axons of certain nuclei and nerve tracts. Those diseases affect all parts of the NS from the cortex to the peripheral neurones. This group of diseases belongs to the genetically conditioned diseases.

### 6.11.1 Parkinson disease (paralysis agitans)

**Parkinson disease** (PD) is a chronic degenerative disease of the CNS, that is characterized by **the progressing hypokinetic rigidity syndrom**. It occurs in older ages over 50 yrs as an idiopathic disease and it is associated with some age related changes.

As a secondary disease it is often associated with a previous inflammatory (**postencephalitic form**) injurious (repeated cerebral commotion) or toxic (neurotropic drugs, CO poisoning, Hg), damage to the CNS. In case of toxic damage to the CNS it is thought that there is a disturbed balance of the brain neurotransmitters. The cause of which might even be the disturbed vascular supply of the brain (**arteriopathy**). The pathologicoanatomical substrate of the PD is **degeneration and atrophy of the extrapyramidal nuclei**, and mainly the cells of **substantia nigra** and **basal ganglia**. There will be degeneration of the nigral neurons, that lead to corpus pallidum, where they produce dopamine. This is how **the dopamine production in the basal ganglia is reduced** and its inhibiting effect on the transmission of neuronal impulses in the extrapyramidal tract that regulates the intentional and fine motor movements is eliminated. **The extrapyramidal system** joins the highest motor centers (the cortex) to the effector motor cells (the anterior horn cells) of the spinal cord. What is left of the basal ganglia in the midbrain is the pons cerebri and a joining complex between the basal ganglia and other parts of the cerebrum, cerebellum and spinal cord. Its function lies in the facilitation and inhibition of the neuronal activity of the anterior horn cells so that it integrates the sensory impulses in a way that makes the tendon reflexes continuous and coordinated. The most important **neurotransmitter** in this system is **dopamine** (but also catecholamines and 5-hydroxytryptamine), **acetylcholin** and **gammaaminobuteric acid** (GABA).

In the healthy adults the dopaminergic and cholinergic extrapyramidal systems are in a state of equilibrium. Due to the neuronal degeneration in the substantia nigra, where dopamine is formed, in PD,

there will be **loss of equilibrium in the extrapyramidal system** due to **the dopamine deficit**. Dopamine belongs to a large group of mediators. Nowadays the original Dale's principle do not apply any more: one neuron one transmitter. It was proved that more than one neurotransmitter might present in one cell. Usually one transmitter has got multiple receptors and hence the final result might be variable. This situation might occur in substantia nigra in the neostriate (extrapyramidal tract), where the glycinergic neurons for example are inhibited by the dopaminergic tracts, and at the same time the dopaminergic tracts are under the inhibition of the gamma aminobuteric acid system (GABA) of the corpus striatum. In the corpus striatum itself the glycinergic inhibitory circle on the contrary to the previous example, lies between the GABA-ergic and DOPA-ergic neurons. The disturbances of these bonds that are in equilibrium leads to an inadequate processing of information and hence to the disturbance of not only motor but also some cognitive functions.

The function of extrapyramidal motor regulation lies in multiple junctions, control and feed back inhibition to direct the movement. The feed back circle might form even between the cortex, the basal ganglia (corpus striatum) and thalamus. Between the corpus striatum and thalamus the main neurotransmitters are acetylcholine and GABA (activation). Substantia nigra plays an essential role here due to the formation of DOPA (inhibition), that helps to modulate, and balance the programmed motor action. In cases of PD the destruction of the inhibitory part of the pathway results in the overwhelming of cholinergic activity (tremor, rigidity, non coordinated or even abnormal muscle movements), possibly akinesia.

The disease is clinically manifested with **a muscular tonus disturbances**, the patient has a mask face, sometimes with some grimaces, the typical hand tremor and **the typical finger movements known as pin rolling**. The abnormal **postural tonus** is manifested with changing the center of body weight (bending) with a stiff, tongue, dragging behind the lower limbs when walking. Some neuroendocrine signs and dementia might complete the picture of the disease.

**The treatment** arises from the need to supply the organism with L-DOPA as a precursor of dopamine, that is produced in the targeted structures by the process of decarboxylation. The problem is that this de-

carboxylation might occur in the peripheral tissues as well so it might exhaust the original substrate determined for the CNS. That is why we give drugs that inhibit the peripheral decarboxylase enzyme, as an adjuvant therapy so less dopamine will be formed in the peripheries and more L-DOPA might reach the CNS.

PD therapy was one of the first areas of the CNS pathology where **neurotransplantation** was applied. It is not true that the nervous system tissue do not produce an immune reaction. The non prominent immune reactions of the CNS in the normal situations are due to the very low permeability of the blood-brain barrier. Upon its destruction there will be a whole series of diseases that have immunological basis. Despite this fact many transplantations were provided for patients with PD. The transplant should consist of tissue that is rich with dopaminergic neurons from the adrenal cortex. The results show that this therapy is not long lasting. Although there will be some improvement post transplantation yet it is only temporary. We might decrease the doses of drugs, yet the patients have to continue the treatment with L-DOPA.

### 6.11.2 Alzheimer disease

**Alzheimer disease** is a very commonly occurring neurologic disorder. Formerly believed to occur mostly in persons under 65 yrs of age, Alzheimer disease has now been demonstrated to be one of the most common causes of severe cognitive dysfunction in older persons. Alzheimer disease is found in 2% to 3% of the general population and in 5% to 6% of persons 65 yrs of age or older. Presenile dementia of the Alzheimer type is a rare disorder in which persons, typically in their 50s, develop a rapidly progressing deterioration in cognitive function. Senile dementia of the Alzheimer type is the common disorder developing in persons after the age of 65.

**Pathogenesis.** The exact cause of Alzheimer disease is unknown. Several possible causes are currently under investigation. Alzheimer disease has recently been linked to chemical changes – a loss of the enzyme choline acetyltransferase resulting in a selective deficit in acetylcholine in acetylcholine-releasing neurons. Alzheimer disease has also been recently linked to the uninhibited activity of ribonuclease, an enzyme that breaks down RNA in neurons. The link between the pathology of Alzheimer disease and alu-

minium has been established and results from the degenerating neurons releasing detectable amounts of aluminium. Researchers have not yet been able to isolate a virus that causes Alzheimer disease, but submicroscopic proteinaceous infectious particles "prions" have been isolated. These prions have already been linked to at least one other form of degenerative brain disease. Antibrain antibodies may account for Alzheimer disease, and an autoimmune etiology is also being investigated. Regarding a genetic etiology, Alzheimer disease may be due to an autosomal dominant gene. An extra copy of a gene on chromosome 21 may be responsible for the production of protein amyloid in cells from both patients with Alzheimer disease and Down syndrome. Familial risk appears to be greatest in families affected by the classic early onset of Alzheimer disease. The risk when a sibling develop Alzheimer disease after age 70 does not differ from that of the general population.

Microscopically, the protein in the neurons becomes distorted and twisted forming a tangle called a **neurofibrillary tangle**. There is an accumulation of these bundles of paired helical abnormal protein fibres (filaments) within the neurons. Groups of nerve cells, especially terminal axons, degenerate and coalesce around a fibrous core. These areas of degeneration appear like plaques under microscopy and are, therefore, called **senile plaques**. These plaques disrupt nerve impulse transmission. Senile plaques and neurofibrillary tangles are more concentrated in the cerebral cortex and hippocampus. The greater the number of senile plaques and neurofibrillary tangles, the more dysfunction is present.

#### 6.11.2.1 Clinical manifestation

Initial clinical manifestation are insidious and often attributed to forgetfulness, emotional upset, or other illness. The individual becomes progressively more forgetful over time, particularly when related to recent events. Memory loss increases as the disorder advances and the person become disoriented and confused. The ability to concentrate declines. Abstraction, problem-solving, and judgment gradually deteriorate. There is a failure in mathematical calculation ability, language, and visuo-spatial orientation. Dyspraxia may appear. The mental status changes induce behavioral changes including irritability, agitation, and restlessness. Mood changes also result from the deterioration in cognition. The

person may become anxious, depressed, hostile, emotionally labile, and prone to mood swings. Motor changes may occur if the posterior frontal lobes are involved. The individual exhibits rigidity (paratonia) with flexion posturing, propulsion, and retropulsion.

### 6.11.2.2 Evaluation and treatment

The diagnosis of Alzheimer disease is made by ruling out other causes of a dementing process. A blood-cell membrane aberration is currently being investigated as a biologic marker of Alzheimer disease. The history, including the mental status examination, and the course of the illness are used to diagnose Alzheimer disease. The course of the disorder is highly variable, usually developing over 5 yrs or more.

The treatment of Alzheimer disease is directed at decreasing the need for the impaired cognitive function by a compensation technique, such as memory aids, maintaining those cognitive functions that are not impaired, and maintaining or improving the general state of hygiene, nutrition, and health. Environmental management, counseling, education, pharmacotherapy, and health promotion measures are the foundation upon which a comprehensive treatment program is built.

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## 6.12 Epilepsy

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The term epilepsy includes a group of disorders of the CNS, that are characterized by repeated paroxysmal changes of the nervous function caused by an abnormal electrical activity in the brain. Epilepsy is usually manifested by changes of consciousness of a paroxysmal character, that are usually associated by motor, vegetative, biochemical, and electrophysiological changes.

According to the recent studies about 1% of the population suffers from recurrent epileptic attacks and it is assumed that about 10% of people survives some form of an attack at least once in a lifetime. Inheritance is thought to be an important factor in the formation or predisposition to the attacks, not in the occurrence of the attack itself.

To understand epilepsy as a nosological unit one basic requirement is not fulfilled being one etiological factor. From the etiological point of view we may divide epilepsy into primary and secondary.

1. **Primary epilepsy**, the cause of which was not possible to determine yet using the recent diagnostic methods. It is a functional disorder of the CNS, that usually has an electrophysiological correlation in the EEG recording. The neuroradiological examinations are negative. It forms about 75% of cases. Using the modern diagnostic methods the number of cases with primary epilepsy are decreasing and many cases are diagnosed as secondary epilepsy.
2. **Secondary epilepsy**, or symptomatic, which cause is known, occurs in about 25% of cases.

From the topographical point of view, nowadays we divide epilepsy into:

- focal epilepsy with a defined epileptic focus, most commonly in the cerebral cortex, and
- non focal epilepsy, centrencephalic, in which the epileptic discharge arises from the so called centrencephalic area of the brain and then it is generalized.

### 6.12.1 The etiopathogenesis of the epileptic attack

The pathophysiological basis of the epileptic attack is **the epileptic discharge**. There will be production of pathological rhythmic excitation in a certain population of neurons. It is synchronized and it spreads in the nervous system from the area of its generation either to a bordered area (**partial attacks**) or to the whole CNS (**generalized attacks**). The basis of the epileptic discharge is a change of the neuronal metabolism, that is associated with a high energy expenditure. As an evidence of this is the increased level of the adenosindiphosphate (ADP) and a decreased level of ATP, a lower level of glucose, glycogen and creatinphosphate, and the drop of pH in the blood and the brain.

Three pathogenetic factors may share the manifestation of the epileptic attack: **the epileptic focus, the readiness (predisposition) for epileptic attacks, and the epileptic stimulus**.