ALZHEIMER'S DISEASE – NEUROLOGICAL OR PSYCHIATRIC DISORDER?

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ABSTRACT

Alzheimer's disease (AD), a progressive neurodegenerative disorder, is the most common form of dementia in the elderly. The clinical manifestations of Alzheimer's disease evolve from an initial discrete impairment of recent memory to severe cognitive loss, in time behavioural and psychiatric symptoms becoming obvious and disturbing. The cause of this complex clinical picture is the gradual functional deterioration and eventually loss of all brain cell types, with severe alteration of neuronal networks supporting cognitive processes.

The aim of this paper is to examine different features of AD and to formally establish whether it belongs to the neurological or psychiatric group of disorders. A review of key literature in the field was performed for main attributes of AD neuropathology and pathophysiology. In this respect, we have compared AD with classical psychiatric disorders (schizophrenia, bipolar disorder, obsessive compulsive disorder) and with neurological degenerative disorders (AD, Parkinson's disease, epilepsy, amyotrophic lateral sclerosis, Huntington's disease).

In brief, AD pathogenic mechanisms involve protein aggregation, synapse alteration, oxidative stress, neurotransmitter deficit, intracellular calcium dyshomeostasis and mitochondrial dysfunction, all together finally leading to cell death and brain atrophy. To some extent, some of these features are common for both psychiatric and neurodegenerative disorders. However, from the cellular and molecular pathology perspective, AD seems to be closer to other neurological conditions than to classical psychiatric diseases.

Key words: Alzheimer's disease, brain atrophy, apoptosis, oxidative stress, calcium dyshomeostasis, mitochondrial dysfunction

INTRODUCTION

Alzheimer's disease (AD), a progressive neurodegenerative disorder, is the most common form of dementia in the elderly. The mean disease duration is around 8.5 years between onset of clinical symptoms and death. AD is a disease with an important impact on public health systems in Europe. The epidemiological studies have identified several risk factors for disease development. The proposed risk factors are: non-modifiable (aging, feminine sex, perinatal condition), modifiable by socio-economic interventions (low level of social activities, low education), modifiable by medical interventions (vascular risk factors – hypercholesterolemia, diabetes, arterial hypertension, obesity) (1).

AD is reported to be responsible for approximately 80% of all dementia cases and is the fourth leading cause of death amongst those above 65 years (2). Nevertheless, it is one of the most frequent mental illnesses, approximately 20% of all psychiatric hospital admissions (1).

The first report of the disease is dated more than a century ago, in 1906, by Alois Alzheimer. At that time, the psychiatric and neurological diseases were studied together as related scientific disciplines. Moreover, the first case described by Alzheimer, the famous Auguste Deter, experienced an 'atypical' AD clinical picture, with prominent psychiatric features, such as aggressive behaviour, paranoia and auditory hallucinations. Very recently it was demonstrated that Auguste D. suffered from a

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presenilin-1 mutation (3). In the last decades, neurology and psychiatry separated and it is generally accepted that brain diseases are classified as neurologic or psychiatric depending on the presence or absence of cerebral lesions, respectively.

The aim of this paper is to examine different pathological features of AD and to formally establish whether it belongs to neurological or psychiatric group of disorders. A review of key literature in the field was made for main attributes of AD neuropathology and pathophysiology. In this respect, we have compared AD with classical psychiatric disorders (schizophrenia, bipolar disorder, obsessive compulsive disorder) and with neurological degenerative disorders (AD, Parkinson's disease - PD, epilepsy, amyotrophic lateral sclerosis - ALS, Huntington's disease - HD).

NEUROPATHOLOGY AND PATHOPHYSIOLOGY OF AD IN BRIEF

In AD patients, atrophy starts in the temporal lobe, affecting in time the frontal and parietal lobes as well. The early diagnosis is supported by structural MRI, which shows atrophy of hippocampus. Brain atrophy is a result of both synapse loss and brain cell death. From the neuropathological point of view, AD is characterised by two hallmark lesions: extracellular amyloid plaques (composed of 40-42 residues β amyloid (Aβ) peptide) and intracellular neurofibrillary tangles (NFTs) (composed of abnormal phosphorylated microtubule associated Tau protein). The Aβ peptide derivates from enzymatic cleavage of the amyloid protein precursor (APP). There are three cleavage secretases: α, β, **γ.** The APP is cleaved by either α or β secretase and further by **γ** secretase. The cleavage of APP by α secretase and then by **γ** secretase releases forms which are not toxic for the neurons. Instead, APP cleaved by β secretase and then by **γ** secretase generates two peptides: Aβ 1-40 and Aβ 1-42 (40 or 42 amino acids, respectively). The Aβ species are toxic for both synapses and neurons, eventually causing synapse loss and neuronal loss, Aβ 1-42 being more fibrilloidogenic and toxic as compared to Aβ 1-40. The main compound of intraneuronal NFTs is Tau protein which becomes abnormal structurally and functionally by a process of extensive hyperphosphorylation. The hyperphosphorylated tau is organized into paired helical filaments (PHF) and development of PHF leads to improper functioning of microtubules and axonal transport. Consequently, the cytoskeletal structure is compromised and colapses (4).

Braak and Braak in 1996 described the staging neuropathological criteria for AD: stages I and II are characterized by NFTs in entorhinal cortex and adjacent portions of the hippocampus; stages III and IV involve NFTs spread to limbic regions (both entorhinal and transentorhinal region); stages V and VI are marked by destructions to other regions of the cortex. This extension of lesions progressively aggravates the cognitive deficits (5).

Genetic mutations have been found in both genes coding for Amyloid Precursor Protein (APP) and presenilins, the latter being molecular components of γ-secretase. There are three genes mutations that are responsible for early- onset Alzheimer's disease: the gene for APP found on chromosome 21 and genes encoding for the homologous membrane- bound proteins presenilin 1(PS1) on chromosome 14 and presenilin 2 (PS2) on chromosome 1. The PS1 mutations result in a drastic effect on the Aβ42/ Aβ40 ratio, by an increase of Aβ42 and a reduction of Aβ40, hence determining neuronal toxicity. For late-onset Alzheimer's disease: ε4 allele of Apolipoprotein E (ApoE), encoded on chromosome 19, represent a major genetic risk factor for development of AD (6,7).

As AD progresses, it involves a cascade of mechanisms, ending with neuronal loss, neurotransmitter major deficit at the cortical level and profound alteration of neuronal networks. Aging and a large array of vascular risk factors and external insults apparently trigger protein missfolding and aggregation (8, 9). Aβ, especially in its oligomeric forms, affects neuronal protein trafficking and is toxic for mitochondria in AD patients. NFTs progressively block axonal transport and neural plasticity and accelerate mitochondrial degradation. These pathological processes lead to increased production of reactive oxygen species, which cause extensive oxidative damage and depolarization of the mitochondrial membrane, which further on results in neuronal energy depletion (10, 11). Dysregulation of cellular Ca^{2+} homeostasis is produced by a variety of factors, including ER-stress and alteration of muscarinic receptor-mediated mobilization of ER calcium stores. Local Ca^{2+} signaling is indispensable in neurons for presynaptic release of neurotransmitters and for triggering synaptic plasticity and long term potentiation (12, 13). A reduction in choline acetyltransferase expression and acetylcholine release, alteration of glutamate signaling, noradrenergic and serotoninergic system deficiencies characterize the multiple neurotransmitter deficits in AD. On long term, a decrease synaptic density takes place before neuronal cell death be-

come manifest. Beside Aβ toxicity and neuroexcitotoxicity, impaired proteasome function is another trigger for neuronal loss (14, 15).

ARE NEUROPATHOLOGICAL AND PATHOPHYSIOLOGICAL MECHANISMS IN AD SIMILAR TO OTHER PSYCHIATRIC OR NEUROLOGICAL DISORDERS?

Brain atrophy

From birth to approximately 3 years of age the brain rapidly increase in weight; after that, there is a slow increase until age of 19. Further on brain weight remains stable until the age of 40-45 and a slow decrease follows, explained by white and grey matter volume decrease, accompanied by enlargement of the ventricles and sulci (16).

Psychiatric disorders

In schizophrenia, males (3%) and women (9%) have smaller brains then normal age matched controls. In the bipolar disorder group females have smaller brains then the control ones (17). In a study of obsessive- compulsive disorder (OCD) patients, no global differences for brain volume were reported. However, slight differences in white matter of right parietal areas were found between OCD patients and controls (18).

Neurological disorders

In epilepsy patients hippocampal volume reduction is associated with the ipsilateral seizure focus. Volume reduction has also been reported for the thalamus, caudate nucleus, putamen, amygdala (19 - 23). In Parkinson's disease there are multiple brain areas involved in motility, gait and memory, which seem to be affected. There is a loss in grey and white matter in frontal lobe, basal ganglia, cerebellum (movement related), medial temporal lobe (memory and mood related); parietal lobe (non-motor sensitive symptom related); occipital lobe (visual hallucination - related) (24). In ALS there is grey matter atrophy in motor cortex, medial prefrontal cortex and temporal lobes and white matter atrophy corresponding to corticospinal tract, corpus callosum and inferior longitudinal fasciculus. In ALS the changes are more severe in white matter then in grey matter (25). In contrast to ALS, in HD earliest changes occur in grey matter of the basal ganglia, at the level of caudate nucleus, putamen and globus pallidus. In the evolution of the disease, atrophy extends to frontal and temporal cortical grey and white matter regions. Reduced volumes of hippocampus, entorhinal cortex and brainstem were reported as well (26).

Protein aggregation

Disturbances in protein homeostasis (proteostasis) lead to accumulation of aggregated or insoluble proteins in the cells, which in time alter neuronal transport systems and finally might trigger cell death.

Psychiatric disorders

In schizophrenia, a protein that is encoded by the DISC1 gene seems to undergo such aggregation changes. Dysregulated expression or altered protein structure of DISC1 may predispose individuals to the development of schizophrenia or bipolar disorders. Missfolded DISC1 deposits are the smallest protein aggregates associated to a progressive brain condition (27). However protein aggregation is not a general characteristic of psychiatric disorders. In contrast, all neurodegenerative diseases are characterized by abnormal protein deposits, either inside or outside brain cells.

Neurological disorders

In PD and other synucleinopathies, Lewy bodies are used as a pathological hallmark and they are composed mainly of missfolded α- synuclein (28). ALS is defined by a progressive degeneration of both upper and lower motor neuron systems, giving rise to loss of muscle function. Bunina bodies are abnormal intracellular inclusions, which consist of degenerative products formed as a result of a protein metabolism disorder. They are found usually in the remaining lower motor neurons appearing as small eosinophilic intracytoplasmic deposits. Only two proteins have been shown to be present in Bunina bodies, one is cystatin C and the other is transferrin (29, 30). Unverricht-Lundborg disease (EPM1) is a rare type of inherited progressive myoclonic epilepsy resulting from mutations in the cystatin B gene, CSTB, which encodes a cysteine cathepsin inhibitor. It is hypothesized that cystatin B protein may aggregate in the cell secondary to external insults or aging (31). HD is caused by autosomal dominant mutation in huntingtin gene. Expanded CAG repeats in this gene cause the huntingtin protein to aggregate and form intracellular inclusions (intranuclear and intracytoplasmatic). The protein aggregates are supposed to be toxic, determining disruption of the protein turnover homeostasis (32).

Oxidative stress

The brain represents 2% of the total body, but uses 20 % of oxygen consumed by the body. Oxidative stress results from the oxidant/antioxidant imbalance, in the presence of an excess in oxidants

(reactive oxygen species (ROS), reactive nitrogen species (RNS)) or a reduction in antioxidants (glutathione, thioredoxins). There is overwhelming data showing that oxidative stress gives rise to the free radicals which trigger neuronal loss. The brain is especially vulnerable to oxidative stress due to its low content in antioxidants, polyunsaturated fatty acids and high metal content and to high oxygen utilization.

Psychiatric disorders

In patients suffering from schizophrenia plenty of studies showed a disturbed activity of the oxidant/antioxidant systems. However, the conclusions of these studies are contradictory. It was reported that superoxide dismutase (SOD), GPX and catalase, as major antioxidant enzymes, can both decrease and increase in plasma, serum and red cells. These contrasting results might be explained by different patient profiles (such as positive or negative symptoms) and by type and dosage of treatment. Malondialdehyde (MDA), which is a lipid peroxidation end product, was found to be elevated in red blood cells, plasma and serum of schizophrenic patients (33, 34). Reports for OCD patients support an increased level of MDA and SOD, which play a protective role (35, 36). Regarding bipolar disorders, it is reported that thiobarbituric acid reactive substances (TBARS) (byproduct of lipid peroxidation, measured because ROS are short half-life) and NO activity (compound of RNS) are increased. No modification for SOD, GPX, and catalase was found in the same study (37).

Neurological disorders

In PD, a decreased level of GPX apparently increase susceptibility to neuronal toxic events and overexpose brain cells to free radicals. Decreased level of catalase may be one of the factors responsible for aetiology of PD (34). There are a lot of studies about the protective effect of the SOD in experimental models of PD. An increased plasmatic level of end products of lipid peroxidation (such as MDA and 4-hydroxynonenal) was reported in some studies (38-40). In epileptogenesis and chronic epilepsy the oxidant/antioxidant neuronal systems seem to suffer a permanent alteration. This disequilibrium improves after treatment with antiepileptic drugs in different experimental models. Lipid peroxidation, SOD, GPX and catalyse level were also significantly improved in treated epileptic patients (41). A common cause of ALS is mutation in the gene encoding SOD-1. This is found in approximately 20% of patients with familial ALS. Mutant SOD1 increase its propensity to form aggregates in pathologically affected motor neurons. Cytotoxic high levels of lipid peroxidation end products modify neuronal function by changes in membrane properties (42, 43). The mechanisms by which oxidative stress induces damage in HD include: lipid peroxidation, protein oxidation and DNA mutation and oxidation. Increased MDA levels in brain and peripheral blood have been demonstrated. Decreased Cu/Zn-SOD in peripheral blood has been documented, but this alteration was not found in patients' skin fibroblast culture. Increased free radicals production could result in damage of mitochondrial DNA, due to its proximity to the respiratory chain, and nuclear DNA (44, 45).

Disrupted intracellular calcium homeostasis

Brain ageing is a major risk factor for cognitive impairment. The calcium hypothesis of brain aging hypothesize that aged neurons have less compensatory capacities for dysregulation of Ca^{2+} intracellular concentrations, by time sustained increases of Ca^{2+} leading to cell demise. The most vulnerable in this respect seem to be the hippocampal and cortical neurons. Even under physiological conditions, mitochondrial calcium uptake increase oxidative stress. Increased intracellular Ca^{2+} concentration is transient in physiological conditions, but persistent cellular stress (due to aging and various pathophysiological mechanisms) can lead to prolonged Ca^{2+}overload, which is able to activate apoptosis. Ca^{2+} transfer from cytosol to ER, mitochondria and cell nucleus can demand high energy production and a subsequent neuronal ATP depletion. Depolarization of mitochondria affects as well the capacity to sequester excess Ca^{2+}, which will expose in turn cytosol to increased Ca^{2+} level (46).

Psychiatric disorders

RGS4 (regulator of protein signaling-4) and GAP 43(growth- associated protein 43) are proteins encoded by genes involved in schizophrenia by studies so far. These proteins are expressed at higher levels in cerebral cortex and hippocampus, regions were neurons are most susceptible to Ca^{2+} homeostasis disruption. Expression of Ca^{2+}- buffering proteins such as calbindin D28k and parvalbumin were reported to decrease in schizophrenia brains. Recent studies found that dopamine transmission is regulated by adaptor and signaling proteins called dopamine receptor-interacting proteins (DRIPs): calcyon (which allows D1 receptors to interfere with Ca^{2+} signaling) and NCS-1(Ca^{2+}-binding protein which inhibits desensitization of D2 receptors). In this line of evidence, defects in Ca^{2+} homeostasis might contribute to abnormalities in

the brain dopamine system in schizophrenic patients (46). For obsessive- compulsive disorder we found no reports regarding alteration of Ca2+ homeostasis at the neuronal level. However, one study evaluated the status of serum zinc, cooper, manganese, iron, calcium and magnesium in OCD patients compared to the control and found significant differences (47). Nevertheless, there is no known correlation between serum calcium concentration and Ca^{2+} neuronal homeostasis in general. The protein B-cell lymphoma (Bcl-2) it is well-known as an anti-apoptotic protein. However, Bcl-2 it is a Ca^{2+}-buffering protein as well, acting through direct interaction with cytosolic targets, mitochondria and the endoplasmic reticulum. A decreased level of Bcl-2 protein and its messenger RNA was described in the frontal cortex grey matter in patients with bipolar disorders (48).

Neurological disorders

In PD there are multiple molecular mechanisms involved in Ca^{2+} dysregulation. Probably the first described was linked to the dopamine toxicity hypothesis, which was refuted meanwhile: dopamine cytosolic oxidation was supposed to generate free radicals, with subsequent loss of dopaminergic neurons in the substantia nigra pars compacta and L-type Ca^{2+} channels were involved in cell death. However, different reports showed later that expression of Ca^{2+}- buffering proteins calbindin D28k, calretinin and parvalbumin decreases in PD models. Ca^{+} homeostasis can be modified by environmental insults (pesticide, inflammation) which are involved in PD pathogenesis. Moreover, genetic mutations associated with familial forms of Parkinson disease (DJ-1, Parkin, PINK1) act through increased oxidative stress, mitochondrial dysfunction and alteration of Ca^{2+} homeostasis (46, 49). In ALS, there are experimental arguments that Ca^{2+} overload of mitochondria might induce motor neurons death. The mechanism is still not clear, but different hypotheses have been explored. Transfer of Ca^{2+} from endoplasmic reticulum (ER), where is stored, to cytosol and then to mitochondria triggers the opening of the mitochondrial permeability transition pore (mPTP), release of cytochrome c and downstream activation of apoptosis. Another suggested mechanism is the increased production of mitochondrial ROS. Glutamate-induced excitotoxicity raise the cytosolic calcium concentration leading to neuronal loss through activation of calpains and caspases. Interestingly, spinal motor neurons do not express the Ca^{2+} binding proteins parvalbumin and calbindin D28K, fact which render them more susceptible to programmed cell death (46,50). Alteration of Ca^{2+} homeostasis plays an important role in induction and maintenance of epilepsy. The Ca^{2+} hypothesis of epileptogenesis suggests that: a) initially, there is a neuronal injury phase in which Ca^{2+} reaches high levels, but not enough to trigger cell death; b) in the second phase (the latency phase), Ca^{2+} level remains relatively increased, initiating many second messenger effects that modify neuronal plasticity; c) in chronic epilepsy increased neuronal intracellular Ca^{2+} maintains the spontaneous recurrent seizures, by lowering the excitability threshold. Epilepsy has many different causes, but the molecular mechanism for brain damage is the same: increased extracellular glutamate concentration lead to a sustained increase in Ca^{2+} levels, which in turn activates neuronal apoptosis (46, 51). Changes in abnormal protein huntingtin (Htt) in HT have as well a causative role in disturbance of the neuronal Ca^{2+} homeostasis. Mutant form of Htt is associated with mitochondria toxicity with opening of the mPTP. Further on, mutant Htt associates with increased activity of inositol triphosphate receptors (IP_3R) in the ER, facilitating Ca^{2+} release from the ER to the mitochondria. Finally, Ca^{2+} overload accumulated over time can lead to medium spiny neurons death in the corpus striatum (46).

Mitochondrial dysfunction

Mitochondria are cytoplasmic organelles that provide essential energy through synthesis of adenosine triphosphate (ATP). Mitochondrial pathology could be the consequence of genetic mutations, secondary to neurotransmission deficit or the result of the environmental detrimental factors. Because of their high energy demands, neurons have the highest mitochondrial volume fraction.

Psychiatric disorders

In the brain tissue of schizophrenia and bipolar patients morphological changes of mitochondria have been observed and in the prefrontal cortex mitochondria were significantly reduced in size. Furthermore, schizophrenic patients have fewer mitochondria in the striatum. These data suggest increased mitochondrial DNA mutation and polymorphism rates. Because of mitochondrial DNA abnormalities, mosaicism could cause some brain areas to be affected, but not others (52). In OCD, one study reports that mutations or polymorphic variants in mitochondrial DNA- encoded genes result in oxidative stress (53).

Neurological disorders

Altered mitochondrial function is related to the pathogenesis of PD by a wide variety of experimental and clinical studies. Decreased complex I activity was found in substantia nigra, skeletal mus-

cle and peripheral blood in parkinsonian patients. Environmental toxins have been proved as complex I inhibitors in PD, causing dopaminergic cell loss in substantia nigra. Genes associated with Parkinson disease (Parkin, PINK1, DJ-1, alpha- synuclein) have been found to induce defects of mitochondrial function. Mitochondrial DNA damage is seen frequently in the absence of nuclear damage in brainstem neurons. The mechanism for this mitochondrial DNA damage is possibly related to oxidative stress (54,55). In ALS patients, there are reports supporting a cytochrome c oxidase subunit I deficiency due to mutations in the mitochondrial DNA. In ALS, it is argued that changes occur in mitochondrial respiratory chain enzymes and mitochondrial programmed cell death proteins (55). Increase in mitochondrial oxidative stress and subsequent neuronal loss have been demonstrated as well in epileptogenesis. In recurrent seizures there is a subsequent neuronal hypermetabolism with increased cellular glucose uptake. Oxidative stress, already mentioned above, allows metabolites production like ROS and RNS. Further on, these events lead to protein aggregation, lipid peroxidation, changes in mitochondrial DNA and nuclear DNA, complex I enzyme dysfunction, Ca^{2+} overload and in the end apoptosis and neuronal loss (56). Recent studies revealed in HD a reduced activity of complexes II, III and IV of electron transport chain of oxidative phosphorylation. Defective mitochondrial activity results in low levels of ATP and cause synaptic loss. Imbalance between high level expression of genes of fission and low level expression of genes of fusion lead to mitochondrial dysfunction in HD patients brain. Increased DNA damage and decreased cytochrome b levels were found as well in HD patients (57).

Neurotransmission deficit

All brain functions are characterized by a structural support of specific brain areas connected between them and with the effector structures, and by a functional support of refined information transmission and integration, mediated by a limited range of neurotransmitters. Alteration either of brain structures or of neurotransmission patterns determines the clinical expression of central nervous system diseases. Classically, neurological diseases include the pathology involving brain structural damage and psychiatric diseases pathology of neurotransmission only. However, most of neurological diseases are characterized by drastic changes in neurotransmission patterns as well (58).

Psychiatric disorders

In schizophrenia, there is widely accepted that a glutamatergic system dysregulation is involved, which counterbalance inhibitory activity of GABAergic neurons. Reduction of dendritic spines, innervated by glutamatergic axon terminals, was found in prefrontal cortex of schizophrenic patients (59,60). Moreover, striatal dopamine, the main neurotransmitter involved in normal voluntary movement, affect and cognition, is reduced and dopaminergic synapses are defective in schizophrenic patients (61). Imbalance of dopamine and other neurotransmitters is responsible for the prefrontal cortex cognitive dysfunction in bipolar patients, with an important role in the switch process. Higher urinary cyclic adenosine monophosphate (cAMP), urinary norepinephrine and dopamine have been found in maniac patients. Discovery of genetic polymorphism in the serotoninergic system in bipolar patients support the hypothesis that serotonin deficit is involved in this disorder as well (62, 63).

Neurological disorders

There is overwhelming data about the dopamine dysbalance in basal ganglia in PD patients (dopaminergic hypothesis). Progressive loss of dopaminergic nigro-striatal neurons reduces the dopamine levels in the striatum, which prevent excitation of medium spiny neurons and finally initiation of movement. However, neurotransmission alterations in PD are vast, including cholinergic, serotoninergic, noradrenergic pathways, being responsible for the non-motor array of symptoms as well (cognitive impairment, depression, psychotic behaviour, etc.) (64). During epileptogenesis takes place a reorganization of glutamatergic and GABAergic transmission due to failure of mechanisms that normally stop the seizure focus activity. In models of epilepsy and epileptic patients, increased neuronal hyperexcitability compromise GABAergic synaptic transmission and a reduction in number of GABAergic synapses occurs (65). In ALS, a relative overactivity of the glutamatergic system is reported as well. Glycine signalling is another neurotransmission mechanism which is impaired in ALS, low level of glycine being reported in spinal cords of ALS patients (66). It is also proven that an imbalance between excitatory and inhibitory neurotransmitters occurs in HD, leading to interruption of information transmission from cerebral cortex to basal ganglia (67).

Synapse loss

Dendritic spines are dynamic structures that mediate neuronal responsiveness and plasticity. As de-

scribed below, synapse loss is a common feature of neurodegenerative diseases but recent reports demonstrate it in psychiatric disorders as well.

Psychiatric disorders

Disturbance in spine homeostasis and reactivity in schizophrenia results in neuronal networks malfunction, negative symptoms and cognitive deficits. Abnormal dynamics of dendritic spines is accompanied by changes in transcription and translation of neuronal synaptic proteins. Such proteins are synaptophysin, growth-associated protein-43 (GAP-43), complexin I and complexin II, which suffer significant expression and cell localization alterations in the anterior cingulate cortex of schizophrenic patients (68). Synaptophysin, complexin II and GAP-43 were found to be downregulated in bipolar disorder and loss of synaptophysin correlated with a decreased synaptic density in the affected regions (69). The decrease of GAP-43 expression might be responsible for impaired synaptic plasticity and the reduction of complexin II, but not complexin I suggests that the excitatory connections are particularly affected (68, 69). Neural cell adhesion molecule (N-CAM), another synaptic protein which plays an important role in synaptic stabilization, is abnormally expressed as well in bipolar disorders and this change might be linked to subsequent cognitive impairment, increased lateral ventricle volume and decreased hippocampal volume (70). Despite the fact that etiology, pathophysiology and molecular basis of OCD remain unknown, synapse loss was reported in animal models for this disease as well, at the level of cortico-striatal circuitry (71).

Neurological disorders

In PD failure of synapses in neuronal networks modulating movement is one of the well-known pathophysiological mechanisms. As mentioned above, abnormal protein aggregation, mainly of alpha- synuclein is characteristically found both in neuronal perikarya and terminals, impeding the normal axonal transport and neurotransmitter release. The large quantity of alpha- synuclein aggregates in neuronal processes has pathological effects for dendritic spines, with a subsequent reduction of pre- and post-synaptic protein markers. Losses of dendritic spines were reported in neurons of prefrontal cortex, basal ganglia, striatal different regions and susbtantia nigra (72). One of the frequent causes of temporal lobe epilepsy is hippocampal sclerosis. Different reports demonstrate that in hippocampal sclerosis cases there is a substantial reduction of synapse density in CA1 field, due to gliosis and neuronal loss, and the remaining synapses have few synaptic contacts. In contrast, in the transitional subiculum/CA1 region and subiculum region of these patients the number of synapses is persevered (73). In ALS patients, during the transition from the presymptomatic to symptomatic phase, motoneurons suffer a progressive reduction in their synaptic coverage, under oxidative and nitric oxide (NO) stress. Further on, synaptic alterations produce an imbalance in the ratio of inhibitory/excitatory synapses which facilitates glutamate-mediated neuroexcitotoxicity, mentioned above. (74). Changes in dendritic spines of HD patients are followed by synaptic loss, which apparently starts approximately a decade before the clinical diagnosis. Recent studies of synapse loss in HD point out a complex mechanism which includes elevated extrasynaptic NMDA receptor signalling and loss of brain-derived neurotrophic factor (BDNF) synthesis and release (75).

Neuronal death

The concept of neurodegeneration involves a progressive cell loss, mainly due to apoptotic neuronal death, located to central nervous system regions specific to every particular neurodegenerative disease. Pathogenic events leading to neuronal death were presented in all subchapters above. In brief, toxic protein aggregates and damaged organelles accumulate in neurons and lead to neuronal dysfunction and eventually neuronal death. Classically, neuronal death is a hall mark of neurological and not of psychiatric disorders.

Psychiatric disorders

DNA damage might be a feature of altered neuronal function in schizophrenic and bipolar disorders patients. Studies have shown in schizophrenia a downregulation of apoptosis genes, with antioxidant genes expressed at the same level to control subjects. In bipolar patients the same study indicated an upregulation of pro-apoptosis genes and a downregulation of antioxidant-related genes (76). To our knowledge, there are no reports about neuronal loss in OCD to date.

Neurological disorders

Starting with the first observations of Tretiakoff (1919) a substantial amount of reports demonstrated progressive neuronal loss in PD. Even though the precise trigger of cell death is not clearly established, accumulation of abnormal protein aggregates seems to play a central role. Alpha-synuclein is normally degraded by macroautophagy and chaperone- mediated autophagy (CMA). Inhibition of CMA and macroautophagy leads to a gradual accumulation of alpha- synuclein. Moreover, in fa-

milial PD mutated DJ-1, parkin, PINK1 or LRRK are all interfering with the autophagic pathway. Increased oxidative stress in autophagic cells was repeatedly reported in dopaminergic neurons and it participates to cell death initiation (14). Seizures are both a result and a cause of brain damage. Massive depolarization of neurons induces excessive glutamate release which increases intracellular Ca^{2+}, which in turn induces a cascade of mechanism that ultimately results in cell death, as mentioned in the detailed subchapter above. Prolonged seizures and status epilepticus ultimately lead to a complex and pathological reorganization of the local synaptic networks. *Direct* neuronal loss results from neuroexcitotoxicity, which arises from enhanced and extended neuronal activation. *Indirect* neuronal death results from the inability of the circulatory system to supply enough oxygen and glucose for the high hypermetabolic demand (77,78). In ALS increased autophagy was observed in presymptomatic stage and symptomatic stage with progressively decreasing number of upper and lower motor neurons. Even though again, excessive glutamate release was incriminated to trigger extensive neuronal loss, riluzole, an inhibitor of glutamate release, has a very limited efficacy in delaying disease progression (14,79). In HD, the autophagic process of cell death might be triggered by activation of endosomal- lysosomal system, due to accumulation of mutant huntingtin protein. Sequestration of mTOR protein in mutant huntingtin aggregates impairs its kinase activity and induces autophagy in a protective way (14, 80).

CONCLUSIONS

Neurology and psychiatry are very close fields of medicine, both in clinical practice and research, since both focus on functions and disorders of a single organ, the brain. There are multiple molecular, biophysical and biochemical mechanisms altered in neurodegenerative disorders, which formally belong to the wide spectrum of neurological diseases. In AD particularly, these mechanisms include protein aggregation, synapse alteration, neuronal loss, oxidative stress, neurotransmitter deficit, intracellular calcium dyshomeostasis and mitochondrial dysfunction, leading eventually to neuronal loss, brain atrophy and multiple cognitive deficits. Recent reports show that at least some of these features begin to be reported for classical psychiatric disorders (such as schizophrenia, bipolar disorders and obsessive compulsive disorders). Regardless of the criteria used, any theoretical analysis is difficult to conclude whether AD should be classified as a neurological or a psychiatric disorder. However, from the cellular and molecular pathology perspective, AD seems to be closer to other neurological conditions than to classical psychiatric diseases.

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