

Neurobiological arguments for a pathogenic multifactorial disconnective model of cognitive disorders from Alzheimer's disease in elderly people

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Abstract

Incidence of Alzheimer's disease (AD) in people over 75 years is much higher, and the progression of cognitive deficit become faster, leading to a decrease of quality of life for patients and their families. In this context, it is proposed a multifactorial pathogenic model of disconnected cognitive circuits, which is combined with genetic and vascular-cerebral vulnerability elements, allowing an aggressive progression of neurodegenerative factors, favoring onset of dementia. Data from research studies on animal model (rat) highlighted central role of cerebral cholinergic deficit (which is amplified by cerebral ischemia) on the background of apolipoprotein E4 (ApoE4) genotype, favoring multifactorial disconnected mechanisms, by excess of beta-amyloid (β -A) or increase of vascular dysfunction. Depressive disorder, social stress and traumatic brain injury are favoring the excess in production of β -A. Hippocampal structure disconnects the cognitive circuits, and from a neuropsychological point of view can be many patterns, which are correlated with neuroimaging (hippocampal atrophy, cerebral siderosis, white matter hyperintensity, ventriculomegaly) or biological (hyperhomocysteinemia) factors. Identifying the pathogenic model of multifactorial disconnectivity in the rapid evolution of cognitive deficit in patients with AD may create the premises for an early diagnosis and treatment, based on the biological, neuropsychological and clinical elements.

Keywords: ApoE4 genotype, small vessel disease, cerebral amyloid angiopathy, hyperhomocysteinemia, dementia.

Introduction

The current epidemiological data highlights the significant increase in the incidence of Alzheimer's disease (AD) in people over 75 years old, the aging of the population anticipating the explosive growth of this cognitive impairment [1]. AD is invalidant disorder "with social, economic and health care impact is enormous and slowly progresses to a loss of functional abilities and finally to complete dependents" [2]. According to *World Health Organization* (WHO), the proportion of people over 65 years is set to increase from 6.8% in 2000 to 16.5% by 2050, with high societal cost estimated to be US \$ 315 million in 2005 with about 70% of cost occurring in developed countries" [2, 3]. In this context, the recognition of new pathogenic multifactorial models in which disconnective processes play a central role may allow for an early and differentiated therapeutic approach that would lead to benefits in terms of cognitive recovery and improvement of the quality of life of patients with this disorder and the reduction of health care costs.

Etiopathogenesis of AD

Etiopathogenically, there are two classical typologies of this disease:

- Type I with onset at young age (less than 65 years) and strong genetic determinism in the familial or early

form of the disease, representing 5% of all Alzheimer's dementia. The genetic determinant is represented by the mutations of presenilin 1 and 2 (PS1 and PS2), with 230 such variations identified as well as favoring an excessive production of beta-amyloid (β -A) due to the involvement of amyloid precursor protein (APP) variants [4]. Gene mutations for cerebral amyloid angiopathy (CAA)-related PS1 have been identified. This context raises the suspicion of an important vascular component (Dermaut, 2001) even in the formulas considered as typical of the early-onset familial Alzheimer's disease (EOFAD) neurodegenerative pathology [4].

- Late-onset type II (over 65 years), in which the genetic fingerprint may exist, but the neurodegenerative-type mechanisms are responsible for the genomic deviations of the apolipoprotein E4 (APOE4) spectrum – the sporadic form of AD [5].

The aggressiveness of neurodegenerative elements is potentiated by the decline in the competence of neurochemical, metabolic and cerebral vascular factors. The imbalance of these factors alters the functional ratio of the neuron/astroglial unit, amplifies excitotoxic mechanisms that potentiate the aggression of neurodegenerative elements (PS1 and PS2, ApoE4 and β -A, neurofibrillary degeneration). Thus, the inability to maintain intersynaptic connectivity in the cognitive circuits with the installation of a disconnective syndrome [6] is triggered because of the

cancellation of the neurogenesis capacity and the reduction of neuroprotection leading to functional and structural changes at the hippocampus and cortico-subcortical level

(Figure 1). In this context, it is increasingly argued that sporadic AD is fraught with disconnective pathology.

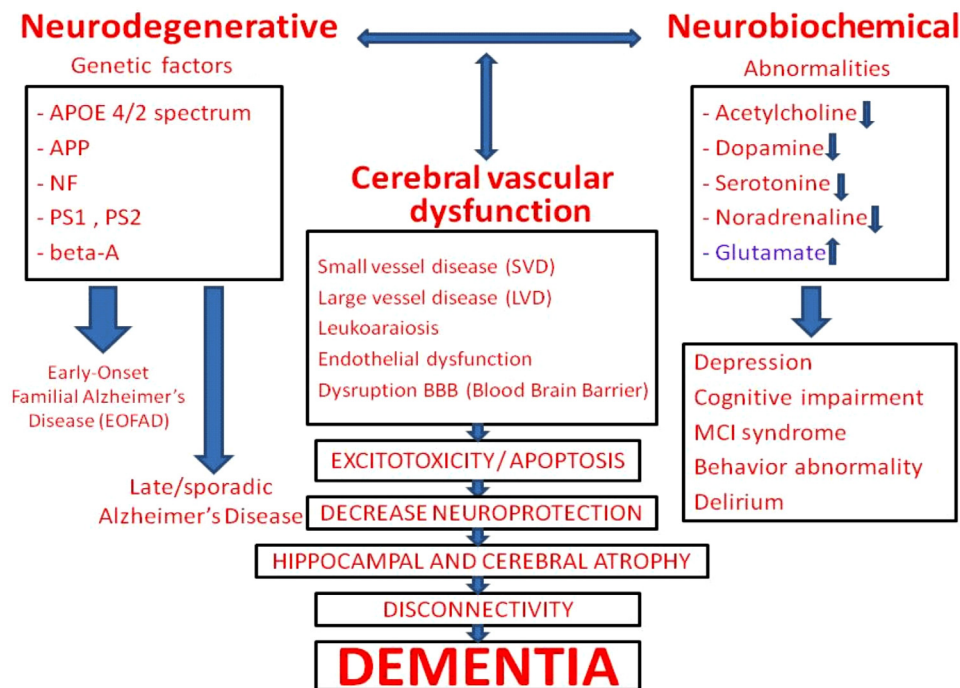


Figure 1 – Pathogenic multifactorial disconnected model of cognitive disorders from Alzheimer's disease in elderly people. ApoE: Apolipoprotein E; APP: Amyloid precursor protein; beta-A: β -Amyloid; MCI: Mild cognitive impairment; NF: Neurofibromin; PS1: Presenilin 1; PS2: Presenilin 2.

Pathogenic multifactorial disconnected model

Our AD with late onset (type II, sporadic form) *versus* familial form (early onset AD, type I, familial form) has a less expressed and polymorph genetic background, the neurodegenerative process being favored by particular pathogenic mechanisms of disconnective type in the context of cerebral aging on the background of genetic and vascular vulnerability:

- Significant decrease in acetylcholinergic trans-

mission [7] is located in the central axis of cognitive impairment in AD, as demonstrated experimentally in animal model "Kopelman cholinergic blockade".

Cholinergic blockade [8], performed with atropine in rats, produces apoptotic neuronal destruction with vacuolar degeneration in the frontal cortex (Figure 2) and the hippocampus (Figure 3), important structures of the cholinergic cognitive circuits. The association of ischemic vascular factor favors cholinergic neuronal destruction and aggravation of cognitive deficits.

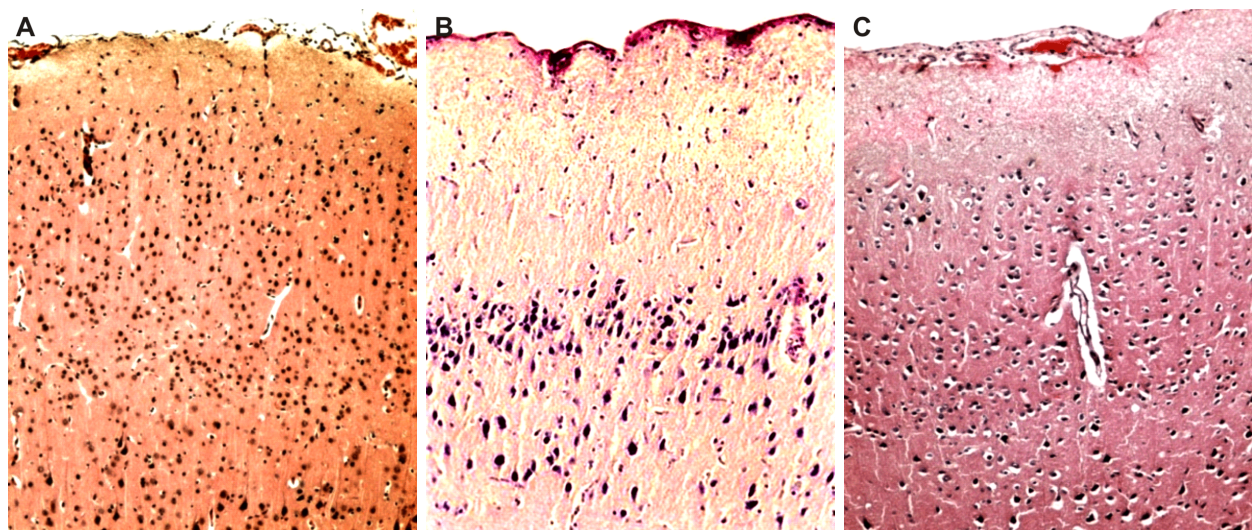


Figure 2 – Frontal cortex after cholinergic blockade with atropine and ischemia achieved by decreased cerebral flow through bilateral carotid deprivation in rat (HE staining, $\times 200$): (A) Frontal cortex of the control group; (B) Frontal cortex after cholinergic blockade with neuronal destruction, apoptosis and vacuolar change; (C) Frontal cortex ischemia accentuates vacuolar change and neuronal destruction [9].

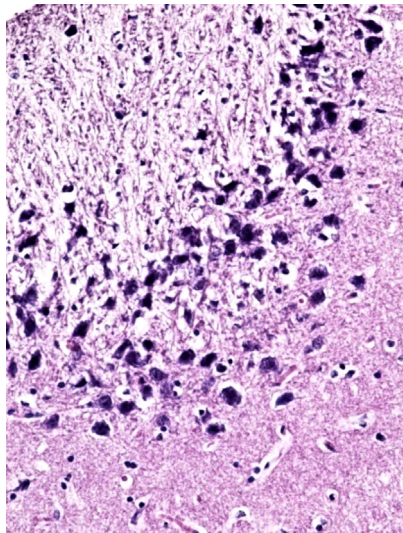


Figure 3 – Vacuolar change degeneration, neuronal pyknosis and hippocampal neuronal destruction in the rat using atropine cholinergic blockade model under ischemic conditions (HE staining, $\times 200$) [9].

Thus, administering atropine to rats under ischemic conditions caused by bilateral carotid deprivation produces degeneration of the Meynert nucleus by mechanisms of the neuronal and degenerative type of vacuolar apoptosis (Figure 4).

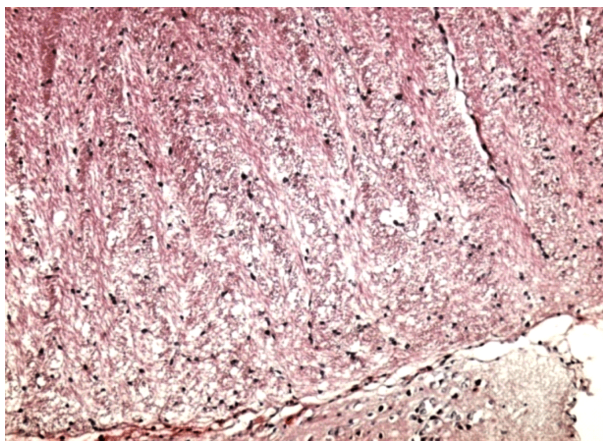


Figure 4 – Neuronal and vacuolar destruction of Meynert nucleus after cholinergic blocking and atherosclerotic ischemia and bilateral carotid occlusion in rats (HE staining, $\times 200$) [9].

- **Loss of connections and alteration of neuro-protective mechanisms favored by genotypic genetic vulnerability of *APOE4*** results in the disconnection of cholinergic circuits with emerging Meynert nucleus potentiated by axonal dysfunctions with disruption of transport at this level, and nerve growth factor (NGF) incapacity to protect the cholinergic system against β -A aggression [10, 11]. β -A accumulation mechanisms are multiple, involving genetic vulnerabilities and molecular or cellular mechanisms (Figure 5), favored by depressive disorders, traumatic brain injury and social stress.

- **Axonal dysfunctions** are specific to brain injuries caused by head trauma [12], the intensity of which may be moderate and severe and characterized by activation of microtubular transport, neurofibrillary filament fragmentation and hyperphosphorylation (neurofibrillary

degeneration) or potential neurodegenerative mechanisms “axon self destruction” [13].

- **There is a direct, quantitative ratio of β -A deposits** in the hippocampus and cortical areas, demonstrated by specific neuroimaging techniques [14], directly correlated with diminishing cognitive efficiency. The amount of β -A can thus be considered a biological, indirect neuro-imaging marker of cholinergic transmission efficiency.

The role of stroke and cerebral vascular factors in the disconnective pathogenic pattern of AD

Models of the development of cognitive impairment in AD highlight the dysfunction of cholinergic cognitive circuits and the amplification of their progression through cerebral hypoperfusion. The vascular mechanisms involved in this model are non-amyloidosis, predominantly of ischemic type, small vessel disease (SVD) or amyloidosis related following β -A deposition in the cerebral cortex, achieving CAA [15] (Figure 6).

Cerebral SVD can be 15–26% at the base of ischemic stroke accompanied by cognitive impairment and post-stroke depression. There is a genetic predisposition represented by the autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) or a mutation of the gene that controls type IV collagen fibers (COLA-A1). Clinically, this subtype may associate with depression and retinal vasculopathy [16]. CAA has insufficient genetic support elucidated, the only valid evidence being the correlation of the *APOE4* spectrum with sporadic CAA [17].

Clinically, very important is the early identification of cognitive inability: the progressive decrease of the mnemonic function, the flexibility of the decision and the speed of information processing. The occurrence of lacunar amnesia indicates the development of mild cognitive impairment (MCI) syndrome [18] with the occurrence of neuro-imagistic hippocampus atrophy associated with decreased glucose metabolism [19].

It is necessary to correlate MCI syndrome with potential neurobiological models that can highlight particular aspects that predict the passage/progression of MCI syndrome to Alzheimer's dementia through disconnective mechanisms of cognitive circuits.

- **The disconnectivity of cognitive circuits controlled by the hippocampal structure** (Figure 7) involves the successive fall of connections with clinical and neurobiological particularities.

- **The hippocampal connection with striatum and basal ganglion** disrupts the regulation of dopaminergic transmission at this level with two important components:

- A lack of dopaminergic stimulation of the frontal cortex, with the occurrence of hypofrontality syndrome, apathy and hypobulia, acetylcholine released by the hippocampus, controlling dopaminergic transmission at this level;

- Hypodopaminergia at this level determines the alteration of cognitive information integration in the basal ganglion system, with a gap between sensitive-sensorial information and its cognitive integration, as well as motor execution, with or without extrapyramidal components.

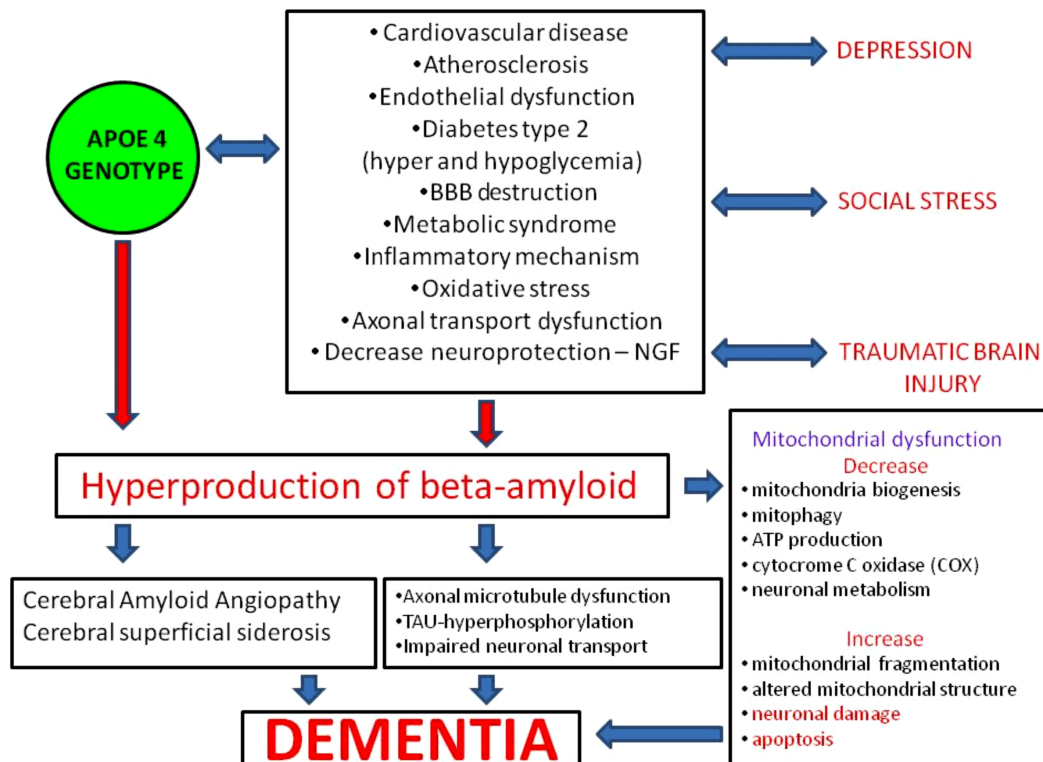


Figure 5 – Multifactorial disconnective mechanisms of dementia in advanced age Alzheimer's disease, potentiated by APOE4 genotype, hyperproduction of beta-amyloid, depression, social stress and traumatic brain injury. ApoE4: Apolipoprotein E4; ATP: Adenosine triphosphate; BBB: Blood-brain barrier; NGF: Nerve growth factor.

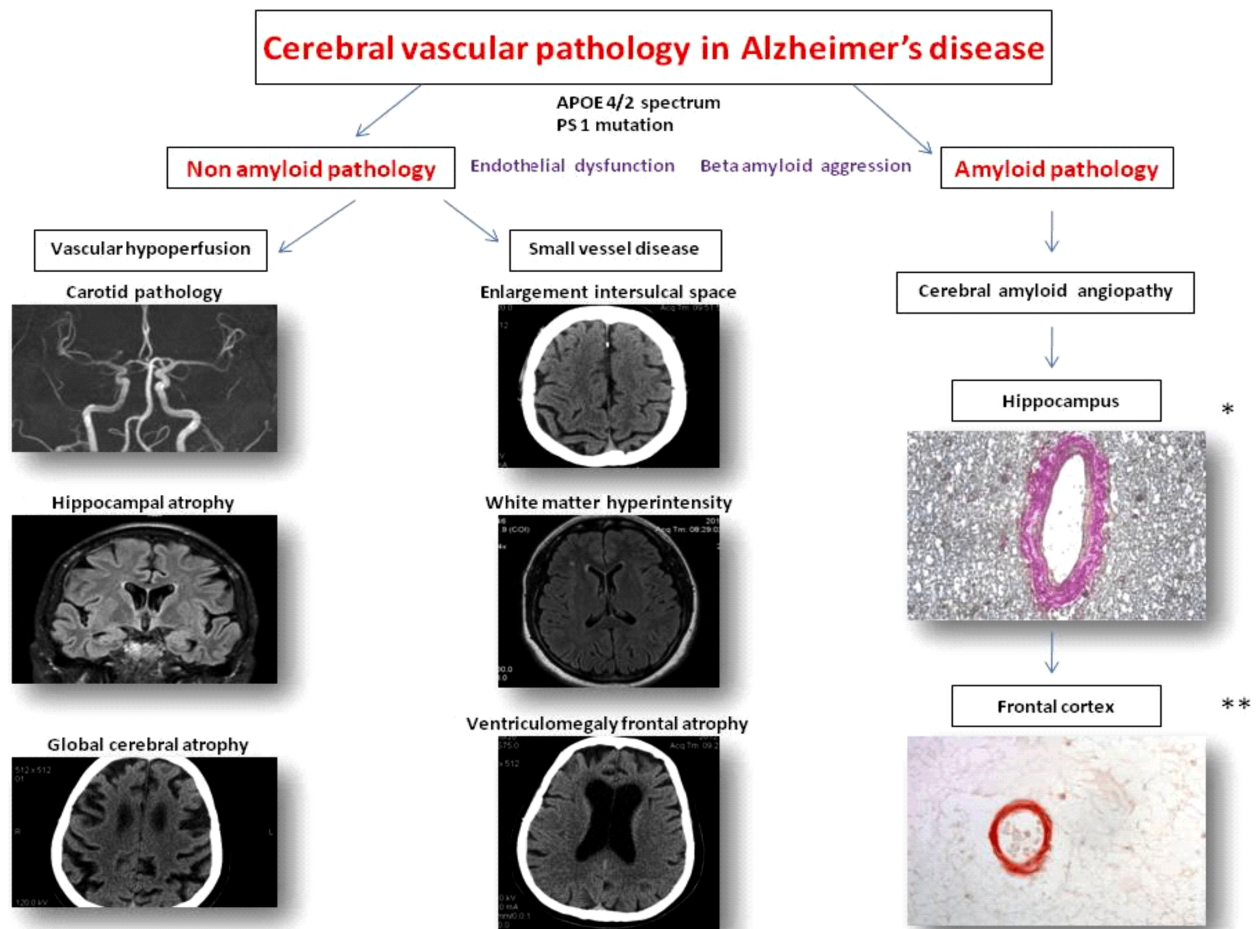


Figure 6 – Models of cerebral vascular pathology in Alzheimer's disease (*Professor Florin Bogdan collection; **Professor Daniel Pirici collection). ApoE: Apolipoprotein E4; PS1: Presenilin 1.

• **The hippocampal connection with the thalamus** alters sensory-motor integrative cognition, disrupting cognitive flexibility and generating an inability to integrate sensory-motor cognition [20] into a decisional project:

– This disconnectivity also includes hyperalgetic pathology and very rapid deterioration of cognitive impairment;

– Thalamic function is correlated with vascular factors and perfusion of the Percheron artery.

• **The hippocampal connection with the frontal**

cortex [21] in the anterior pole and with the cerebellum in the posterior pole leads to a disconnective cortico-hippocampus-cerebellum syndrome that significantly alters the working memory and the decisional capacity.

• Affective-emotional cognition is strictly correlated with the **loss of hippocampal connectivity to the amygdalian, limbic and parieto-temporal cortex** [22], causing behavioral disorders, depression or anxious changes that make it almost impossible to maintain the patient at the level of family assistance.

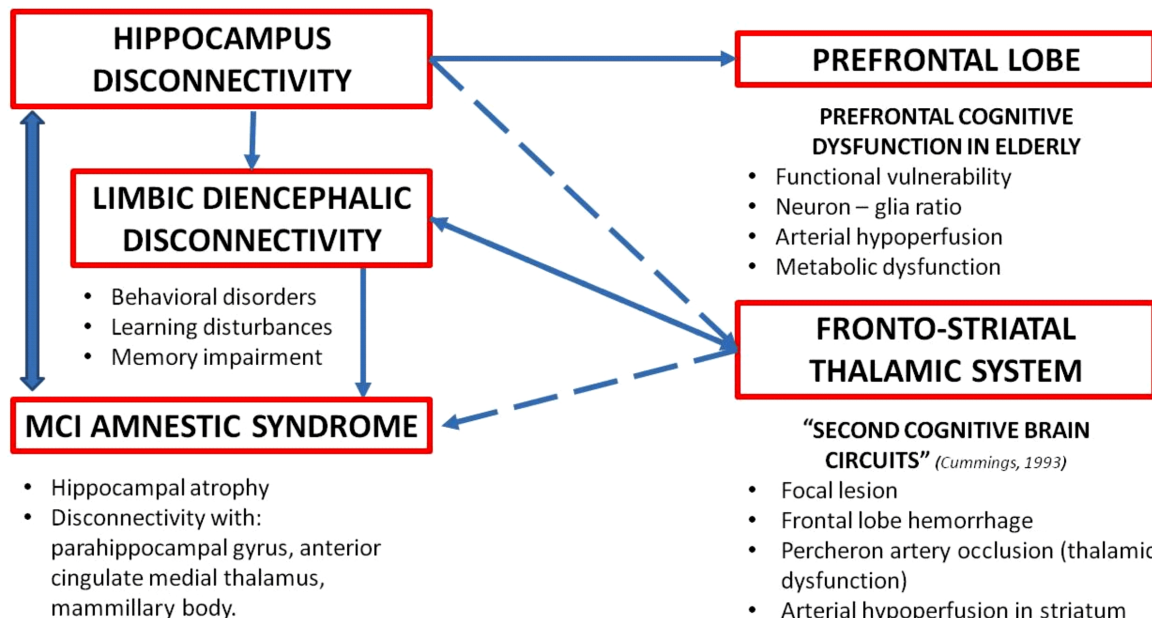


Figure 7 – Complex neurobiological and clinical aspects of mild cognitive impairment (MCI) amnesic syndrome from Alzheimer's disease through hippocampal disconnectivity in elderly.

The role of depression in the multimodal disconnective pathogenic model of AD

The hippocampus plays a pivotal role in the cognitive circuit system, hippocampal dysfunction causing the systematic fall of the other areas involved in the cognitive process according to the domino principle. If in the MCI syndrome, hippocampal volume decrease and amnesia are sufficient clinical and imaging factors to support the diagnosis, switching to AD is dependent on the speed of disruption of hippocampal circuit connectivity to other cognitive structures. The association of depressive pathology, pathology that has a high prevalence in the elderly and MCI syndrome – 32% [23] favoring hippocampal atrophic mechanisms and disconnective processes [24, 25]. Thus, the progression of cognitive decline from MCI to Alzheimer's dementia [26], depression being a validated evolutionary risk factor [27] (Figures 8 and 9).

The hippocampal connection with the frontal cortex is a special one and the structural and functional integrity of the fronto-hippocampal circuits acquires a significant predictive value in assessing the risk of passing MCI syndrome to AD. Comorbidity with depressive disorder potentiates the disconnectivity of this circuit by involving mechanisms of the stroke mechanisms that have as a biological marker hyperhomocysteinemia [28], suggesting the genetic relationship with cerebral autosomal dominant

arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) or SVD cerebral vascular pathology but also endothelial dysfunction with inflammatory and cytokines reactions (Figure 10).

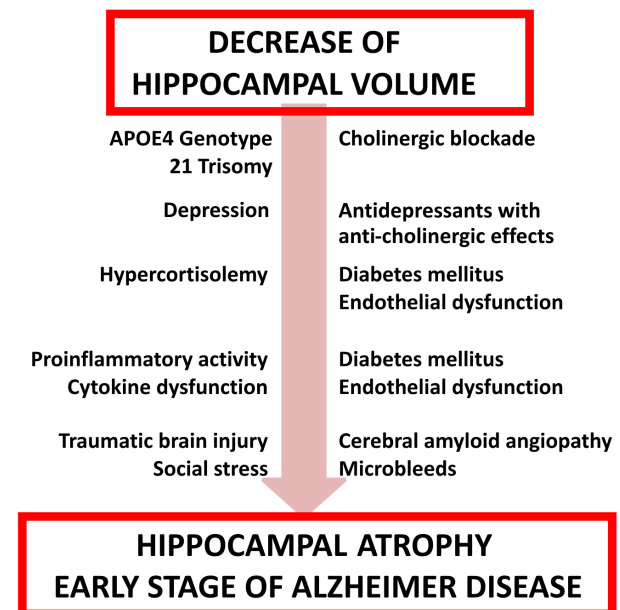


Figure 8 – Multifactorial mechanisms involved in increasing the risk of progression of hippocampal atrophy in patients with mild cognitive impairment (MCI) and depressive disorder.

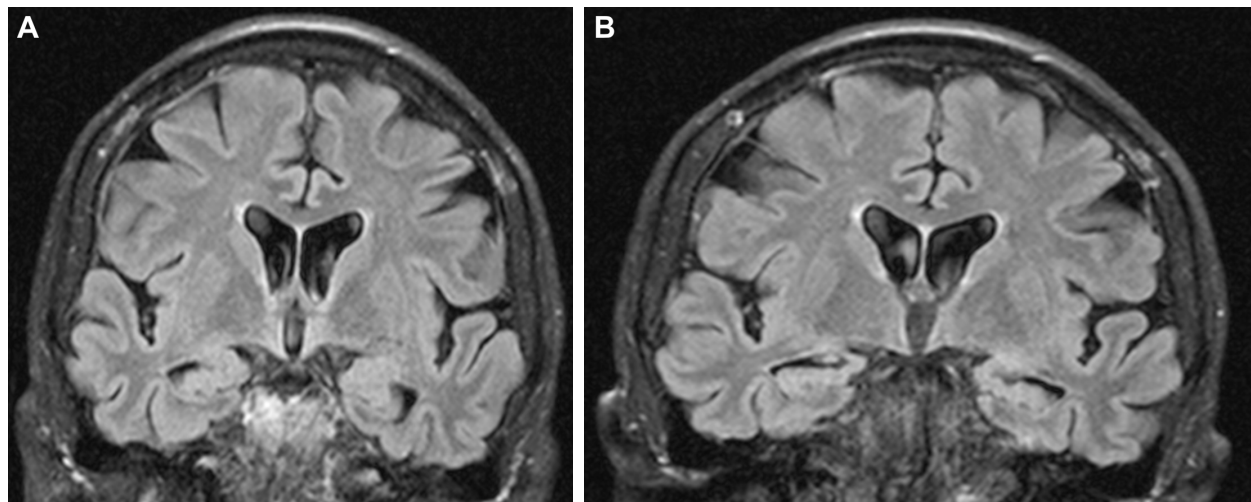


Figure 9 – Hippocampal atrophy in a patient with mild cognitive impairment (MCI) syndrome and depression (Professor Dragoş Marinescu collection).

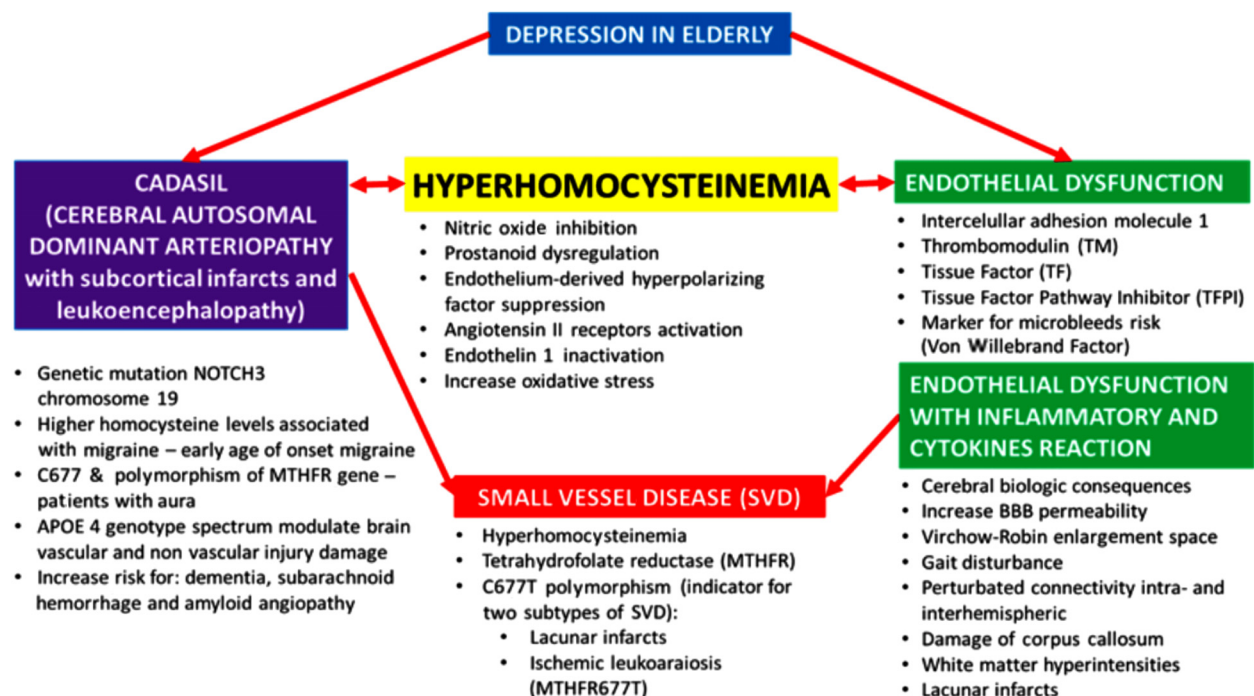


Figure 10 – Hyperhomocysteinemia: biological indicator of vascular disconnective mechanisms in patients with mild cognitive impairment (MCI) and depressive disorder. BBB: Blood-brain barrier.

The presence of hyperhomocysteinemia is becoming an important biological marker that predicts an unfavorable cognitive impairment in AD as it indicates interaction mechanisms of fibrinogen β -A that “exacerbates Alzheimer’s disease pathology” [29].

Functionality of the frontal lobe is dependent on the integrity of the fetal and infant development process [30], while the ability to associate and connectivity is a consequence of the maturation and myelination process that ends around the age of 18.

Hypoxic-ischemic encephalopathy of the newborn produces through hyperglutamatergic mechanisms significant changes in hippocampal circuits [31], especially in the dentate gyrus area (DG) with the CA1-CA3 Ammon’s horn. This encephalopathy profoundly alters neurogenesis areas, found at dentate gyrus level, significantly reducing the number and structure of the stem cells, in an animal

model [32] and hypoxic process produces the alteration of the cerebral vascular infusion in the periventricular and subventricular zones (periventricular white matter hyperintensity “leukomalacia”). For this cerebral injury, serum S100 protein is a prognostic biological marker [33]. Ventriculomegaly and neuroimaging changes – periventricular white matter hyperintensity becoming neuroimaging markers for the supportive neurogenesis incapacity. In the adult, there are data supporting structural changes through hypoxic encephalopathy [34].

Based on these evidence, it can be argued that the predictability of subsequent development of AD may be dependent not on neurodegenerative or vascular mechanisms but on the primary alteration of neurogenesis by neurodevelopment abnormalities (epigenetic risk factors).

This type of structural functional vulnerability of the

hippocampal-frontal connection associates premorbid cognitive difficulties with MCI syndrome characterized by:

- Incapacity to temporarily integrate sensory information with an inadequate dismetric motor response.
- The retrospective analysis of recent sensory information is deficient, the motor response being the erroneous motivation for which this type of sensory-motor cognitive deficit has been integrated into the concept of “preparatory set considered inclusive component of motor attention” [35]. This observation brings to mind the problem of motor deficit, an understated notion today;
- Deficient integration of the action in the temporal space;
- Functional errors of working memory;
- The loss or weakening of inhibitory control and the potential for triggering auto- or hetero-aggression-related anti-social behaviors or the occurrence of automatic behaviors, such as the stereotypes of outpatient automation, automated movements.

• **Cognitive deficit development is precipitated by vascular vulnerability factors** in particular by CAA [19, 36], affecting executive function against a syndrome type MCI with vascular component [37]. CAA major risk is represented by intracerebral hemorrhage accelerating cognitive decline, by relating to a high incidence of cognitive impairment, 87.5% at four months from hemorrhagic stroke [38].

CAA is itself a form of transmission gene family or not that occur early in life (before the age of 65 years old) [39] and is clinically characterized by rapidly progressive cognitive deterioration accompanied by intense headache that does not respond to specific medication and by an important deficit in the speed of processing of sensory information. This subtype of CAA has a high risk of producing intracerebral microhemorrhages (microbleeds) [40], but also intracerebral lobular hemorrhage [41] independent of other cardiovascular or cerebrovascular risk factors, with the exception of anticoagulation therapy associated with cardiac or renal arterial hypertension [42]. The important neuroimaging marker is the appearance of cerebral siderosis in the context of the absence of obvious neurological manifestations [43] (Figure 11).



Figure 11 – The presence of cortical and cerebellar siderosis in a patient with late Alzheimer's disease.

In the absence of adequate therapy within 1.5 years of clinical diagnosis of CAA, severe intracerebral hemorrhagic accidents with significant neurological deficit, many post-stroke dementias with prodromal phase, CAA type syndrome with hyperhomocysteinemia, confirmed by post-mortem studies [44].

Repeated brain injury precipitates the development of CAA pathology at frontal or hippocampus level [45].

Based on clinical and neurobiological evidence, theory pathogenic model of disconnective type of cognitive deterioration among elderly suffering from AD, bring into discussion the diminishing importance of neuro-degenerative factors against cerebrovascular factors and mechanisms of axonal transport and mitochondrial dysfunction in terms of decreasing neuroprotection.

The hippocampus disconnectivity supported by experiments in animal model (rat) supports the major role of the cholinergic system in cognition, produced by cholinergic blockade Kopelman model, highlighting the vacuolar degeneration and neural destructions in the hippocampus, frontal cortex and basal nucleus of Meynert. The major role of circuits cognitive [46], with the emergence from the hippocampus, highlights neurocognitive changes clinically suggestive for MCI syndrome correlated with the presence lacunar amnesia, as well as progression of cognitive deterioration anticipated by disconnected mechanisms from the frontal cortex with altered fronto-striatal circuits “second cognitive brain circuits” [21] and the limbic system.

Risk factors for the disconnectivity progression of the hippocampus with the frontal cortex are *APOE4* gene spectrum, β -A hyperproduction and especially the amyloid and non-amyloid cerebral vascular component.

Non-amyloid vascular cerebral disease pathology represented by SVD and vascular hypoperfusion are the major vascular neuroimaging markers, such as ventriculomegaly, cortical and hippocampal global atrophy, inter-sulcate space widening, white matter hyperintensities and angiographic presence of endoarterial changes. The cumulative neuroimaging markers associated with MCI syndrome anticipate the passage and rapid progression of cognitive impairment to dementia in AD. β -A deposits in the cerebral vessels cause changes in cerebrovascular amyloidosis (CAA) with increased incidence, 32% of patients over the age of 80 years and MCI syndrome, characterized neuropsychologically by “decreased perceptual speed with deficits in perceptual memory” [21, 31]. It is known the major risk of CAA for strokes or intracerebral lobular/microbleeds hemorrhages, evidenced neuroimagingistically by cerebral cortical siderosis. CAA is a major risk for intracerebral hemorrhage with severe cognitive and neurological defects severely darkens prognosis and increases care costs [47].

✚ Conclusions

The progression of the disconnected multifactorial syndrome can be favored by depression, traumatic brain injury (TBI) or social stress, involving endothelial dysfunction mechanisms, disruption of the blood-brain barrier, microglial, cytokinetic and pro-inflammatory activation, multiplying the multifactorial pathogenic models.

Addressing cognitive disorders based on the disconnective multifactorial model can provide an opportunity for recognizing the risk of transforming MCI syndrome into Alzheimer's dementia and developing possible early therapeutic intervention algorithms. Proper diagnosis and early therapeutic intervention as well as secondary and tertiary prophylactic measures can limit the amplification of each pathogenic mechanism presented in our model while increasing neuroprotection and diminishing the social stress caused by the stigma of cognitive deficits can lead to delaying the progression of cognitive impairment and improving the quality of life in patients with late-onset AD and their families. We appreciate that the multifactor disconnective model hypothesis requires further modifications and confirmations based on extensive clinical studies that can validate the proposed biological indicators. The validation of these indicators can provide a solid ethical foundation for sustaining early therapeutic intervention in this cognitive impairment that may become a serious public health issue in the coming years.

Conflict of interests

The authors declare that they have no conflict of interests.

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