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Perinatal Programming – New Insights into the Origins of Neurodegenerative Disorders.

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Abstract

Neurodegenerative diseases, including Alzheimer's disease (AD), constitute a problem of great significance in aging societies. The origin and underlying causes have not been established yet. The lately discovered phenomenon of foetal programming explains the connection between perinatal episodes and the development of chronic diseases in the later stages of life.

The aim of this review is to show that altered foetal programming may connect perinatal asphyxia and the development of AD later in life.

It is believed that most cases of AD arise through interactions between genetic and environmental factors. Among all the exposures, transient brain hypoxia has been extensively studied recently. The role of hypoxia in the early developmental period as a trigger for developing AD in adults through altered programming of genes expression cannot be excluded. It is possible that severe hypoxia in early life can cause biochemical changes, including long-lasting alterations in gene expression, leading to neurodegenerative disorders in adults.

The prevention of neurodegenerative diseases should focus on events from the earliest periods of life. Better recognition of underlying mechanisms is necessary for further investigations and the development of novel therapeutic methods.

Keywords: Perinatal programming, Perinatal asphyxia, Newborn, Genes expression, Neurodegenerative disorders, Alzheimer's disease.

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Introduction

Alzheimer's disease (AD) is the most common cause of dementia and the leading morbidity and mortality cause in the aging population. Clinically, AD is characterized as a progressive and gradual loss of cognitive functions, ending with complete decrease of all physical functions and death. The morphologic hallmarks of AD present as diffuse and neuritic plaques, marked by extracellular amyloid beta deposition, and neurofibrillary tangles comprising of the intracellular accumulation of hyperphosphorylated tau (p-tau) protein [1].

It is estimated that nowadays 44 million people suffer from AD, and there are approximately 7.7 million new cases every year. According to the World Health Organization's prognosis, i 65 million people are supposed to suffer from AD in 2030 and in 2050 over 115 million [2].

Alzheimer's disease is classified into two main types: early-onset familial AD (FAD) and sporadic late-onset (LOAD). FAD is caused by known mutations, however this form states less than 5% of all cases. Although sporadic AD occurs in most patients (over 95%), its cause has not been determined yet, which provides a wide field of interest for many research groups [1].

As AD causes and pathological mechanisms have not been completely discovered yet, here is no possibility to invent causative treatment that could prevent the development of the disease or suppress its progression.

The aim of this review is to show, on the basis of data from available literature, that the phenomenon of altered fetal programming may give basis for the connection between perinatal asphyxia and the development of AD or other neurodegenerative diseases later in life.

Literature Review

State of Knowledge

A number of theories have been created to explain causes of AD, however none of them has proved to be sufficient so far.

The oldest theory is the so-called "cholinergic hypothesis", which provides the basis for presently accessible pharmacologic treatment methods [3]. The theory proposes that AD is caused by reduced synthesis of acetylcholine. This hypothesis was not strongly supported and pharmaceuticals that were supposed to regulate acetylcholine deficit, turned out to be ineffective [3].

In the early 1990s the "amyloid hypothesis" was formulated. According to this theory, amyloid plaques, which originate in the brain, cause the earliest and critical changes significant for developing AD. Amyloid-β (Aβ) peptides come into existence as a result of proteolytic processing of amyloid precursor

protein (APP) through secretases β and γ. In conformity with the hypothesis, impairment of mechanisms that regulate Aβ concentration to keep it within non-toxic ranges, is responsible for the development of AD [4].

Another hypothesis, the so-called "tau hypothesis", assumes that chain of pathologic events starts with tau protein abnormalities [5]. In this model, hyperphosphorylated tau threads begin to bind, forming neurofibrillary tangles inside nerve cell bodies [6]. This leads to the disintegration of microtubules and destruction of neuronal system of transport [7]. Eventually, biochemical communication among neurons deteriorates? And then cell death occurs [8].

None of the above mentioned theories met the expectations and did not completely explain the mechanisms underlying Alzheimer ' s disease. Although genetic mutations play unquestionable role in the development of FAD, more and more studies confirm the possible influence of environmental factors on the occurrence and development of sporadic AD [9-11]. It is believed that in most cases of the development of AD is the result of interactions between genetic and environmental factors. Out of all environmental factors, hypoxia has been extensively studied recently [12]. The detection of immunoreactivity of β-amyloid peptide, presenilins, apolipoproteins, α-synuclein and hyperphosphorylated tau protein in animal brains after episodes of ischemia [13-17], in human brains after episodes of ischemia [18-22] and the occurrence of these proteins in the brains of patients with AD have suggested common molecular mechanisms of neuronal death, pathological proteins accumulation and dementia in both brain ischemia and Alzheimer's diseases. Altogether, it is hypothesized that the previous brain ischemia could be the main cause of sporadic Alzheimer's disease [23-29].

Ongoing interest in brain ischemia has provided data showing that ischemia may be involved in the pathogenesis of Alzheimer disease. Experimental brain hypoxia produces stereotypical pattern of selective neurons degeneration, imitating neuropathology found in AD [29-31].

Pathological process last long after the end of acute phase of hypoxia [29-33]. Brain pathology model that is observed in experimental brain hypoxia presents many common features with AD degenerative processes [34]. It was found that hypoxemic brain injury increases APP expression, proteolytic decay of the peptide and Aβ accumulation [15,34,35]. It was established that transient brain hypoxia induces expression of β and γ secretases [17]. The abovementioned changes were linked with the presence of apoptosis markers, suggesting another connection with hypoxia and subsequent neurodegeneration leading to dementia development [34]. It was ascertained that all genes that are involved in Aβ metabolism can participate in both acute and prolonged production of this peptide and be the cause of chronic pathologic processes in previously unoxygenated brain [31,36]. Several research teams have reported that hypoxia *in vivo* causes APP cleavage into Aβ, which results in increased extracellular accumulation of β-amyloid peptide [15,37]. Aβ accumulation in response to brain hypoxia seems to be not only transient phenomenon, since β-amyloid peptide aggregates and plaque-like structures were observed in unoxygenated animals even 9 months after hypoxemic episode.

Current investigations focus also on hyperphosphorylation of tau protein in brains of animals after hypoxemic episode [17,34]. Abnormal phosphorylation of tau protein leads to the loss of microtubule binding capacity and it is thought to contribute to the subsequent formation of neurofibrillary tangles.

Another link between ischemia-induced changes and the development of Alzheimer-related neuropathology is inflammation. Undoubtedly, neuroinflammation is a major component in the maturation of ischemic brain injury. Brain ischemia may also exacerbate Alzheimer-related inflammatory responses and therefore contribute to the progressive loss of neurons [31].

Several lines of evidence also suggest that the integrity of blood-brain barrier contribute to the pathology of Alzheimer's disease-type. Apart from protecting the brain tissue from pathogens and toxic proteins in circulating blood stream, blood-brain barrier also actively participates in the clearance of soluble β-amyloid peptide from the brain into the blood stream [31].

Summarizing, data gathered from studies on animal models suggest that hypoxemic brain episode results in excessive APP cleavage, increased production of amyloid-β and abnormal tau phosphorylation, which may lead to progressive neurodegeneration [29].

It must be emphasized that AD begins very deceitfully, the moment when the trigger mechanism acts and neurodegenerative process begins still remains unknown [38]. Therefore, it cannot be excluded that hypoxia in perinatal period may result in the development of AD in adult life through perinatal programming influencing expression of particular genes.

The theory of fetal and perinatal programming presumes that adverse environmental conditions which occur at a critical, sensitive period of early life has permanent effects on the structure, physiology and metabolism [1]. On the one hand, these changes express fetal or neonatal adaptation to hypoxia, malnutrition or toxaemia and determine survival, on the other hand they may cause abnormal function of organs in adult life. Changes in phenotype of intensively developing organism, dependent on environmental influence, are most possibly caused by epigenetic mechanisms [39].

Oxygen plays an important role in growing and maturation of all organs and systems in the early stage of the development. The central nervous system is particularly dependent on appropriate oxygen concentration. In connection with the aforementioned, hypoxemic episode in the early period of the development may result in significant deterioration of neurologic function in the later stages of life [40].

Perinatal asphyxia, also called intrauterine hypoxia (IH), or birth asphyxia, occurs when the foetus is deprived of an adequate supply of oxygen. IH is used to describe inadequate oxygen availability during the gestation period; birth asphyxia can result from the inadequate supply of oxygen immediately

prior to, during or just after delivery. IH may occur due to variety of causes, such as cord prolapse, cord occlusion, or placental infarction. Birth asphyxia may occur due to prolonged labour, breech delivery in full-term infants, placental abruption, and maternal sedation. Oxygen deprivation is the most common cause of perinatal brain injury. The incidence of perinatal asphyxia is about 8 per 1000 live births. Some of these new-borns develop severe complications in the form of neonatal encephalopathy and cerebral palsy, whereas some of them present only mild neurologic deficiencies, for example dyslexia or attention deficit disorder [41]. Interestingly, some new-borns after IH episode does not present obvious neurologic deficiencies. This raises the question, how such transient hypoxia influences long-term function of cells still viable after hypoxic stress. It seems possible that symptoms may display in adult life [40].

Severe hypoxia in the early period of life may cause cell death. It is also possible that hypoxia induces biochemical changes, resulting in permanent changes in gene expression [40]. Epigenetic mechanisms, including DNA methylation and histones modification, cause such long-term results [42]. To sum up: epigenetic changes are crucial in controlling longer term effects of stresses, such as hypoxia through modifying gene expression [40].

This phenomenon arouse interest among research groups, mainly conducting laboratory experiments on cell cultures and animals. In their study, Zhang et al. [43] exposed pregnant mice to high altitude hypoxia. After the delivery, the pups were observed for 9 months and underwent repeated learning and memory tests. Afterwards, they were sacrificed and electron microscopy examination, neuropathology evaluation and neurochemistry assays were performed on the brain sections of the pups. The researchers found that mice exposed to prenatal hypoxia presented deficit in a spatial learning and memory. Moreover, brain sections revealed a significantly higher level of amyloid precursor protein, lower level of the Aβ-degrading enzyme neprilysin, and increased Aβ accumulation in the brain of prenatal hypoxic mice in comparison to the control group. They also demonstrated striking neuropathologic changes in mice exposed to hypoxia in the prenatal period, showing increased phosphorylation of tau, decreased hypoxia-induced factor, and enhanced activation of astrocytes and microglia. The authors suggested that although the characteristic features of AD appear later in life, hypoxemia in the prenatal stage may contribute to the pathogenesis of the disease, supporting the notion that environmental factors can trigger or aggravate AD.

Next, Benterud et al. [44] conducted an interesting study on newborn pigs. The aim of their study was to investigate the role of biomarkers in neurodegenerative disorders during hypoxia-reoxygenation in neonatal pig model. The newborn pigs included in the study underwent controlled severe or moderate hypoxia. After the hypoxic challenge the pigs were reoxygenated with air and observed for 9.5 hours and then the cerebrospinal fluid (CSF) was collected via lumbar puncture. The study revealed that the level of Beta-Amyloid 1 – 42 (AB42) in CSF was significantly lower in the pigs exposed to severe hypoxia compared with the control group. According to data from literature, decreased AB42 in CSF is supposed to be the first biomarker change to occur in AD [45,46]. In preclinical stages of AD the level of AB42 in CSF is reduced [46] and the authors of the aforementioned study found a similar pattern in their neonatal hypoxia-reoxygenation model. The hypothesis was formed that neurons injured after neonatal hypoxia-reoxygenation could be more prone to increased oxidative stress in late adulthood and, as a consequence, more prone to neurodegenerative disorders, such as AD [47].

Discussion and Conclusion

Although in current literature there is almost no data concerning the changes in AD-related proteins concentration and AD-related gene expression in people after perinatal asphyxia the necessity to conduct such studies seems obvious. Finding evidence for common pathological mechanisms in new-borns after perinatal asphyxia and in neurodegenerative diseases in adults would bring much wider view on the etiology of AD.

Summing up, the mechanism in which early life episodes contribute to the development of neurodegenerative diseases in adulthood is emerging as a new fascinating research focus. The abovementioned assumptions indicate that " prevention of neurodegenerative diseases should focus on episodes from the earliest periods of human life, making a new field for obstetricians and neonatologists: prevention of neurodegenerative disorders in adults."

Authors' Contributions

Both authors have made substantial contributions to the conception and design of the work. A.T. was a major contributor in writing the manuscript as well as in collecting and analyzing data. All authors read and approved the final manuscript.

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