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Review

Fetal programming of Parkinson's and Alzheimer's diseases: the role of epigenetic factors

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Proceedings

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Abstract

In this paper, the main epigenetic factors involved in shaping the brain's physical structure during development will be reviewed, with special emphasis on those related to Parkinson's disease and Alzheimer's disease in adulthood. These factors are: preterm delivery, maternal diet, trace metals, intrauterine infection, maternal stress, drugs, alcohol. Epigenetics may allow a novel therapeutic and preventive approach for neurodegeneration.

Keywords

Fetal programming, Parkinson's disease, Alzheimer's disease, epigenetics, neurodegeneration.

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Introduction

It is well known that an adverse intrauterine environment in the early phases of human brain development might increase the risk of insurgence of neurodegenerative disorders later in life [1]. Thus, fetal programming of the human brain in the prenatal and perinatal period is emerging as a fascinating new field of research. A connection between multiple epigenetic factors acting on fetal development during gestation and the susceptibility or resistance to develop neurodegenerative disorders, including Parkinson's disease (PD) and Alzheimer's disease (AD) in adulthood, probably exists [2] (**Fig. 1**). The practical consequence is that research on prevention of neurodegenerative diseases must be focused on epigenetic events taking place early in life, before birth [3].

In this paper, the main epigenetic factors involved in shaping the brain's physical structure during development will be reviewed, underlying their role in determining quantitative and qualitative changes in brain structure. Finally, the fetal susceptibility to develop PD or AD in adulthood will be discussed.

Preterm delivery and programming: an intriguing relationship

Prematurity represents a growing health problem, due to the number of extremely preterm infants carrying brain injury who survive with neurodevelopmental problems. Premature birth might contribute itself to the late-life development of neurodegenerative diseases, including PD and AD (**Fig. 2**), with the occurrence of marked pathological changes of oligodendrocyte precursors in preterm babies, resulting in deficient myelinogenesis in the perinatal period, ending with structural disturbances in the white matter organization [4]. Specific factors of prematurity are presented below:

a. the early exposure of the newborn to a difficult "hyperoxygenated" postnatal environment;
b. the early unexpected removal of the baby from a protective milieu;

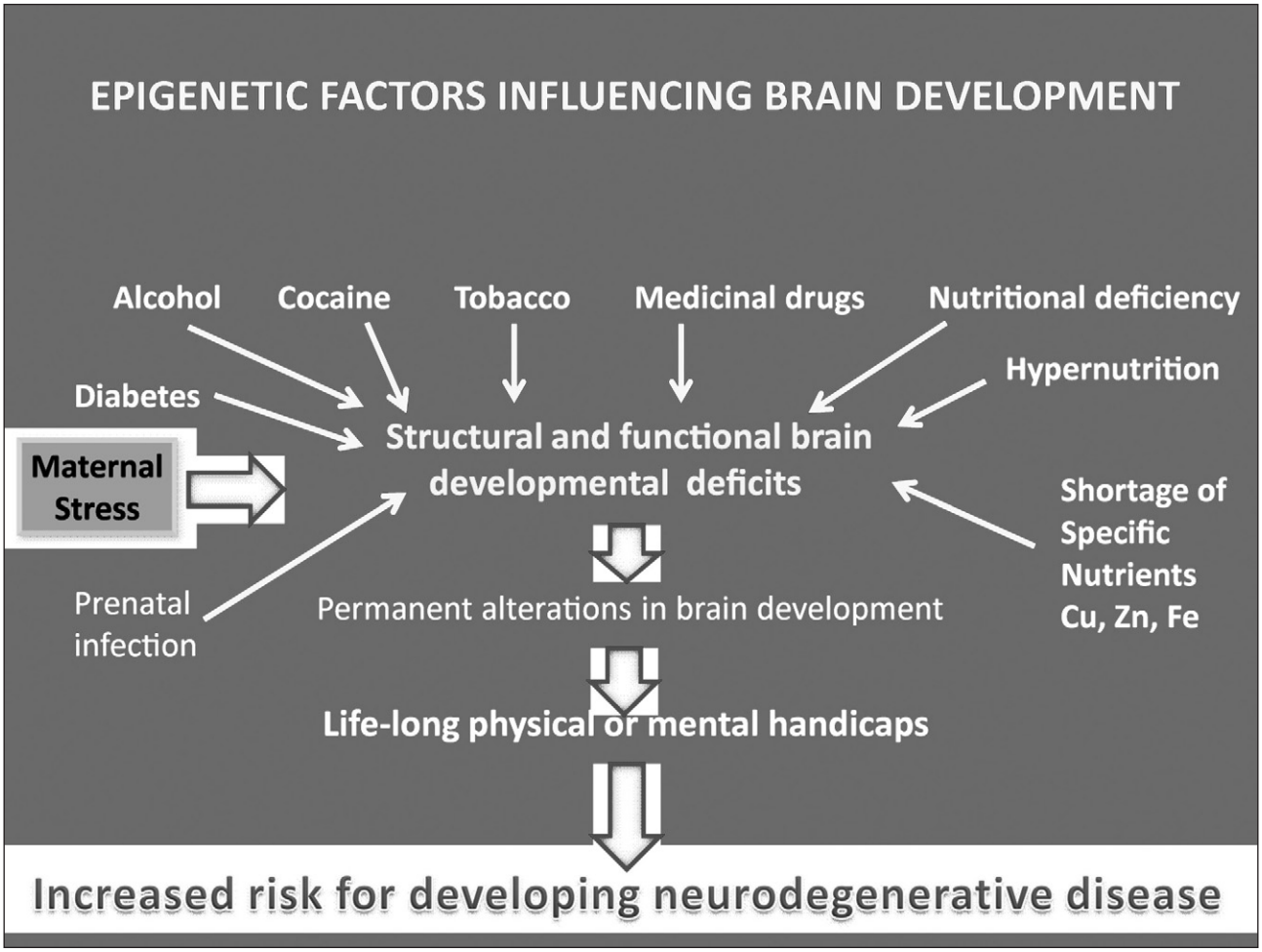

Figure 1. Epigenetic factors influencing brain development.

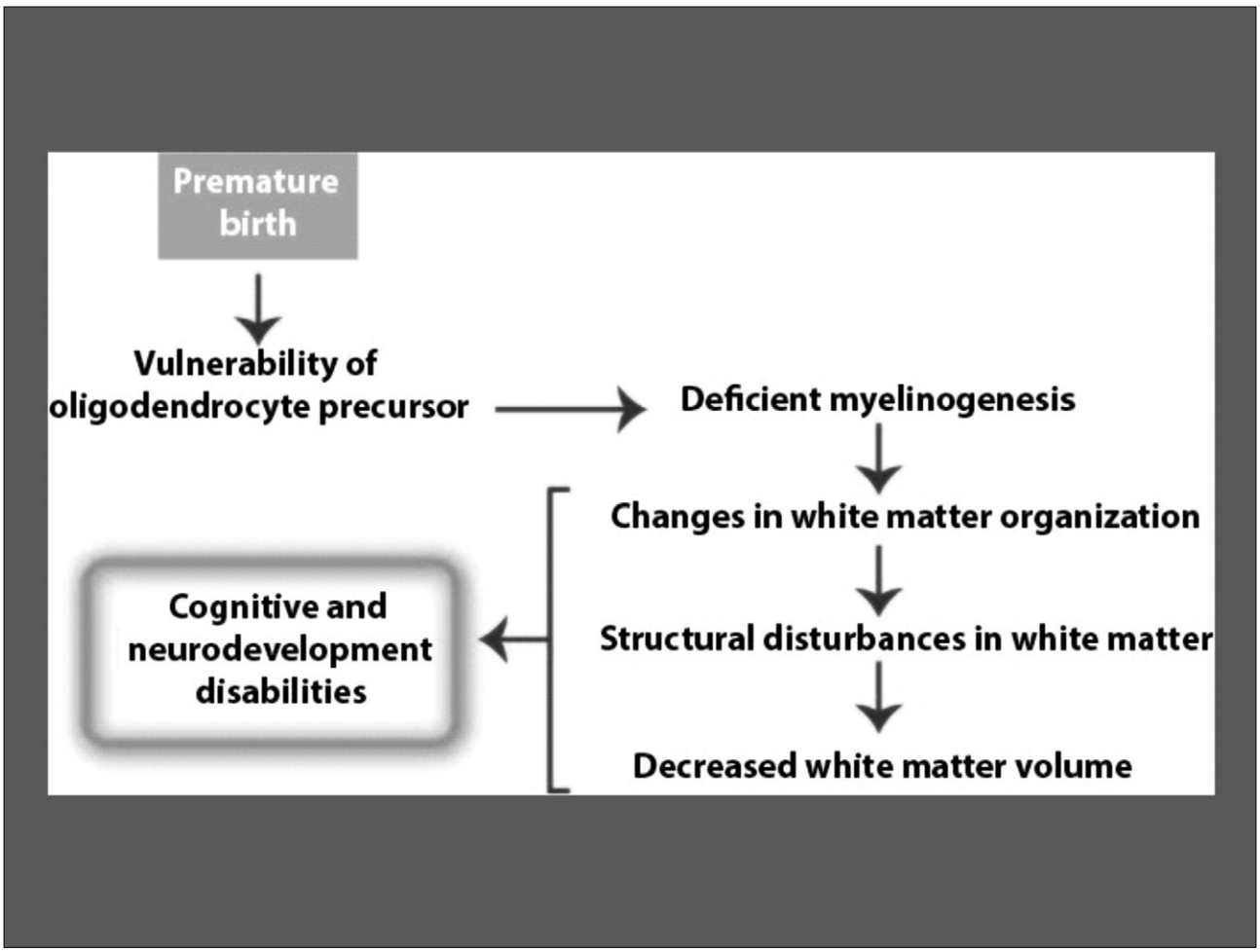

Figure 2. Preterm infants and neurodevelopmental pathological changes.

c. early visual impairment [5], particularly frequent in very low birth weight infants [6].

Maternal diet and the fetal brain

Maternal nutrition has a significative impact on fetal brain development. Mismatching between fetal demand and maternal supply is at the basis of low birth weight, and of metabolic and endocrine changes ending with a higher risk of developing neurodegenerative diseases later in life [7]. Maternal malnutrition, such as prenatal protein insufficiency, could be associated with the insurgence of deficits in learning and behavior in the postnatal period, by intellectual disturbances, and by attention deficit disorders and cognitive impairments later in life.

The rapidly growing and migrating human brain fetal cells are more vulnerable to specific nutrient deficiency. Proteins, polyunsaturated fatty acids (PUFA), vitamin A, choline, folate and trace elements are the most important nutrients involved in the regulation of neuronal and glial cell growth and development [8]. Neurochemical changes following nutrient deficiency, regarding timing, type of reduction and duration, include alterations in neurotransmitter synthesis and neurotransmitter reuptake [9] with specific regional alteration of neuronal performances [10, 11].

Placenta seems to have a major role in the fetal programming of neurodevelopmental. In fact placental cells regulate selective permeability to nutrients and exposure to toxicants. Moreover, placenta is critical in modulating the immune system as well as in the availability of endocrine factors to the embryo. Placental pathology is associated with growth restriction, fetal hypoxia, alteration of fetal brain development and neurological complications later in life. As a consequence, placental dysfunction is a key factor of growing importance in the prenatal programming of neurodevelopmental disorders, including AD and PD [12].

Trace metals: small amounts, big impact

Trace elements are essential components of many enzymes and transcription factors: thus, optimum amounts of trace metals are requested at critical stages of fetal brain development during gestation [13]. Zinc, iron and copper are the most relevant micronutrients associated with brain damage during embryonic and fetal life; both "not enough" or "too much" concentrations of these trace metals could be associated with persistent effects on development of the central nervous system [14]. A very important observation is that their consequences on the developing brain may not be clearly apparent at birth, often becoming manifest later in life [15].

Iron is necessary for life. All living cells need iron for respiration and other fundamental biological processes. Conversely, excessive amounts of iron may become toxic for developing organisms [16]. Iron uptake by the fetus occurs through the placenta; iron ions are of fundamental importance for myelination and neutrotrasmitter production [17]. Iron deficiency during gestation is associated with:

a. the decrease of cytochrome C oxidase activity in neuronal and glial cells, especially in hippocampus and frontal cortex [18];
b. interference with dopamine synthesis in striatal neurons [17];
c. interference with synaptogenesis, resulting in structural changes in the developing hippocampus [19];
d. changes in neurobehavioral development in premature infants, clinically evidenced by abnormal neurologic reflexes [20].

Many conditions may alter iron supply to the fetus, including maternal iron deficiency-related anemia, maternal hypertension, maternal diabetes mellitus [21, 22], uretroplacental insufficiency and chronic hypoxia [23].

Intrauterine inflammation and infections

Inflammation is probably one of the possible pathogenetic mechanisms at the basis of the insurgence of neurodegenerative diseases in adulthood, including PD [24]. Intrauterine infection is characterized by the release into the amniotic liquid of lipopolysaccarides (LPS), which may trigger tumor necrosis factor-alpha (TNF-α) release by monocytes and dendritic cells, ending with the appearance of chorionamnionitis. Brain inflammation after LPS is associated with reduced myelination, loss of cortical neurons and of olygodendrocytes [25]. Infants at risk for developing brain white matter lesions in the fetal brain can also be identified by the concentrations of interleukin-6 and interleukin-1 beta in amniotic fluid [26]. Perinatal systemic inflammation alters the developmental program of the white matter, inducing a long-lasting myelination deficit accompanied by cognitive defects [27].

The principal consequence of chorionamnionitis is the block of normal development of dopaminergic neurons in the fetal brain, with loss of nigral cells in the substantia nigra [28]. Newborns born with limited striatal neurochemical reserves due to a reduced nigral cell count are more susceptible to PD development, even fifty years later. Influenza virus has been suggested to play a relevant role among PD-related chorionamnionitis [29]. The pathological consequences at brain level of intrauterine infection are a reduction in serotonin in the medial prefrontal cortex and the hippocampus, favoring the insurgence of psychiatric disorders later in life [30], including autism, schizophrenia and cerebral palsy. Prenatal infection could also cause a damage related to increased oxidative stress in the fetal brain. The increased risk for developing schizophrenia later in life has been hypothesized to be associated with maternal infection by influenza virus, measles, rubella, and varicella virus [31].

Microglia probably is involved in the neuroinflammatory status of the fetal brain following intrauterine infection. Synaptic dysfunction and synaptic loss are first hits in the progression towards the clinical insurgence of AD or PD [32].

Maternal stress is equal to fetal brain stress

The biological mechanisms that represent the interplay between the exposure of the human being to early life stress and the vulnerability to neuropsychiatric disorders in adulthood have been, at least in part, recently clarified. Stressful events occurring in the prenatal and perinatal period may interfere on fetal brain development. Neurodegenerative disorders later in life include cognitive decline, depressive episodes, depression, anti-social personality disorders, schizophrenia and AD [33, 34]. Other authors report autistic spectrum disorders, as well as learning deficits, depression and schizophrenia [35]. Multiple specific brain regions are specifically affected by perinatal stress, including cerebral cortex, cerebellum, hippocampus,

hypothalamus, amygdala and corpus callosum, leading to abnormal cognitive and behavioral and psychosocial outcomes in childhood and adulthood [36].

Stressful events in the perinatal period, like maternal separation at birth, alter cortical pathways:

a. the serotonin signaling in the prefrontal cortex, resulting in an anxiety-like phenotype in adulthood [37, 38];
b. the plasma free tryptophan levels, which are elevated and result in increased synthesis of 5-HT in fetal brain, with alterations in the control of brain development [39].

Thus, stressful events occurring early in life may change brain function later in life due to excessive signaling through 5-HT2A receptors in neurons of the prefrontal cerebral cortex [40]. Recently, glia has been hypothesized to play a critical role in the pathogenesis of many neuropsychiatric disorders. A recent review on this topic underlined that males are more likely to present developmental associated autism spectrum disorders or schizophrenia. In contrast, females are more likely to develop anxiety disorders and depression later in life, after the onset of adolescence [41].

Drugs: a potential poison for the developing brain

Many drugs administered during the prenatal and/or the perinatal period may trigger neuronal and/or glial cell apoptosis in the vulnerable developing human brain. Sedatives and anticonvulsivant drugs promote apoptosis of fetal neurons, shaping a susceptibility to develop neurodegenerative diseases in adulthood [42].

Prenatal exposure to exogenous glucocorticoids, such as in maternal stress, may have adverse effects on the fetal brain. A prenatal overexposure of the fetus to excess glucocorticoids is associated with low birth weight and higher plasma cortisol levels in childhood. These data clearly indicate a hypothalamic-pitituitary-adrenal (HPA) axis programming with permanent hyperactivity during the life span, resulting in susceptibility to develop neuropsychiatric disorders in adulthood. In particular, glucocorticoid prenatal programming is responsible for permanent changes in the expression of specific transcription factors, ending with the permanent increased expression of glucocorticoid receptors (GRs) in the fetal brain. These events compromise fetal brain growth and result in the insurgence of attention deficits and poorer cognitive performance in childhood [43].

The fetal alcohol spectrum disorders

In the fetal alcohol syndrome (FAS), the fetus is exposed to high maternal ethanol serum levels, which may trigger acute neurodegeneration of Purkinje cells and other neuronal populations including neurons in the cortical plate of the developing cerebral cortex (**Fig. 3**) [44]. In Purkinje cells, the toxicity is related to alcohol-induced mitochondrial damage with cytochrome release from mitochondria, caspase-3 activation and apoptosis of targeted neuronal cells [45]. Alcohol exposure may also cause an elevation of cytosolic free calcium in cortical and in cerebellar neurons (**Fig. 4**). The most relevant molecular consequences of calcium overload in neurons are represented by a decreased expression of Bcl-2 and by the increased expression of BAX, both responsible for the insurgence of apoptotic cell death in prenatal cortical and cerebellar neurons [46]. Fetal alcohol spectrum disorders (FASD) are the leading cause of mental retardation in newborns, favouring neurodegeneration later in life [47].

It is well known from recent researches that early alcohol exposure causes excitation/inhibition imbalance resulting in perturbed local and regional network signaling and therefore in neurobehavioral pathology [48].

The “two hits” hypothesis in the pathogenesis of Parkinson’s disease

Brain injury in PD, a neurodegenerative disorder that occurs after 50 years of age, is a progressive selective loss of neuromelanin-containing dopaminergic neurons in the substantia nigra and locus coeruleus, associated with a permanent inflammatory reaction with microglial activation (**Fig. 5**). Despite clinical presentation in adulthood, in recent years the role of exposure early in life to environmental risk factors is emerging as a principal factor in the pathogenesis of the progressive damage in the substantia nigra [28]. According with the “two hits” hypothesis, developmental exposure to a specific neurotoxicant (“first hit”) could represent the initial factor triggering fetal programming of PD, resulting in neuronal cell loss (**Fig. 6**) and high vulnerability to a second environmental risk factor occurring in adulthood (“second hit”). Developmental exposure probably represents the first imprint in the developing brain, determining the PD phenotype characterized at histological level by a deficient substantia nigra with a low burden

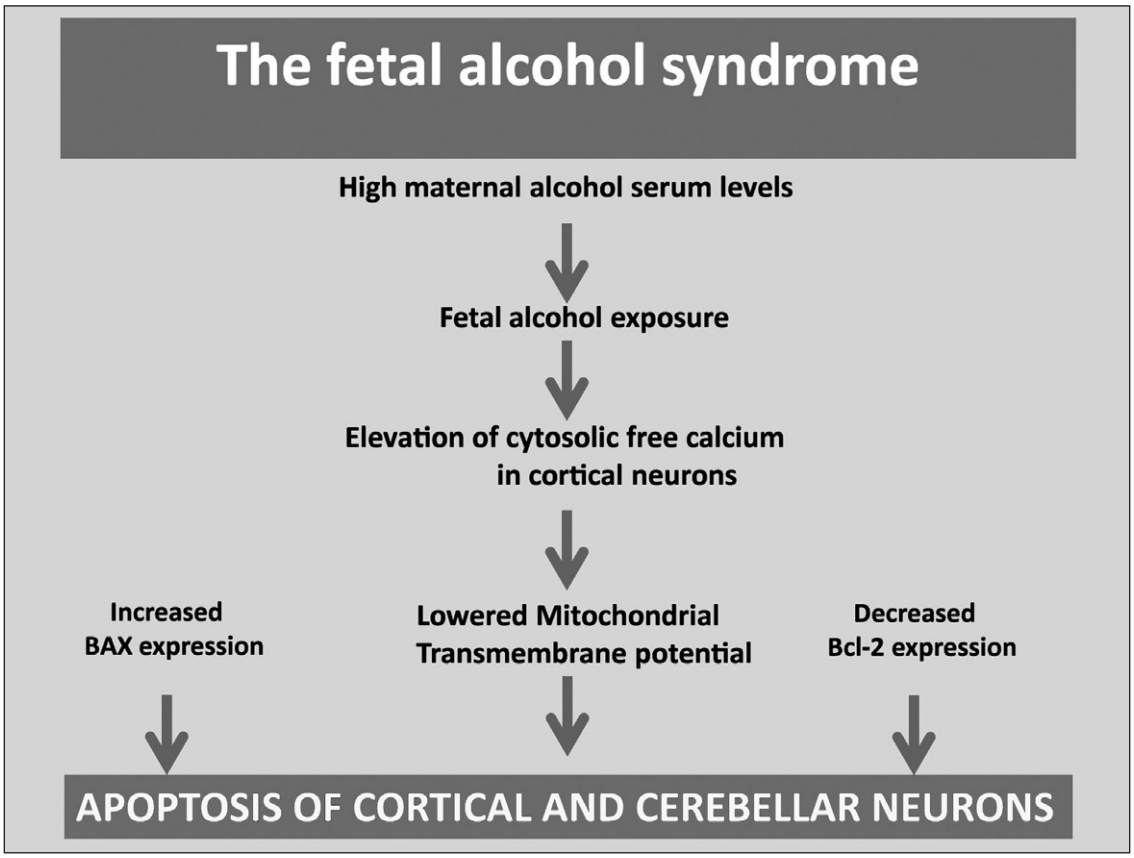

Figure 3. The fetal alcohol syndrome (FAS).

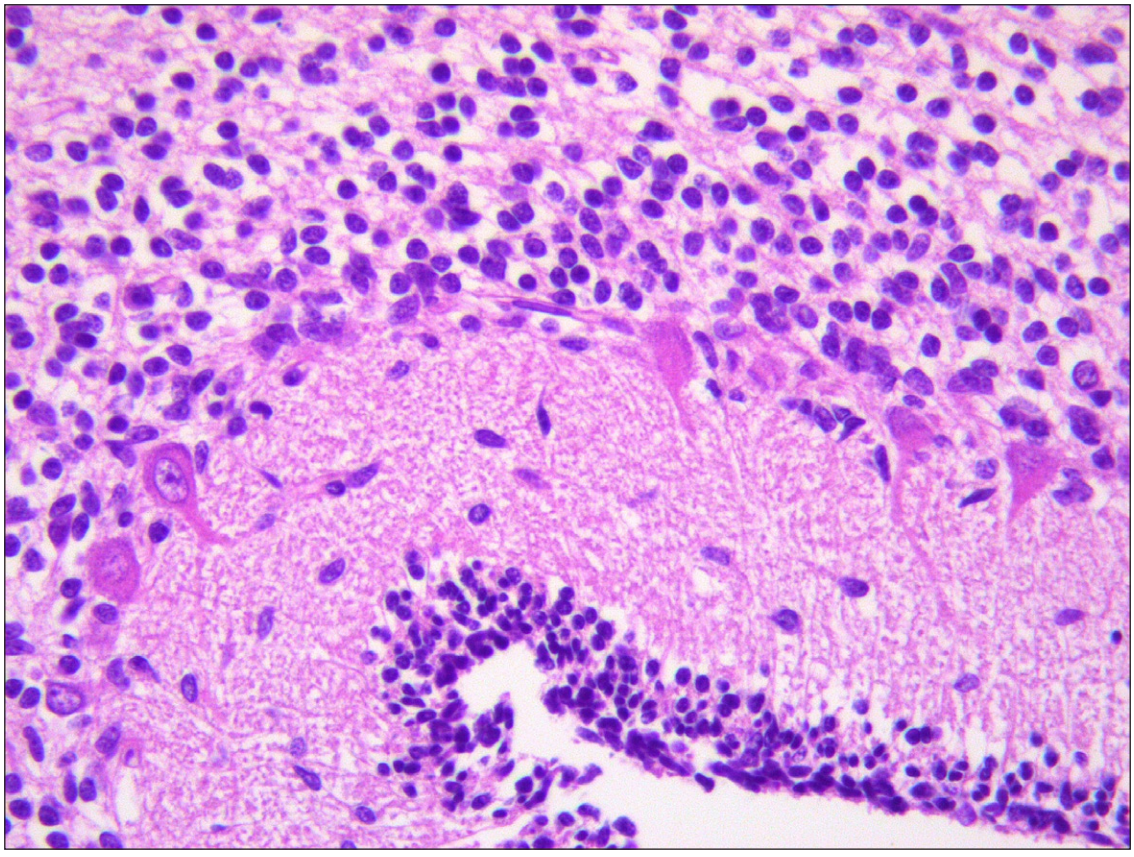

Figure 4. Apoptosis of Purkinje cells in developing human cerebellum.

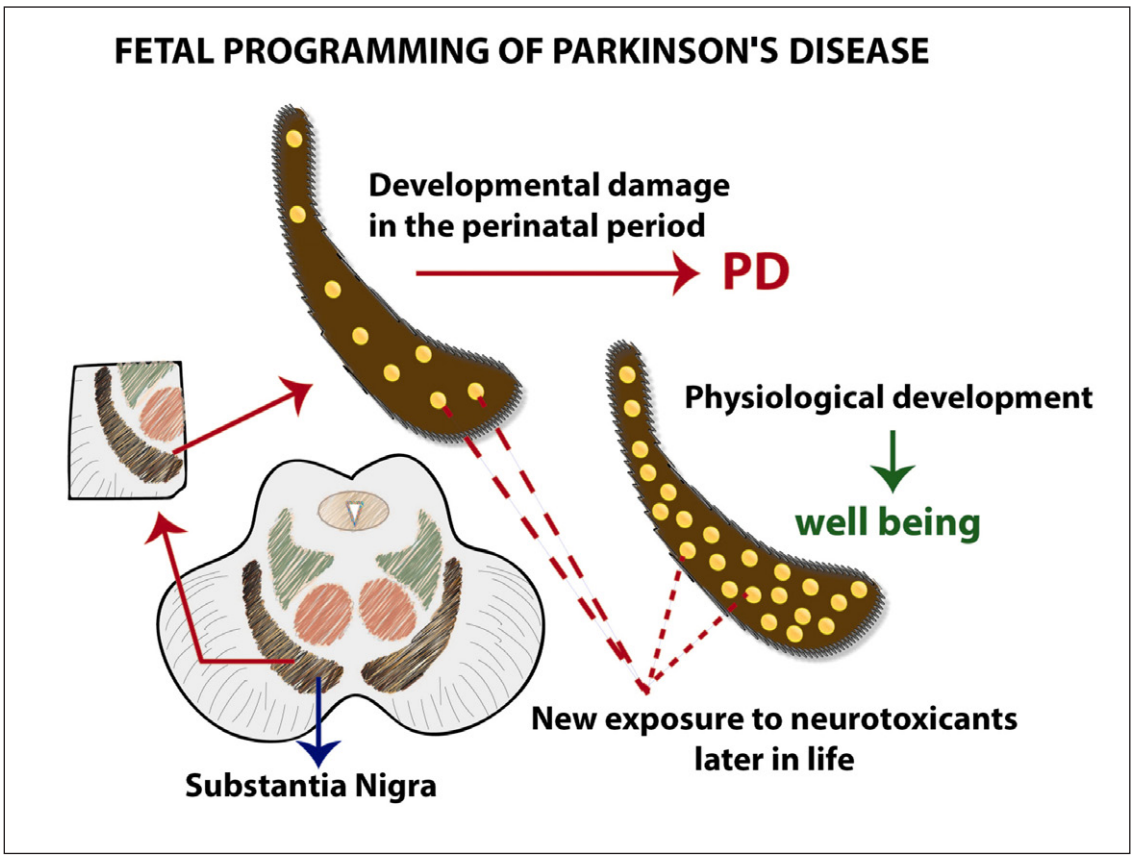

Figure 5. Fetal programming of Parkinson's disease (PD).

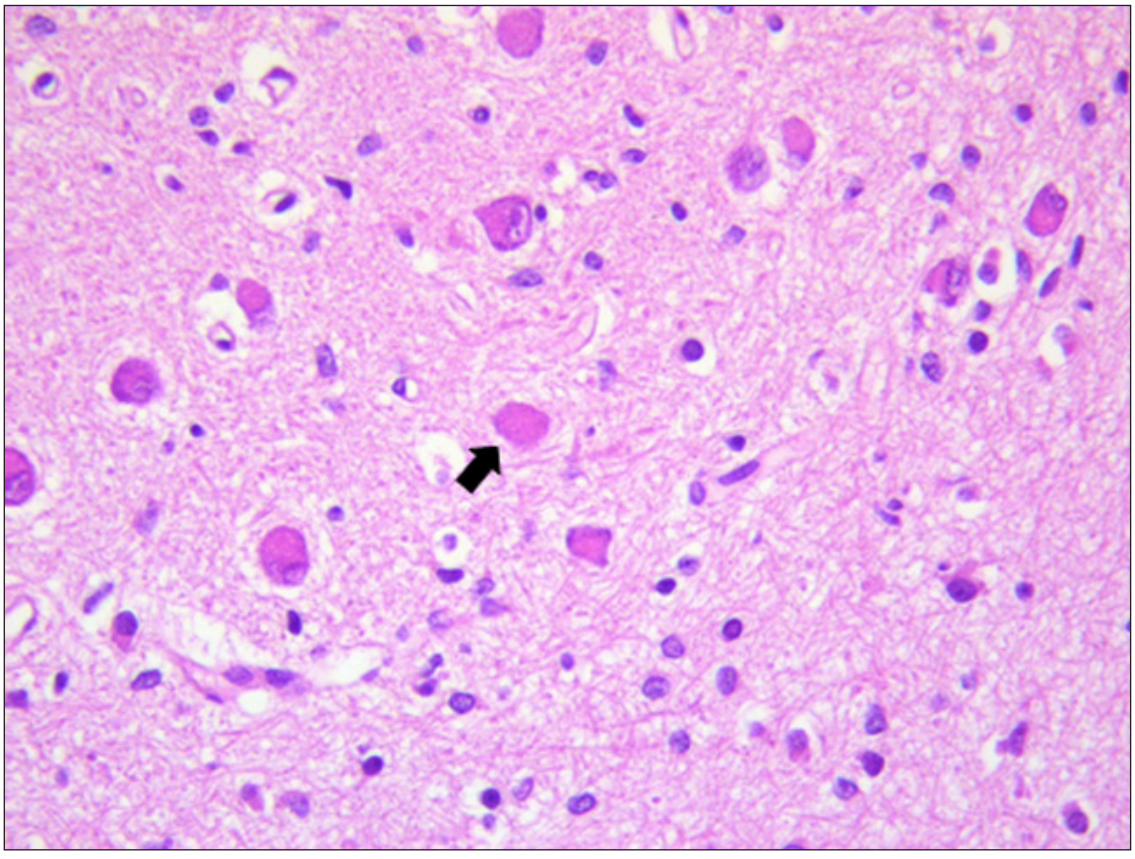

Figure 6. Neuronal cell loss due to apoptosis; diffuse cerebral edema.

of dopaminergic neurons corresponding to a limited nigro-striatal neurochemical reserve [49]. The low number of dopaminergic neurons in the substantia nigra and the developmental damage could remain subclinical during life. The fundamental role of early exposure to toxicants utilized in agriculture, including herbicides and fungicides, had been prospected by an elegant classic study [50]. Among 22 early onset PD patients enrolled in that study, 20 were born and were living in small villages and in rural areas and drank well water during the first 15 years of life; the other 2 patients were born and were living in town and were not on well water. Rural life is certainly characterized by a higher exposure to toxicants such as herbicides and fungicides (**Fig. 7**).

Fetal programming of Alzheimer's disease

Recent data suggest that AD may have its origins early in life [51]. Probably AD is not caused by a single etiologic factor, but it is the result of the interplay between multiple genetic and environmental epigenetic factors through the life course, determining the "AD phenotype". Early life predisposing factors to AD insurgence later in life are maternal stress, intrauterine infections, poor maternal and perinatal nutrition [52].

Conclusions

Neurogenerative diseases (**Fig. 8**), in particular AD and other dementias, are expected to increase dramatically within few decades. New solutions are needed to win the so-called AD "epidemics". Epigenetic changes can have influences on the health status as profound as those exerted by mutations but, unlike mutations, epigenetic changes are reversible and responsive to environmental changes [53-56]. This assumption implicates that research on prevention of neurodegenerative diseases should be centered on events taking place early in life, during gestation and in the perinatal period.

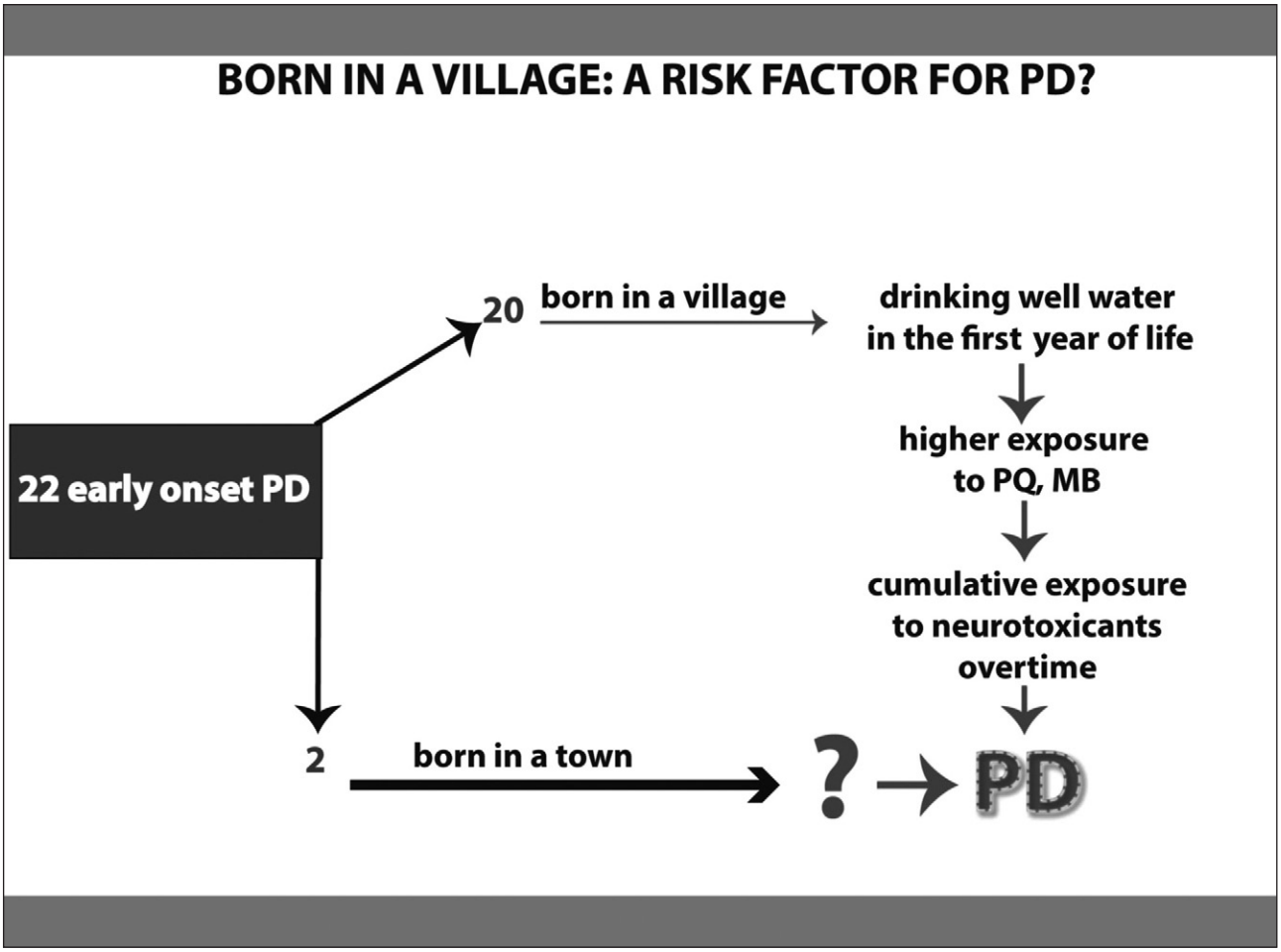

Figure 7. Born in a village: a risk factor for Parkinson's disease (PD)? Results of a classic study (Rajput et al., 1987 [50]) and a more recent article (Thriruchelvam et al., 2002 [49]). PQ: paraquat; MB: maneb.

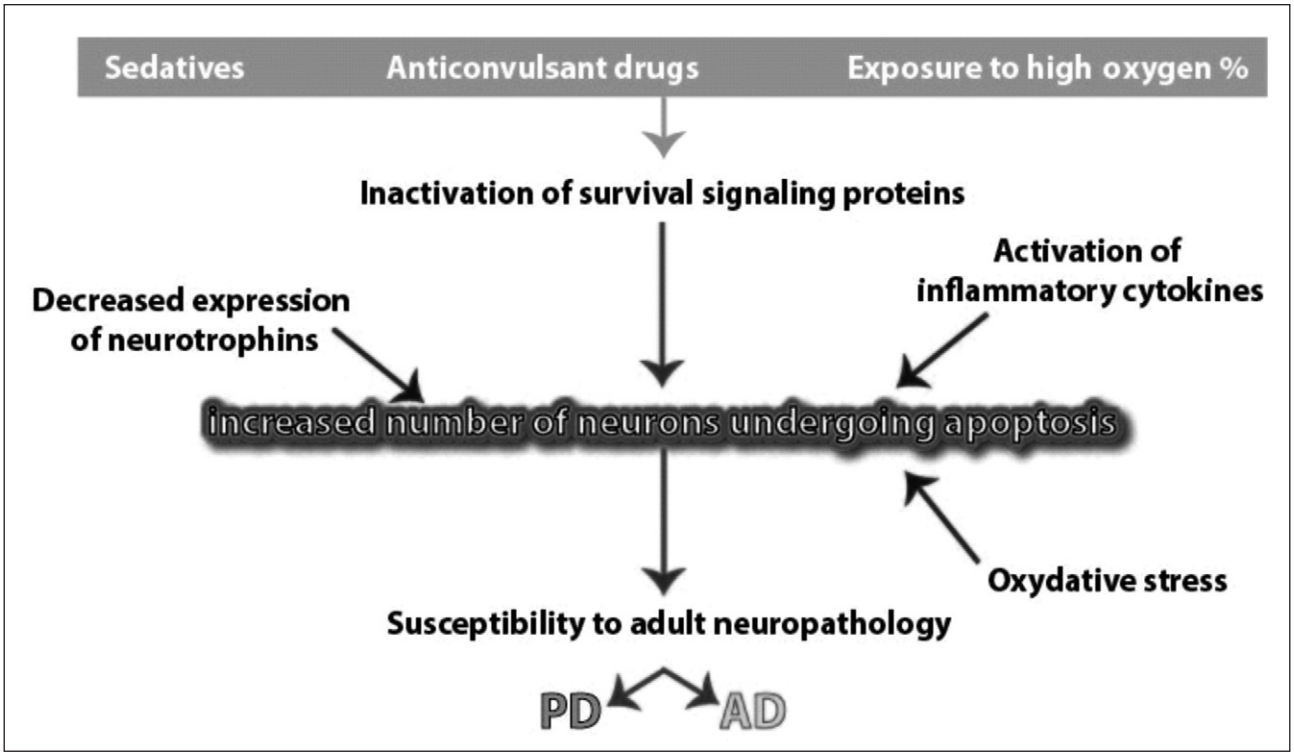

Figure 8. Alzheimer's disease (AD) and Parkinson's disease (PD).

Declaration of interest

The Authors declare that there is no conflict of interest.

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