Chapter 6

Neurocognitive Dysfunctions in Iron Deficiency Patients

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Additional information is available at the end of the chapter

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Abstract

In this chapter, the authors described the actuality of the investigations of neurocognitive dysfunctions in patients with iron deficiency. In infants, the incidence of iron deficiency is 73%; the probability of its transition to iron deficiency anemia is very high. The development of myelin at an early age reduces the production of myelin, and the formation of g-aminobutyric acid worsens the metabolism of dopamine in the striatal brain, which leads to slowing of motor function and behavioral problems in the child. Children with iron deficiency conditions are prone to developmental delays, reduced school performance, and behavioral disorders. In older adults, cognitive dysfunctions depend on complications of the vascular nature, complicated by comorbid iron deficiency. Concomitant pathology also influences iron homeostasis. The regulating mechanisms of iron deficiency, as the same cognitive deficiency, despite the age involve more than 200 proteins from iron homeostasis, appropriate cofactors: derivatives of vitamin B, copper, manganese, zinc ions, enzymes, cell growth factors, etc. All these partners could influence separately or together to the development of iron deficiency and a complication of it neurocognitive dysfunctions. The combination of iron deficiency anemia and iron deficiency with comorbid pathology often exacerbates cognitive problems and requires a weighted approach to the choice of therapeutic correction tactics.

Keywords: iron deficiency, neurocognitive dysfunction, comorbid pathology, iron homeostasis

1. Introduction

Iron deficiency (ID) and iron deficiency anemia (IDA) could have multifocal pathologic effects [1–3]. However, one of the most socially significant consequences of ID is the burden to the cognitive abilities of the population [4–6]. At present, the prevalence of iron deficiency and iron deficiency anemia is 2–6% among European children. Given the importance of iron deficiency relative to proper cognitive development and the alterations that can persist through adulthood because of this deficiency, the objective of this study was to review the current state of knowledge about this health problem [7]. In fact, there is a consensus that ID, without, concurrent anemia, has the same negative impact on cognition, behavior, and motor skills that can persist in the long-term [8]. So, the verification of ID in young age can be particularly important, because of the influence on the mental health and further cognitive functions during the whole life of the people [9–11].

Neurophysiologic methodologies are noninvasive approaches that can provide information about the functional integration of the CNS [12, 13]. For example, dramatic decreases in latencies in auditory and visual evoked potentials in infancy are often used to index the overall intactness and maturation of the CNS. Progressively, shorter latencies, until adult levels are achieved, are thought to reflect the increasing speed of transmission through sensory pathways, resulting in large part from increased myelination of the auditory and optic nerves and at the intracerebral level [14, 15].

Pathophysiological mechanisms of unfavorable impact on nervous system started in utero [16, 17]. The essential factors modifying the ID neurotoxicity are its depth and duration [18, 19]. Evidence suggests that neonatal Fe status may be compromised as a consequence of maternal ID [20, 21]. Genes, infections, malnutrition, and other factors affecting fetal brain development are a major component of risk for a child's emotional development and later mental illnesses, including schizophrenia, bipolar disorder, and autism [22–25]. As part of comprehensive maternal and fetal care, prenatal nutrient interventions should be further considered as uniquely effective first steps in decreasing risk for future mental illnesses and cognitive dysfunctions in newborn children [26–28]. Moreover, this fact makes the study of cognitive impairments in ID states especially urgent, because in recent years, the survival of preterm newborns has increased. Many of them have problems with iron deficiency. Every year in France, almost 35,000 babies (4–4.5%) are born at 35–36 weeks, 13,000 (1.5%) at 32–34 weeks, and 13,000 (1.5%) at less than 32 weeks (i.e., very preterm) [29]. In 2008, deliveries at 32–33, 34–36, and 37–38 weeks accounted for 1.2, 7.5, and 29.7%, respectively, of all births in the United States. Currently, depth preterm infants born at 32–33 weeks gestation and infants born at 34–36 weeks gestation make up the largest subgroup of preterm infants and contributors to more than 80% of premature births in the United States [30]. Multiple births currently account for nearly 3.5% of all births in the United States [31]. The health of neonates born to women carrying multiple fetuses is of concern, as this group alone is responsible for 15% of all preterm births and 20% of all low birth weight infants born in the United States [32]. More than 110,000 newborns in Russia are preterm [33].

IDA and ID often develop in children and adults with other diseases that lead to impaired cognitive functions. Moreover, in such a situation, intellectual dysfunctions are formed because

of the action of several pathophysiological mechanisms. Feinstein in 1970 had introduced the concept of comorbidity, defining it as the presence of a separate additional clinical episode that exists or can manifest itself against the background of the current disease and always differs from it [34]. In addition, the introduction of perinatal factors, a number of concomitant diseases (comorbid diseases) occur in a person at different periods of his life [35, 36].

Obesity and ID are two of the most common nutritional disorders in the world. In children, both conditions deserve particular attention. ID and obesity have been independently associated with poor cognitive function, but now the pathophysiological mechanism(s) linking obesity, ID, and cognitive dysfunction is unknown. Questions related to neuronal effects of insulin remain largely controversial. However, in the last decade, convincing evidence has been obtained that insulin and insulin-receptor signaling the brain system is necessary for normal functioning neurons [37]. Dysfunction of this system leads to the development of neurodegenerative diseases [38–40]. The interaction between ID and obesity in determining cognitive dysfunction could be driven by elevated hepcidin and reduced iron bioavailability in obese children. Pediatricians should bear in mind the potential effect of obesity-related ID on cognition in obese children and the need to evaluate both iron status and the presence of cognitive dysfunction [41, 42].

When considering the position of "iron as a victim" in obesity, emphasis is placed on mechanisms that cause sideropenia, as well as the accumulation of iron in adipose tissue. It is assumed that from this moment, the story "iron as a suspect" begins in the pathogenesis of obesity. There is a possibility of forming a vicious circle, in which ID, cumulating of iron in adipose tissue and direct obesity, is self-sustaining processes [43]. Several studies revealed an association between obesity and ID in children and, in some cases, a reduced response to oral supplementation of iron [44]. Randomized trials of low-dose iron supplementation (≤60 mg daily) for pregnant women are warranting testing the relationship between iron oxidative stress and insulin resistance/gestational diabetes, especially for iron-replete women. The connecting mechanism, however, is not completely known. This review is focused on the following: ID in obese children and the role of hepcidin in the connection between body fat and poor iron status; iron status and consequences on health, in particular on cognitive function; cognitive function and obesity; suggestion of a possible link between cognitive dysfunction and ID in pediatric obesity; and implications for therapy and future research [45].

There are a vast number of conditions affecting iron metabolism in all age groups [46–48]. Some of this leads to the appearance of ID, for example, with acute hemorrhage or chronic pathology. Recent studies addressing the physiological effects of poor iron status on physical performance, including work productivity, voluntary activity, and athletic performance in postmenopausal women are addressed. Similarly, the effects of iron status on neurological performance, including cognition, effect, and behavior, are observed [49]. Cognitive impairment is common in elderly heart failure patients and is independently associated with anemia and renal dysfunction. Further studies are needed to assess whether optimal treatment of anemia and chronic kidney disease may prevent the development of cognitive impairment in heart failure patients [50].

ID was identified as a risk factor regarding the severity of several symptoms even without low hemoglobin level among chronic hemodialysis patients, and supplementation of iron was

considered efficacious for improving critical symptoms affecting those undergoing maintenance dialysis [51].

Normally, timely recovery of the required number of red blood cells leads to rapid compensation of the patient's condition, but adverse effects of IDA or ID could influence insufficient cognitive function in many acute and chronic diseases in adults [52].

The primary pathological mechanism of the concomitant diseases is hypoxemia of the brain tissue, stress-mediated vascular reactions, chronic inflammation in obesity, etc. [53–55]. Common causes of absolute ID in heart failure patients are drug interactions, poor dietary iron intake, gastrointestinal malabsorption, and gastrointestinal blood loss [56–59]. ID is a frequent comorbidity in preserved ejection fraction and is associated with reduced exercise capacity and quality of life. Its prevalence increases with increasing severity of diastolic dysfunction [60]. Anemia in elderly patients with concomitant atherosclerosis and arterial hypotension is a significant risk factor for transient ischemic attacks and ischemic stroke, and diabetes is the adverse impact for cognitive abilities. IDA and subcortical ischemic change might be associated with increased risks for cognitive impairment among the elderly [61, 62].

At the current stages of science, many problems of synergy between ID and comorbid diseases for cognitive functions in patients have not been resolved, which makes it challenging to choose effective therapy.

2. Neurocognitive dysfunctions

The Latin term "cognitio"—the functioning of human cognition, more precisely, is the ability to understand the ongoing process. Tolman first proposed the formulation in 1948 [63]. Cognition began to be studied not only in philosophy but also in the specific sciences—psychology, physiology, medicine, pedagogy, etc. [64, 65]. Cognitive functions are perception, ingenuity, the ability to get acquainted with new information and memorize it, attention, speech, orientation in space and time, and motor skills. In children with ID, cognitive impairments lead to a delay in intellectual development, difficulties in educating. Based on the fact that neurons are the morphological substratum for cognitive functions, scientists often use the term neurocognitive. However, the most base evidence data were achieved in children population. The initial status of children could be determined by the results of complex clinical and psychological diagnosis, which are aimed at assessing the cognitive and motor spheres. The panels of the tests to diagnose the neurocognitive and motor dysfunctions in children and adults include numerous tests, widely used in current medicine [66, 67].

Examples of the tests to diagnose neurocognitive dysfunctions:

1. Visual selective reminding TOMAL samples of various domains of memory in children and adolescents, ages 5 years 0 months through 19 years 11 months, 30 days. The TOMAL is composed of a core battery of 10 subtests, including 5 verbal and 5 nonverbal subtests, as well as supplementary subtests (3 verbal and 1 nonverbal). Four TOMAL subtests assess retrieval both immediately upon stimulus presentation and following a 30-min filled

delay. Among the 10 core subtests, memory for stories involves immediate and delayed free recall of short verbal narratives and word selective reminding is a verbal list learning task that includes a delayed free recall condition [68].

2. First proposed by Swiss psychologist André Rey in 1941 and further standardized by Paul-Alexandre Osterrieth in 1944, it is frequently used to further explain any secondary effect of brain injury in neurological patients, to test for the presence of dementia, or to study the degree of cognitive development in children. The "Rey– Alexander Osterrieth complex figure test" (ROCF) is a neuropsychological assessment in which examinees are asking to reproduce a complicated line drawing, on the first copy it freehand (recognition), and then drawing from memory (recall) [69]. Many different cognitive abilities are needed for a correct performance, and the test, therefore, permits the evaluation of different functions, such as visuospatial abilities, memory, attention, planning, and working memory (executive functions) [70].

3. Verbal fluency tests are semantic verbal fluency tests with the categories Animals and Fruit and could be used for lexical/phonemic ability versions due to the educational heterogeneity of the local population, which sometimes limits the use of instruments that require knowledge acquired through higher formal education [71].

4. Visual-motor integration is using the Beery-Buktenica Developmental Test of Visual-Motor Integration (Beery VMI) (Beery, 1989; Beery, 1996; Beery and Beery, 2004). The Beery VMI is comprised of drawings of geometric forms that increase in difficulty. The forms are copied with paper and pencil and scored based on objective scoring criteria outlined in the test manuals according to how accurately they were copied when compared to the original. The Beery VMI has been demonstrating good reliability and validity as reported in the manual [72, 73].

5. The "Bruninx-Ozeretskii test" was estimate using for motor function of the person. The child is asked to perform a series of game tasks available for understanding children from 4 years. The person is given a clear instruction describing the nature of the task, and then the researcher shows the child an image on the cardboard a card showing a child performing the same task. With difficulties in perception of the patient information, the researcher, as an example, performs the task itself and then invites the child to repeat it. The result is integrated into the indicator "General motor rating", presenting in the form of a percentile scale with the maximum and minimum values from 20 to 80. The Achenbach System of Empirically Based Assessment, created by Thomas Achenbach [74, 75], is a collection of questionnaires used to assess adaptive and maladaptive behavior and overall functioning in individuals. The system includes report forms for multiple informants—the Child Behavior Checklist is used for caregivers to fill out ratings of their child's behavior; the Youth Self Report Form (YSR) is used for children to rate their own behavior; and the Teacher Report Form is used for teachers to rate their pupil's behavior. The ASEBA seeks to capture consistencies or variations in behavior across different situations and with different interaction partners [76].

6. IntegNeuroTM is standardized and semiautomated computerized battery assesses sensorimotor function, attention, new learning and memory, language fluency, executive

function, and estimated intelligence. A total of 50 healthy individuals were included in the study. Correlational analyses revealed highly significant associations between the two cognitive batteries. These results support the use of IntegNeuroTM as a computerized cognitive system. Additional studies are needed to examine the clinical utility of the battery [77].

This tests and/or other could be used not only at the baseline but also for monitoring neurocognitive dysfunctions.

3. Iron deficiency and nervous system

The concentration of iron in the brain reaches 21.3 mg per 100 mg, whereas in the liver—only 13.4 mg per 100 mg. Iron serves as a critical cofactor for proteins involved in a host of biological processes. Iron is of central importance to many vital processes because the metal is a catalytic component of crucial metabolic enzymes in the citric acid cycle, mitochondrial respiration, replication, or neurotransmitter synthesis [78]. Synapse growth is examined specifically in conditions of iron deficiency in the Drosophila. It is shown that projections of the small ventrolateral clock neurons to the protocerebrum of the adult Drosophila brain are significantly reduced upon chelation of iron from the diet. This growth defect persists even when iron is restored to the diet. Genetic neuronal knockdown of ferritin 1 or ferritin 2, critical components of iron storage and transport, does not affect synapse growth in these cells. Together, these data indicate that dietary iron is necessary for central brain synapse formation in the fly and further validate the use of this model to study the function of iron homeostasis on brain development [79–81].

In the monkey model, scientists show that both during and after a period of ID, iron-dependent neural processes are affected, which raises the potential concern that the anemia commonly experienced by many growing infants that could have a protracted effect on the developing brain. To further investigate the effects of ID on the immature brain, 49 infant rhesus monkeys were evaluated across the first year of life. The mothers, and subsequently the infants after weaning, were maintained on a standardized diet containing 180 mg/kg of iron and were not provided other iron-rich foods as treats or supplements. As the infants grew, they were all screened with hematological tests, which documented that 16 (33.3%) became markedly ID between 4 and 8 months of age. During this anemic period and subsequently at 1 year of age, cerebrospinal fluid (CSF) specimens were collected to compare monoamine activity in the ID and iron-sufficient infants. Monoamine neurotransmitters and metabolite levels were normal at 4 and 8 months of age, but by 1 year, the formerly anemic monkeys had significantly lower dopamine and significantly higher norepinephrine levels. These findings indicate that ID can affect the developmental trajectory of these two important neurotransmitter systems, which are associated with emotionality and behavioral performance, and further that the impact on the young monkey was most evident during the period of recovery [82].

ID in the first year of life can have a negative impact on the processes of postnatal central nervous system (CNS) formation, which can have long-term consequences for the development

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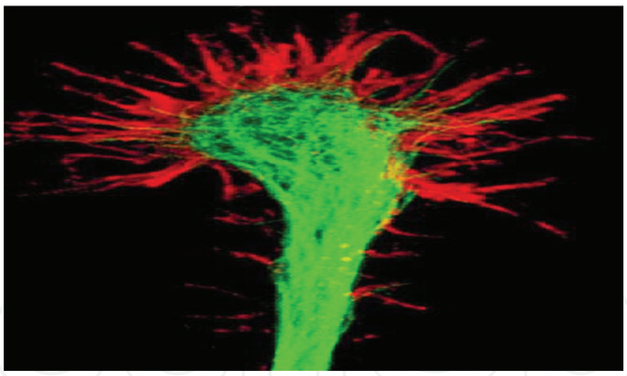

Figure 1. Growth cone of axon (https://www.turkaramamotoru.com/ru/).

of the child [83]. Several decades ago, it was believed that new brain cells in an adult are not formed. That person can study only up to 25 years, and then the brain has lost the chance to be educated. Those intellectual abilities are inherited or inherent in quality, and they cannot be developed during the life. Now we know that this is not so. The human brain develops all his life (**Figure 1**). In the world literature, the influence of ID and IDA on the functioning of the human and animal organism, including on the nervous system is discussed [81, 84].

By the time of birth, the baby's brain is immature. Nevertheless, with each month the child learns more and more. To make the signals go quickly and in the right direction, the nerve fibers in an adult person are isolated. Just like electrical wires. A substance that performs the role of isolation is called a myelin or myelin sheath. Nerve cells maintain a connection with each other with the help of processes, which are called dendrites and axons or nerve fibers [85, 86]. Signals on these fibers almost instantly move from cell to cell. It is like how electricity flows through the wires (**Figure 2**). Genes control myelination. To activate them, the cells of the brain need iron. ID inhibits myelination, as it does not allow cells to maintain high activity of these genes. Therefore, children with ID can develop hyperactivity and lack of attention in the future. From the fact that myelin is in lack, the nervous system will not learn to isolate and direct the signals well [87].

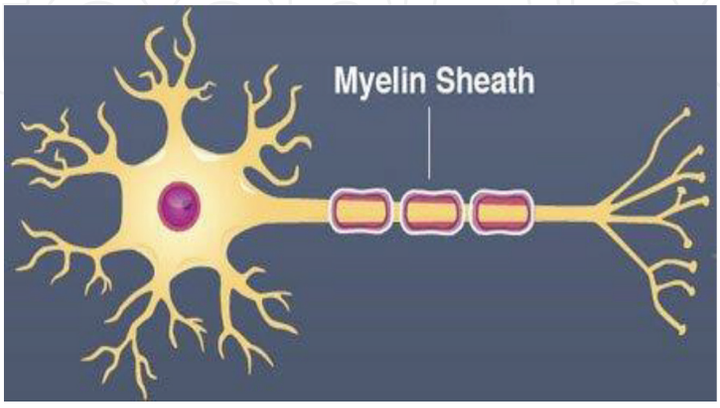

Figure 2. Location of myelin sheath in neuron (https://www.goconqr.com/en-US/p/615525).

Iron homeostasis impairment is also a component of peripheral neuropathies [88]. The main function of the peripheral nervous system (PNS) is to collect impulses from the periphery and transfer them to the CNS, where they are integrated to generate an adequate response. PNS neurons extend over a significant length that in humans can reach above 1 m in extension [89]. Thus, a correct and fast conduction of electrical impulses is essential for rapid and maximal response. In vertebrates, this is achieved by the generation of myelin [90]. Besides providing axonal insulation, several evidences indicate that myelin is essential also for neuronal protection. In the absence of myelin, axons degenerate, and this is the main cause of morbidity in demyelinating and demyelinating disorders. The homeostasis of iron in the PNS influence, on its transport across the blood-nerve barrier, its involvement in myelination [16].

Restless legs syndrome is one of the examples of peripheral neuropathies. The pathophysiology of idiopathic restless legs syndrome is still incompletely understood; however, it is well established that disturbances of dopaminergic function and alterations of iron homeostasis are involved in its pathogenesis [91–93]. Concerning iron metabolism, the general hypothesis is that iron deficiency is common in RLS patients, as reflected by reduced iron levels in brain sections, measurements of decreased iron levels in the cerebrospinal fluid, and imaging studies indicating iron dyshomeostasis in the brain [94].

The quality and quantity of sleep are increasingly recognized as important factors in human development, with concomitant effects on affective behavior and cognitive performance [95]. In addition to biological mechanisms, cultural factors are also important determinants of sleep practices and behaviors in infants, children, and adolescents, and influence both the type and frequency of sleep problems found in the pediatric population [96]. IDA in infancy is associated with long-lasting neurofunctional effects despite iron treatment; the normal development of sleep patterns might be affecting. Night polysomnographic recordings were performed in 55 healthy 4-year-old children (former IDA = 27 and nonanemic controls = 28). Both groups were followed from infancy and were similar in background characteristics. The duration of each waking episode was measured, as was the duration of each episode of no rapid eye movement (NREM) sleep stages 1 (NREM1), 2 (NREM2), and 3–4 (SWS), and rapid eye movement (REM) sleep. The data were analyzed according to the successive thirds of the total sleep time (TST). Relative to controls, former IDA children showed: (a) longer duration of REM sleep episodes in the first third and shorter in the last third, (b) more REM sleep episodes in the first third and fewer in the second third, and (c) shorter latency to the first REM sleep episode and shorter NREM stage 2 and SWS episodes within the first sleep cycle. The results show that early IDA is associated with long-lasting alterations in the temporal organization of sleep patterns [97, 98].

The work reveals CNS developmental delay through the study of qEEG (less rapid and slower frequencies) which recovered significantly with iron supplementation. It is concluded that IDA constitutes a high risk factor for a lag of CNS maturation [99]. Neuroscientists who use MRI in a special functional mode also found activation of whole areas of the brain during their use. And they also saw "holes" in the activity of the brain, in those people, which lead an unhealthy lifestyle or get micronutrients: iron, other trace elements, and vitamins [94]. Genes also control neuroplasticity. Iron is necessary for their activation. Fetal-neonatal

iron deficiency dysregulated genes important for hippocampal development both acutely and persistently into early adulthood [100, 101]. A number of studies have shown that cognitive functions, especially memory in women with iron deficiency, are reduced compared with their peers without deficiency. In other words, their brains do not have enough resources to train. However, unlike myelination, active neuroplasticity is not limited in time, but occurs throughout life [102].

The rate of development of the nervous system of the child also slows down with ID [103]. For complex skills, extensive neural networks are needed. To have neural networks, myelin is needed. If it is not enough, new skills are late. This is most noticeable in speech. Children with latent ID or anemia in their first year of life usually start talking later. Evoked potentials provide noninvasive measures of nerve transmission and CNS functioning. Auditory brainstem responses and visual evoked potentials show dramatic changes in infancy, largely as a result of progressive myelination. Because iron is required for normal myelination, pathway transmission in these sensory systems is affected by early iron deficiency. Absolute latencies for all auditory brainstem responses and visual evoked were significantly longer in former IDA children [104, 105].

Some studies have established that cognitive impairment may be closely associated with neuroanatomical damage and zinc metabolism in the hippocampus due to iron deficiency, which may result from abnormal cholinergic function. The hippocampus is the focus of many studies today, since this brain structure has high zinc concentration and is highly involved in many forms of cognitive deficits as a consequence of cholinergic deficiency and has achieved prominence because of dementia in aging and Alzheimer's disease [106]. Thus, it is now apparent that cognitive impairment may not be attributed to a single neurotransmitter, but rather, alterations and interactions of several systems in different brain regions. In animal models of iron deficiency, it is apparent that dopaminergic interaction with the opiate system and cholinergic neurotransmission may be defective [107].

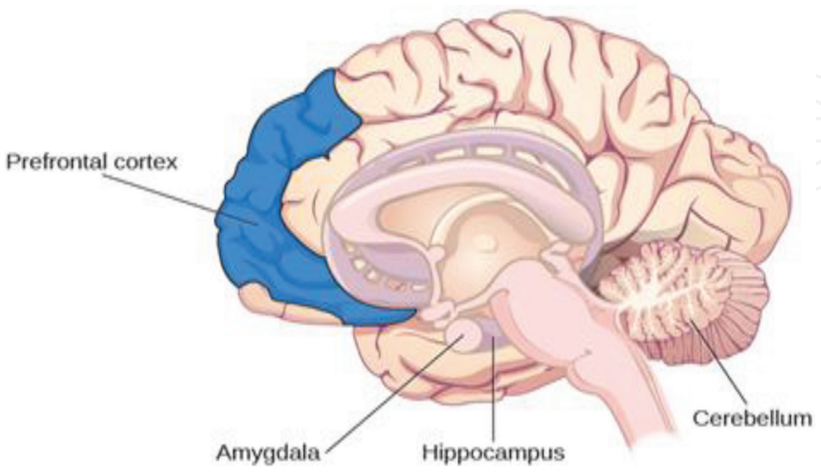

Figure 3. The location of hippocampus (http://www.thinglink.com/scene/834791711828869120).

Memory can also suffer from lack of iron in early childhood. The hippocampus is the region of the brain responsible for memory. It forms, stores, and reproduces the knowledge and experience of a person. The quality of memory and the speed of reproduction depend on the development of neural networks of the hippocampus. The main parts of the brain involved with memory are the amygdala, the hippocampus, the cerebellum, and the prefrontal cortex (**Figure 3**).

Studying the effect of iron deficiency on the hippocampus of laboratory animals, scientists discovered an interesting fact. In rats suffering from iron deficiency in utero, the hippocampus at birth is less in volume than in their peers, with which the gland lacked. Moreover, these changes persist when rats grow [108, 109]. It is assumed that the human iron deficiency affects the hippocampus in a similar way [110]. In addition, it is assumed that changes in dopamine metabolism in the brain occur in response to ID, as well as altered serotonergic neurotransmission and dopamine receptor function [7, 111].

Chronic ID during development, independent of anemia, alters the adult mouse hippocampal transcriptome. Restoring iron status during a known critical period of hippocampal neurodevelopment incompletely normalized these changes, suggesting a need for additional studies to identify the most effective timeline for iron therapy and adjunctive treatments that can fully restore ID-induced molecular changes, particularly in human populations in whom chronic ID is endemic [112].

The problem of attention deficit hyperactivity disorder (ADHD) is actually everywhere. Different international groups confirmed the correlation of iron serum parameters, serum ferritin, and ADHD. Indian pediatricians with a high level of significant found that serum ferritin level was significantly lower among ADHD patients. This finding is consistent with multiple previous studies [113, 114]. Many other studies reported an association between iron deficiency and ADHD [115, 116].

Based on the stroke registry at the Hospital for Sick Children (Toronto, Ontario, Canada), physicians found that comparatively previously healthy children with stroke were 10 times more likely to have IDA than healthy children without stroke. Furthermore, children with iron deficiency anemia accounted for more than half of all stroke cases in children without an underlying medical illness, which suggests that iron deficiency anemia is a significant risk factor for stroke in otherwise healthy young children. Primary prevention and early identification of iron deficiency anemia must remain a priority [117].

4. Iron deficiency and cognition

In fact, patients with chronic ID are presented with lower grades in the language, perception of ambient sound, and motor measures compared with children with normal dietary iron status [118, 119]. Moreover, Lozoff et al., the most productive researcher of this term, reported that changes in the mesolimbic pathway, positive influence, and inherent reward could support the explanation of the altered social-emotional behavior described in children with ID. Thus, the status of iron appears to be the decisive determinant of cognitive functioning in children,

and its destruction implies significant consequences for the health of the child. Improvement of iron status in 12-months and 6-years children has diminished the public health threat associated with iron depletion in the population studied [120]. Therefore, actions to prevent iron depletion in infancy remains are very important [121, 122].

The infant period of life with ID dramatically influence at the intellectual functions. Iron deficiency in first year of life occurs at a time point of rapid neural development and when morphological, biochemical, and bioenergetics alterations take place. The structures of the brain can either become abnormal because of ID in utero or in early postnatal life because iron is essential for proper neurogenesis and differentiation of certain brain cells and brain regions [123, 124]. Early ID alters the transcriptome, metabolome, structure, intracellular signaling pathways, and electrophysiology of the developing hippocampus, the brain region responsible for recognition learning and memory. Until recently, it was unclear whether these effects are directly due to lack of iron interacting with important transcriptional, translational, or post-translational processes or to indirect effects such as hypoxia due to anemia or stress [125].

Data indicate poorer object permanence and short-term memory encoding and/or retrieval in infants with IDA at 9 months. These cognitive effects were attributable, in part, to IDA-related deficits in socioemotional function. Children with poor socioemotional performance seem to be more vulnerable to the effects of IDA on cognitive function IDA [126, 127]. Improved iron status at 12 months and 6 years has diminished the public health threat associated with iron depletion in the population studied [128].

Several previous studies have shown that children with low levels of iron in their blood do worse than those who without ID on tests that measure cognitive skills, such as thinking, learning, and memory, according to the background information in the article [129]. Researches from the University of Michigan studied the long-term effects of ID and socioeconomic status in a group of 185 children from an urban area in Costa Rica. The children, who were an average of 17 months old when the study began in 1983–1985, were screened for ID at their first visit. They were given cognitive tests (on which the index, or overall average score, is 100) then and again at ages 5, 11–14, 15–18, and 19 years. Those who had low iron levels in infancy even after 3 months of iron therapy were compared with those who had normal iron levels either without or after treatment. The gap in cognitive scores between iron-deficient and non-ID teens had widened to 25 points (70.4 vs. 95.3). "The observed pattern appears to make sense in terms of the cumulative and transactional nature of cognitive development." Acquisition of new skills is intimately linked to mastery of skills at an earlier developmental level. If direct and indirect effects of early ID on the brain disrupted or delayed basic developmental processes, there could be a snowball effect. In an economically stressed family environment, there might not be the resources or capacity to help children compensate. The authors conclude that the results highlight the necessity to identify the children at risk for ID and prevent or treat the condition in infancy [130].

Rates of ID are high among healthy young women. Cognitive impairment occurs secondary to ID in infants and children, but evaluation of the impact on cognition among young women is inconsistent. The aim of the research was to determine the suitability of the IntegNeuro test battery for assessing cognitive function in ID and iron-sufficient young women. A pilot

double-blinded, placebo-controlled intervention trial was conducted in iron-deficient (serum ferritin ≤20 μg/L and hemoglobin >120 g/L) and iron-sufficient young women (18–35 years). Cognitive function and hematological markers of iron status were measured at baseline and follow-up. Iron-deficient participants (n = 24) were randomized to receive placebo, 60 or 80 mg elemental iron daily supplements for 16 weeks. A control group of iron-sufficient participants (n = 8) was allocated to placebo. Change scores for impulsivity and attention were significantly greater in plasma ferritin improvers than in nonimprovers ($p = 0.004$, $p = 0.026$). IntegNeuro was easy to administer and acceptable to young women. Based on the differences in memory and attention scores between iron-deficient participants on iron treatment and those on placebo, it was decided that between 26 and 84 participants would be required in each iron treatment group for an adequately powered extension of this pilot study [131].

In Archangelsk, Russia ID without iron deficiency anemia was diagnosed in 46.7% of the children among 90 children aged 7–8 years attending comprehensive schools. Contingency of Toulouse-Piéron test results with the level of serum iron was evaluated by means of Pearson $\chi 2$-test, the effect being determined by "phi" coefficient. Statistically significant association was detected between the level of serum iron and AIP of Toulouse-Piéron test ($\chi 2 = 21.878$ and $p = 0.039$) with a relatively strong effect ($\varphi = 0.493$). The study has shown that ID without IDA has a negative effect on the accuracy of information processing [132].

ID and, in an even greater degree, IDA affects the formation of such a complex psychosocial effect as social isolation [133]. The consequences of this phenomenon during schooling can restrain the realization of the child's cognitive abilities. Children who are iron deficient (ID) or iron-deficient anemic (IDA) have been shown to seek and receive less stimulation from their caregivers, contributing to functional isolation. Over time, the reduced interactions between child and caregiver are thought to interfere with the acquisition of normative social competencies and adversely affect the child's development [31].

5. Deficiency of iron in patients with imbalance of micronutrients

Numerous vitamins, macro- and microelements, indispensable components, and nutrition of a person represent the value of the micronutrient complex, since they are necessary for the occurrence of numerous biochemical reactions in the body, including ensuring human intellectual abilities. Micronutrients are chemically and physiologically active substances that are able to interact with other substances, as well as with each other. These interactions can lead to an increase or decrease in the effect of taking vitamin-mineral complexes. For example, calcium and zinc reduce the absorption of iron. Moreover, the addition of vitamins A, C, and others—strengthen, contributing to the correction of IDA and ID.

A frequent cause of neurocognitive impairment is a mono or poly-micronutrient deficiency. The micronutrient deficiency mostly delivers during pregnancy [134, 135]. For an example widespread iron deficiency, iodine deficiency is a monodeficiency, that is, are due to a lack of only one element. Iron is the most abundant transition metal in biology and an essential cofactor for many cellular enzymes. The literature on the effects of micronutrients on

cognitive, motor, and behavioral development is reviewed focusing mainly on children. Iron, zinc, iodine, and vitamins are discussed. The review is selective and concentrates on the more recent work and areas of controversy. There are well-established associations with poor development and iron and iodine deficiencies but the deficiencies usually occur in disadvantaged circumstances, and establishing causal relationships is difficult [136]. More than 200 proteins of iron homeostasis cannot function without corresponding cofactors: derivatives of group B vitamins, copper ions, manganese, zinc, etc. [137, 138]. For example, 9 copper-containing enzymes and 22 manganese-dependent proteins are involved in the homeostasis of iron.

In addition to iron, microelements such as copper and cobalt, to a lesser extent manganese, zinc, etc., play an important role in the processes of normal development of nervous system. According to the National Nutrition Monitoring Bureau of India, IDA is diagnosed in many healthy children, and two-thirds have clinical symptoms of ID combined with a deficiency of essential trace elements such as iodine, zinc, copper, etc. [139]. Hypermanganesemia in children with SLC39A14 gene mutation (OMIM 608736 8p21.3) is associated with severe ID [140].

Copper is an immediate participant in the transfer of elemental iron to the bone marrow and the formation of mature forms of erythrocytes from their precursors—reticulocytes; it promotes the utilization of iron for the formation of hemoglobin molecules. Physiological variables of iron and copper are related to each other [141]. One of the key enzymes of the "respiratory chain" of electron transfer is cytochrome C oxidase, containing a copper and iron ion as cofactors. Therefore, copper can be considered one of the main synergists of iron [142].

Fe(II) and Cu(II) act synergistically to delay anaerobic growth of bacteria environmentally relevant metal concentrations [143]. The lack of copper also leads to the exhaustion of the nervous system. The deficiency in the activity of Cu, Zn-superoxide dismutase due to genetic defects, and deficiencies in zinc or copper leads to amyotrophic lateral sclerosis, a neurodegenerative disease of motor neurons. In addition to influence the processes of inflammation, the activity of superoxide dismutase affects the hemolysis of erythrocytes and the cellular homeostasis of iron [144]. There are other works determining the place of combined trace elements in the pathogenesis of neurodegenerative diseases [145].

Supplementation studies in infants and elder children revealed that zinc might also play a major role in brain function based on strong evidence from experimental animals. Zinc deficiency gestation in mice, rats, and rhesus monkeys caused impaired learning, reduced attention, and poor memory in their offspring. There is lack of data in humans and inconclusive. With respect to brain function alone, other nutrients such as docosahexaenoic acid (DHA, 22:6 n-3 fatty acid) improve visual acuity and mental development in small-for-gestational-age infants, folate supplementation during pregnancy prevents neural tube defect in infants, and selenium deficiency in animals affects activities of brain enzymes necessary for brain development and function [146, 147]. Critical issues to be considered include: single versus multiple limiting nutrients, critical period of deficiency, responsive indicators and variables that may affect the results as environmental, and psychological and social factors [148, 149].

Studies of trace element deficiency in the children's population of the Chelyabinsk region, carried out in 2014, confirmed the widespread occurrence of ID conditions. More than 40%

of adolescents aged 13–15 years had misbalances of essential trace elements. The most often deficiency of iron was associated with lack of copper, zinc, chromium, phosphorus, and magnesium. Deficiency of iron was more pronouncing against the background of increased content of heavy metals in biosubstrates: hair and blood of the adolescents surveyed [150].

Vitamin D deficiency was also associated with moderate anemia among young children. The role of vitamin D, vitamin B-12, and folic acid in risk for anemia in multi-nutrient deficiency responsible for cognitive development needs to be examined in further studies [151–154].

5.1. The role of erythropoietin in cognitive dysfunctions

Since 1906, thanks to the pioneering work of French scientists, R. Carnot and S. Deflandre, erythropoietin (EPO) has become known primarily as a hemopoietin factor stimulating the formation of red blood cells de novo. They found that after bleeding a rabbit, there was, in its serum 24 h later, some factor which stimulated red cell production in normal rabbits. They called it hemopoietin, but it was later called erythropoietin [155].

EPO (**Figure 4**) is an important renal hormone, and the secretion of which is regulated by such factors as the blood supply of the kidneys, the level of iron in the blood plasma, the cross hormonal effects from the sympathetic nervous system, and endocrine glands [50, 156]. Recently, it became known that EPO, in spite of its name, is important not only for the regulation of erythropoiesis but also for the regulation of the growth and multiplication of cells of a number of other tissues, including, importantly, the cells of the nervous system. Thus, EPO is an important growth factor for neurons [157, 158].

The authors demonstrate with the animal model that EPO would diminish the deleterious effects of a social stressor in mice. Indeed, EPO induced anxiolytic and antidepressant-like responses in a forced swim test, open field, elevated-plus maze, and a novelty test and appeared to blunt some of the negative behavioral effects of a social stressor. Furthermore, EPO promoted adult hippocampal neurogenesis, an important feature of effective antidepressants. The EPO could be recommended as a possible adjunct treatment for affective disorders, as well as other stressor-associated disorders of impaired neuroplasticity [159, 160].

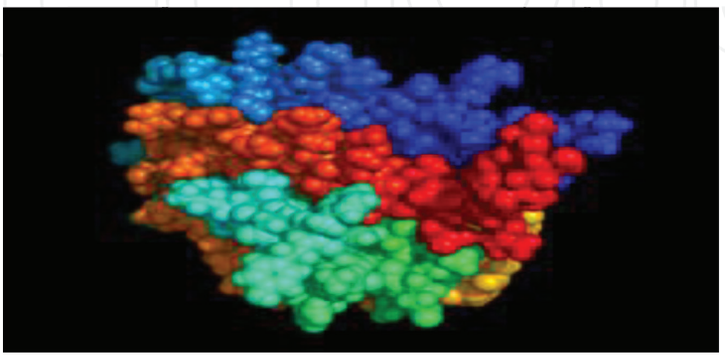

Figure 4. The structure of the erythropoietin molecule (http://en.turkcewiki.org/wiki/Erythropoiesis-stimulating_agent).

http://dx.doi.org/10.5772/intechopen.82620

EPO, which is widely prescribed to treat anemia, has recently emerged as a potent neurotrophic factor with robust actions on the brain. A slight decrease in the level of EPO is also observed in patients with depressed states not suffering from chronic renal failure, in part because, as it turned out in recent years, the brain is also one of the places of EPO secretion, where it plays the role of a neuropeptide. EPO receptors are found in areas of the brain important for cognitive functioning, such as the hippocampus and the prefrontal cortex. One of the important reasons for the development of depression and cognitive impairment in chronic renal failure patients is the reduction in the secretion of EPO by the kidneys. The introduction of recombinant human EPO in patients with CRF improves their overall well-being, cognitive function and reduces the level of depression regardless of the effectiveness of treatment with erythropoietin anemia [161]. It has been shown that the administration of recombinant human EPO-alpha or beta has an antidepressant effect and improves the cognitive function of patients with depression, even those who do not suffer from renal failure [162, 163]. It is also interesting to note that the most effective antidepressant treatment/electroconvulsive therapy is accompanied by a marked increase in the secretion of EPO by brain tissue. It has also been shown that the additional administration of exogenous EPO can not only enhance the antidepressant effect of electroconvulsive therapy but also reduce the cognitive impairment caused by electroconvulsive therapy [164, 165].

In one of the first prospectively designed studies IDA, evaluation of the better neurocognitive outcomes was found of preterm infants randomized to receive Darbepoetin (Darbe) in compared with placebo. Preterm infants had significantly higher cognitive scores compared with the placebo group. Authors reported decreased transfusions and donor exposures in preterm infants randomized to Darbe or EPO compared with placebo. As these erythropoiesis-stimulating agents (ESA) have shown promise as neuroprotective agents. Of the original 102 infants (946 ± 196 g and 27.7 ± 1.8 weeks' gestation), 80 (29 EPO, 27 Darbe, and 24 placebo) returned for follow-up. The three groups were comparable for age at testing, birth weight, and gestational age. After adjustment for gender, the analysis of covariance revealed significantly higher cognitive scores among Darbe (96.2 ± 7.3; mean ± SD) and EPO recipients (97.9 ± 14.3) compared with placebo recipients (88.7 ± 13.5; $P = .01$ vs. ESA recipients) as was object permanence ($P = .05$). No ESA recipients had cerebral palsy, compared with five in the placebo group ($P < 0.001$). No differences among groups were found in visual or hearing impairment. In the conclusion, infants randomized to receive ESA had better cognitive outcomes, compared with placebo recipients, at 18–22 months. Darbe and EPO may prove beneficial in improving long-term cognitive outcomes of preterm infants [166].

The possibility of clinical use of drugs, recombinant EPO to protect the brain, presents the main currently known mechanisms for the implementation of its neuroprotective potential, not connected with the influence on erythropoiesis. Several preclinical and clinical studies have demonstrated that systemic administration of EPO is sufficient to produce behavioral effects. Clinical trials have reported striking improvement in cognitive function in schizophrenia patients and treatment resistant depression. EPO has been shown to improve cognitive function in schizophrenia and treatment resistant depressed patients [162].

However, the potent elevation of red blood cell counts by EPO can cause hematological complications in nonanemic patients. The conducted mass-spectrometry-based peptide mapping of carbamoylated Epo (Cepo) tested its ability to improve cognitive function after social defeat stress. Gene expression analysis in discrete brain regions was performed to obtain mechanistic insight of Cepo action. Cepo reversed stress-induced spatial working memory deficits while affecting long-term (24 h) novel object recognition in these rats. Contextual fear conditioning following defeat was enhanced by Cepo, but attenuated in controls. However, Cepo improved fear extinction in all rats compared to vehicle treatment. Cepo induced differential gene expression of VGF and neuritin in the mPFC and discrete hippocampal subfields, with strongest induction in the dorsal hippocampus. Analysis of gene-brain region-behavior interactions showed that Cepo-induced neurotrophic mechanisms influence cognitive function. Carbamoylated EPO can be developed as a therapeutic neurotrophic agent to treat cognitive dysfunction in neuropsychiatric diseases. Due to its distinct mechanism of action, it is unlikely to cross react with the activity of currently prescribed small molecule drugs and can be used as an add-on biologic drug [167].

The use of EPO in preterm infants both for anemia treatment and correction of immunological and neurological status is considered a prospective direction, but it is complicated by the lack or inconsistency of data on the concentration of endogenous EPO in serum. The concentration of serum EPO in preterm infants with a gestational age of 27–36 weeks and 6 days (Apgar scores 4.32 points) was higher by 1 day after birth and did not differ from a group of full-term infants on 10th day. In preterm infants with gestational age 27–31 weeks and 6 days (Apgar score 3.33), the concentration of serum EPO is higher by 1 day and is lower by 10th day after birth. In preterm infants with gestational age 32–36 weeks and 6 days (Apgar score 5.5), the concentration of serum EPO was lower on 1st day after the birth, and it did not differ from indices in the group of full-term infants on 10th day. The concentration of serum EPO in preterm infants with 27–31 weeks 6 days of gestation increases on the 1st, decreases on 10th day after birth as gestational age decreasing, and the total Apgar score reduces [168].

Pro-cognitive effects of EPO occurred across affective disorders. Neuropsychological screening for cognitive dysfunction may be warranted in future cognition trials.

6. Discussion and conclusions

About one-fifth to one-fourth of children around the world has IDA, in which lack of iron causes problems with hemoglobin—the compound that red blood cells used to transport oxygen through the bloodstream. Many more have low iron without anemia. Children from poor, minority, or immigrant backgrounds are more likely to be ID. ID is associated with alterations in many metabolic processes that may impact brain functioning (e.g., mitochondria electron transport, neurotransmitter synthesis and degradation, protein synthesis, and organogenesis).

Although IDA and ID without anemia may be associated with poor cognitive/behavioral outcomes, this has not been sufficiently studied. In particular, there is lack of dose response

studies linking indicators of iron status as continuous risk factors with later cognitive outcomes. The lack of effect in the youngest infants may be because of irreversible effects of ID on the developing brain or the fact that cognitive development and behavior are more difficult to measure in young children [47]. IDA has been consistently linking to altered child affect, energy, and activity, but little knows about how these aberrations affect later development or adjustment in other contexts.

Summarizing the data presented in probably formulates effector mechanisms of influence on the implementation of the ID neurocognitive skills in children and adults:

- hypoxia, tissue hypoxemia
- the enzymatic deficiency in organs of the nervous system and internal environment
- violation of the myelination process, the development of neuropathy
- the development of oxidative stress
- neurodegenerative processes in the central nervous system.

It is extremely difficult to establish a cause-effect relationship between various factors affecting the development of iron deficiency, neurocognitive impairment, and comorbid conditions [2, 11, 20, 36]. For example, it has yet to determine the diagnostic significance of the mutations responsible for the development of severe and/or refractory forms of IDA. Genetic

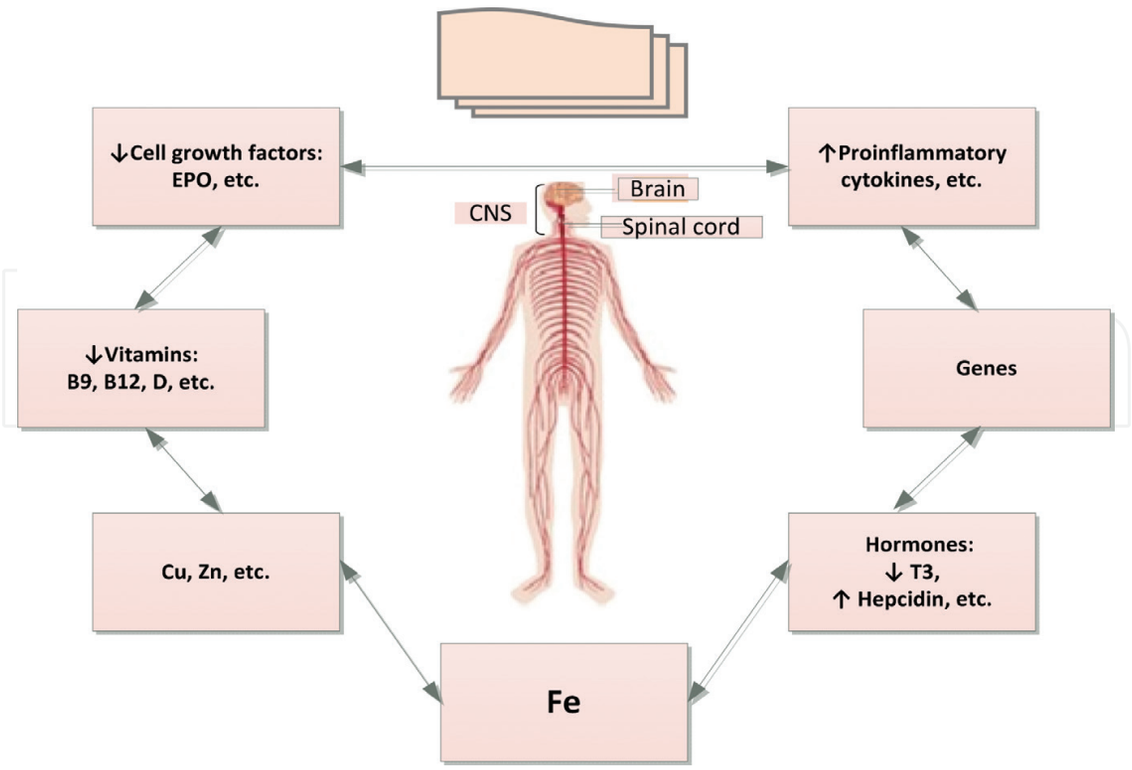

Figure 5. Components of iron homeostasis affecting human neurocognitive development.

causes can involve quantitative or qualitative impairment of globin chain synthesis (thalassemia and sickle cell disease, respectively) [169], or genetically related abnormalities of the erythrocyte, either at the membrane level (pyruvate kinase, glucose-6-phosphate dehydrogenase (G6PD), and stomatocytosis) or concerning enzyme function (hereditary spherocytosis also known as Minkowski-Chauffard syndrome). In addition, a number of rare anemias are related to genetic defects of iron metabolism itself. These defects involve mutations of genes that play a role in systemic or cellular iron metabolism [170]. Despite the relatively low prevalence of iron deficiency in high-income countries using current diagnostic criteria in this healthy cohort, microcytosis was associated with lower cognitive outcomes after 2 years. This research study emphasizes the need to reassess the diagnostic criteria for iron deficiency in young children, while further research is required in studies with adequate nutrition [171].

The metabolic ring of iron homeostasis demonstrates the involvement of a large number of components. However, the establishment of cause-effect relationships is difficult due to differentiate in interpreting the pathogenesis of IDA and cognitive disorders, because of which it is impossible to talk about unidirectional processes in the homeostatic ring of iron (**Figure 5**).

In elderly adults, the cause of cognitive impairment is often vascular lesions of the brain, which can be combined with an imbalance of essential trace elements. Over time, a person begins to show violations of daily behavior due to disruptions in the work of cognitive functions. In children, we need to look mostly for perinatal and post-natal events. So, comprehensive mechanism of the development cognitive dysfunctions in children and elder people needs different protocols for the treatment of ID and IDA.

Difficulties in studying the influence of ID on the level of IQ, individual manifestations of neurocognitive insufficiency, are because they often have a latent character, and in the case of their diagnosis, there are serious problems in deciphering etiology mechanisms and organizing optimal therapy.

Conflicts of interest

The authors declare no conflict of interest.

Author contributions

E. Zhukovskaya retrieved articles, interpreted the results, and drafted and revised the manuscript; A. Karelin contributed in writing the introduction and discussion and interpretation of the findings; and A. Rumyantsev provided critical input to the manuscript and helped with the interpretation of the results.

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