Journal of Trace Elements in Medicine and Biology 60 (2020) 126499

Contents lists available at ScienceDirect

Journal of Trace Elements in Medicine and Biology

journal homepage: www.elsevier.com/locate/jtemb

Review

Neurodevelopmental disorders: Metallomics studies for the identification of potential biomarkers associated to diagnosis and treatment

Catia Scassellati*,[1], Cristian Bonvicini[1], Luisa Benussi, Roberta Ghidoni, Rosanna Squitti

Molecular Markers Laboratory, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy

ARTICLE INFO

Keywords:
Diagnosis
Treatment
Neurodevelopmental disorders
Biomarkers
Metallomics
Biometals
Metallomes

ABSTRACT

Background: Diagnosis and treatment of complex diseases such as Neurodevelopmental Disorders (NDDs) can be resolved through the identification of biomarkers. Metallomics (research on biometals) and metallomes (metalloproteins/metalloenzymes/chaperones) along with genomics, proteomics and metabolomics, can contribute to accelerate and improve this process.

Aim: This review focused on four NDDs pathologies (Schizophrenia, SZ; Attention Deficit Hyperactivity Disorder, ADHD; Autism, ADS; Epilepsy), and we reported, for the first time, different studies on the role played by the principal six essential trace elements (Cobalt, Co; Copper, Cu; Iron, Fe; Manganese, Mn; Selenium, Se; Zinc, Zn) that can influence diagnosis/treatment.

Results: in light of the literature presented, based on meta-analyses, we suggest that Zn (glutamatergic neurotransmission, inflammation, neurodegeneration, autoimmunity alterations), could be a potential diagnostic biomarker associated to SZ. Moreover, considering the single association studies going in the same direction, increased Cu (catecholamine alterations, glucose intolerance, altered lipid metabolism/oxidative stress) and lower Fe (dopaminergic dysfunctions) levels were associated with a specific negative symptomatology. Lower Mn (lipid metabolism/oxidative stress alterations), and lower Se (metabolic syndrome) were linked to SZ. From the meta-analyses in ADHD, it is evidenced that Fe (and ferritin in particular), Mn, and Zn (oxidative stress dysfunctions) could be potential diagnostic biomarkers, mainly associated to severe hyperactive or inattentive symptoms; as well as Cu, Fe, Zn in ADS and Zn in Epilepsy. Fe, Zn and Mn levels seem to be influenced by antipsychotics treatment in SZ; Mn and Zn by methylphenidate treatment in ADHD; Cu and Zn by antiepileptic drugs in Epilepsy.

Conclusions: Although there is controversy and further studies are needed, this work summarizes the state of art of the literature on this topic. We claim to avoid underreporting the impact of essential trace elements in paving the way for biomarkers research for NDDs.

1. Introduction

The identification of biomarkers as diagnostic tool and as predictors of treatment response for childhood/adulthood Neurodevelopmental Disorders (NDDs) is still a long and difficult process. Indeed, these pathologies are complex, heterogeneous conditions, showing considerable clinical overlap [1]. Treatments often involve combination therapies, and genetic and environmental contributions influence their aetiology [2]. However, thanks to the advent of new technologies, immense progress has been made to date, and the genomics, proteomics, and metabolomics has been integrated also by the metallomics (studies on biometals) [3–5]. In fact, two/third of our proteins need a metal for their functions, forming metalloproteins or metalloenzymes (metallomes) [3–5].

This review provides a global view on bio metals implicated in NDDs that could be identified as the focus for future studies in search for potential or new biomarkers useful for the differential diagnosis and as predictors of treatment response, with a potential direct impact on clinical practice. We referred to studies where the meta-analytic approaches have been performed to have enough statistical power to detect significant results, and where the median values of the single trace elements concentrations detected in control subjects are used as the cut-off values. We focus our attention on Schizophrenia (SZ), Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorders (ASD), and Epilepsy as childhood/adulthood NDDs.

* Corresponding author at: Catia Scassellati IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Via Pilastroni 4, 25027 Brescia, Italy.
E-mail address: c.scassellati@fatebenefratelli.eu (C. Scassellati).
[1] These authors have contributed equally to this work.

https://doi.org/10.1016/j.jtemb.2020.126499
Received 20 June 2019; Received in revised form 10 January 2020; Accepted 13 March 2020

Table 1
Essential Trace Elements involved in different metabolic pathways along with their enzymes.

Essential Trace Elements	Biological Function
Co	It is a critical component of Vitamin B12 which is oxygen-sensitive and important for the normal functions of the nervous system. Three classes of cobalt/B12-dependent enzymes, including **isomerases, methyltransferases** and **reductive dehalogenases**, participate in the reactions essential to DNA synthesis, fatty acid synthesis and energy production. Implicated in oxidative stress.
Cu	Between 80 and 95 % of plasma copper is bound to **ceruloplasmin**, an alpha-glycoprotein with amine oxidase and ferroxidase activities; the process of ceruloplasmin binding copper occurs in the liver shortly after hepatic uptake of copper. Other copper-containing enzymes include **tyrosine hydroxylase** and **dopamine hydroxylase**, which produce dopamine and norepinephrine, and **cytochrome c oxidase**, critical for mitochondrial electron transport and energy production. Moreover, it is contained in **superoxide dismutase**, implicated in free radical detoxification, and thus decreased protection against oxygen free radicals. The major copper storage protein is **metallothionein**, which binds a variety of heavy metals extremely tightly and whose promoter is very responsive to induction by heavy metals. It is involved in hemoglobin formation and is essential for bone, tendon, connective tissue (**lysyl oxidase**: cross-linking of collagen and elastin; **sulfhydryl oxidase**: Cross-linking of keratin; **ascorbate oxidase**: Skeletal demineralization), vascular system, and myelin development and maintenance. It may serve as the basis for an accurate control of iron flow to the different tissues. Preterm infants and low birth weight infants are both populations vulnerable to Cu deficiency.
Fe	It is an essential trace element for nearly all living organisms and is a component of haemoglobin, which is vital for the delivery and storage of oxygen. It is also required for cell viability, as it is a constituent of proteins involved in DNA synthesis, cell proliferation, and energy metabolism. Furthermore, Fe is the most abundant transition metal in the brain and is vital for several neurological functions including neurotransmitter synthesis, synaptic plasticity, myelination of neurons, mitochondrial function, and electron transfer. Therefore, an enough iron supply is necessary for neurodevelopmental processes; in fact, reductions in the iron supply at several stages of development result in long-term changes in monoamine neurotransmission that outlast the iron deficient periods. Conversely, iron overload can cause cellular toxicity and neuronal damage via free radical formation and peroxidation of lipid membranes. Iron accumulates as the brain ages and may be linked to motor and cognitive dysfunction in the elderly. **Ferritin** is of utility as a primary marker of iron metabolism because it regulates the binding and storage of iron and plays an important role in maintaining iron metabolism homeostasis and regulating iron content in the brain.
Mn	It is an essential metal for human health, found naturally within the environment and necessary for several enzymes regulating oxidative stress, antioxidant status, mitochondrial function, neurotransmitter synthesis, urea metabolism, autophagy. It is essential for human development and function of the brain. Gastrointestinal absorption is influenced by the iron metabolism: a deficiency of iron increases the absorption of Mn. **Glycosyl transferases**; **glycosaminoglycan synthesis**; **prolidase**: Collagen recycling; **arginase**: Urea synthesis; **glutamine synthetase**: Glutamine synthesis, **superoxide dismutase (SOD):** Antioxidant; **pyruvate**, **carboxylase:** Gluconeogenesis, **phosphoenolpyruvate carboxykinase; isocitrate dehydrogenase**: Krebs cycle.
Se	Antioxidation, Mercury toxicity reduction. It is an important component of **glutathione peroxidase** enzyme. Se deficiency is associated with altered function of GPX enzyme and consequently altered glutathione redox state. Selenium can maintain normal metabolism of the thyroid hormone, prevent cell damage caused by lipid peroxidation and threaten cardiac side effects. There are 25 human selenoproteins, including 5 forms of **glutathione peroxidase**, 3 forms of **thioredoxin reductase**, and 3 **deiodinases**, the latter participating in thyroid hormone metabolism. **Selenoproteins** contain selenocysteine, the 21 st proteinogenic amino acid. In selenocysteine, the oxygen molecule from serine or the sulfur molecule from cysteine is replaced by selenium. glutathione peroxidases (GPxs), thioredoxin reductases (TrxRs) or selenoprotein P (SelP), are strongly involved in antioxidant defence and in maintaining intercellular reducing conditions.
Zn	It is a trace mineral for pre- and postnatal development. Its functions are related to gene expression, cell development and replication, and ribonucleic acid (RNA) and DNA synthesis, which are critical for cell growth, differentiation and metabolism. Zinc plays a structural and regulatory role in several enzymes, through signal transduction, pre-secretory polymers, and gene transcription systems, which are essential for metabolism, growth, and human reproduction. Zinc is involved in the main metabolic pathways of macronutrients, nucleic acids, heme synthesis, connective tissue replacement, tissue synthesis, and embryogenesis. Zinc deficiency may affect cognitive development. Zinc is a cofactor for several enzymes, including **dopamine b-hydroxylase**, **monoamine oxidase**, **thyrosinase**, **ornithine transcarbamylase**, **alkaline phosphatase**, **carbonic anhydrase**, **superoxide dismutase**, **DNA and RNA polymerases**, **lactate dehydrogenase**, **alcohol dehydrogenase**, **insulin-degrading enzyme**, **matrix metalloproteinases**, and **N-acyl D-aspartate acylase**. The functions of these enzymes include catalytic, structural, and regulatory roles.

2. Neurodevelopmental disorders

SZ, ADHD, ASD and Epilepsy are a diverse group of NDDs, resulting from impaired development or maturation of the central nervous system (CNS). NDDs patients are affected in many features of biological functions controlled by the brain; in particular, alterations in sensory, motor executive functions, learning, memory, emotion, anxiety, and social ability [1].

Diagnosis and treatment can be difficult: NDDs are characterized by frequent clinical overlap and many co-morbidities; the treatment often involves a combination of professional therapy, pharmaceuticals, and home-and school-based programs, with about 30 % resistant to drugs therapies. It is, thus, clear that, in the era of the precision medicine, the identification of biomarkers might simplify both the differential diagnosis and the progress in the individualized therapies.

NDDs are known to be highly heritable and several related genes have been identified by genomics studies [6–9]. However, the critical genetic determinants are not still clarified, and the interaction of heritable factors with uncertified lifestyle and environmental factors seem to play a considerable role in their aetiology. More in detail, maternal use of tobacco, alcohol, or illicit drugs during pregnancy, preterm birth, low birth weight, lower socioeconomic status, the physical environment, and prenatal or childhood exposure to certain environmental contaminants represent a broad range of environmental risk factors that may influence the neurodevelopment [2], with a differential contribution in the four NDDs discussed in this review.

The role of metal ions in the brain is directly connected to the development and maintenance of enzymatic activities, learning and memory, mitochondrial functions, myelination, synaptogenesis and plasticity, neurotransmission and inflammation. The disruption of any of these mechanisms or the absorption of toxic metals generates a metal homeostasis imbalance in the brain. This dyshomeostasis represents a further environmental risk factor that determines a cascade of events, leading to abnormal central nervous system development, and resulting in a disease state [5]. Oxidative stress is an additional important player in brain dysfunction. The brain has an extensive capacity to consume large amounts of oxygen, thus it is particularly sensitive to oxidative damage. This condition results from the incomplete reduction of oxygen, leading to the formation of reactive oxygen species, and/or to the decrease and degradation of endogenous antioxidant agents [5]. Thus, many antioxidant compounds and enzymes are of interest in the study of these diseases.

3. Metallomics and metallomes

Metallomics is proposed as a new scientific field that integrates interdisciplinary research for the promotion of biometals science. It is in symbiosis with genomics and proteomics, because the syntheses and metabolic functions of genes and proteins cannot be performed without the aid of various metal ions and metalloenzymes. In metallomics, metalloproteins/metalloenzymes/chaperones are named metallomes, in a similar manner to genomes in genomics and proteomes in proteomics [4,5]. The metalloproteins three-dimensional structure incorporates inorganic ions and comprises nearly 30 % of the proteins. Metalloproteins catalyze significant processes of water oxidation and photosynthesis. Metalloenzymes, a subclass of metalloproteins, perform specific catalytic functions and act on the molecule, termed as the substrate, which undergoes a net chemical transformation, and they are required in biological pathways to preserve life [10]. Chaperones are small cytoplasmic transport proteins needed to ensure that specific trace element can reach its specific dependent target proteins. It is as valid in 2018 as it was discussed in 1951: The functions of bio-elements "may hold of the answers to many unsolved biochemical and biological problems" [11].

For humans, at least 20 chemical elements are essential for specific brain functions [12]. Some are metals such as Cobalt (Co), Chromium (Cr), Copper (Cu), Iron (Fe), Manganese (Mn), Molybdenum (Mo), Zinc (Zn); others are non-metals, such as Selenium (Se). They are essential trace elements, present in biological fluids in concentrations lower than 1 μg per gram of weight, except Fe e Zn that exceed this concentration. Co, Cu, Fe, Mn, Mo, Se and Zn (Table 1) are potentially toxic at high concentration or when not properly bound to proteins, whereas Aluminium (Al), Arsenic (As), Beryllium (Be), Cadmium (Cd), Mercury (Hg), Nickel (Ni), and Lead (Pb) are predominantly toxic and, in particular, Hg, Cd, Cr, Pb are responsible for environmental damages.

Among the essential metals, some are crucial for CNS development, acting before and after birth. For instance, Cu and Zn are involved in a complex regulatory network of proteins and pathways that maintain CNS homeostasis, since from the very early stages.

The two more important proteins controlling Cu balance in the body are two Cu-transporting P-type ATPases (copper-ATPases). They are coded by *ATP7A* and *ATP7B* gene, respectively. Both have dual functions: delivering Cu for incorporation into Cu-dependent enzymes, and removal of Cu excess from cells. Their location in different cell tissues and cell compartments determine their different role as controller of copper balance. ATPase7A is mainly involved in Cu absorption, while ATPase7B in copper excretion. In the CNS, they control Cu transport across the blood brain barrier and blood cerebrospinal fluid barrier. Acting as Cu pumps, ATPase7A and ATPase7B are very important in CNS development [13]. More specifically, ATPase7A is expressed primarily at birth, then its levels decline, particularly in the hippocampus and cerebellum [14]. It is involved in synaptogenesis and axonal outgrowth, and it has been reported to contribute to seizure resistance in hippocampal CA2 pyramidal cells [14]. ATPase7A mediates Cu transport in glutamatergic neurons. Cu release is stimulated by N-methyl-D-aspartate receptor (NMDAR) in the postsynaptic cell that, in turn, down-regulates NMDAR activity, thus protecting neurons from excitotoxicity [13]. Inactivation of ATPase7A in Menkes Disease causes a sharp decrease in Cu transport in brain barrier cells, astrocytes and neurons, causing mental retardation, serious neurological symptoms and neurodegeneration.

ATPase7B is expressed after birth, mainly in the hippocampus, cerebellum and brain cortex, and it has been reported to act primary as mediator of the synthesis of Cu-dependent enzymes, essential for CNS development [15]. Defects of *ATP7B* gene cause Wilson Disease, an inborn error of Cu metabolism that leads to the toxic build-up of the metal in tissues and organs, hepatic failure, psychiatric and neurological symptoms [16], and specific gene variants are associated with an increased risk for Alzheimer's disease [17].

Zn is another very important metal for CNS development and functioning. It is localized almost exclusively within synaptic vesicles of NMDAR glutamatergic terminals, where it inhibits postsynaptic GluN2A (GRIN2A subunit)-NMDARs, causing changes in synaptic integration and plasticity [18].

4. Role of essential trace elements as potential biomarkers in schizophrenia

SZ is a severe, complex, and disabling NDD that affects approximately 1 % of the global population. Delusions and hallucinations are the typical symptoms developed at the time of diagnosis; however, negative symptoms (avolition or diminished emotional expression) are more persistent core symptoms.

4.1. Cobalt

Few studies were conducted for this element. One study did not detect any alterations in the Co peripheral levels in a sample of 105 SZ patients as compared with 106 controls [19], however a negative correlation was found between its levels and some renal parameters such as creatine (CREA) and uric acid (UA). Another study observed an association with negative symptoms and drugs resistance in 67 SZ patients [20] (Table 2). The sample sizes in these studies achieved 80 % power to detect significant differences.

4.2. Copper

There are contrasting results on Cu levels in SZ: some studies showed increased [21–28], others [29–33] decreased levels of Cu. A recent work provided the first evidence of disrupted Cu transport by *ATPase7A* and *ATPase7B* in SZ that results in a Cu-deficient state [34]. Moreover, several studies, summarized in Virit et al. [35], indicate elevated serum ceruloplasmin (Cp) levels in SZ. All together findings support alterations in the catecholamine metabolism process in SZ, mainly linked to severity and negative symptoms [20]. A positive correlation was observed between Cu concentrations and biochemical parameters such as FBG (Fasting Blood Glucose) (glucose metabolism), and TG (Triglycerides) and TP (Total Protein), implicated in lipid metabolism [19]. (Table 2).

Interestingly, it has been reported that antipsychotics treatment reduced the concentration of Cu in SZ to levels comparable to those of controls [27,34]. This suggests an influence of these drugs on Cu levels (Table 2).

4.3. Iron

A recent paper [19] found that serum concentration of Fe was higher in SZ patients as compared to controls, suggesting the involvement of oxidative stress in the pathophysiology of the disorder. Moreover, two liver enzymes, the aspartate aminotransferase (AST) and the alanine aminotransferase (ALT) were found positively associated with Fe concentrations in SZ patients. Indeed, Fe excess has been shown to mediate liver toxicity and hepatic injury via mechanisms of oxidative stress [36,37]. However, other previous works showed lower Fe levels [23,38,27], suggesting Fe effects in dopaminergic system and on the activity and density of dopamine receptors. Interestingly, in first-episode psychosis patients, those with latent Fe deficiency defined by a low serum ferritin levels, had significantly more severe negative symptoms [39] (Table 2).

After antipsychotic drugs treatment, concentration of Fe decreased significantly in male whereas not in the female [27]. This finding is indicative that drugs treatment influences the Fe levels and that this could be gender-specific (Table 2).

Table 2
Essential Trace Elements correlated with symptoms, biochemical parameters and drugs treatment in Neurodevelopmental disorders.

Elements	Metabolic Parameters	Gene	Metabolic alterations	Correlations/Symptoms	Treatment	Neurodevelopmental Disorders
Co	CREA/UA		Renal dysfunctions	Negative correlations/ symptoms	–	SZ
Cu			Catecholamine dysfunctions	Negative symptoms	Yes	SZ
	Cp		Dopaminergic dysfunctions	–		
	Cu	*ATP7A*	Cu-deficient state	–		
	Cu, Cp	*ATP7B*	Cu-deficient state	–		
	FBG		Glucose-intolerance	Positive correlations		
	TG/TP		Lipid metabolism/stress oxidative	Positive correlations		
	Cu, Cp	*ATP7B*	Cu-deficient state	information processing	–	ADHD
			Oxidative stress	–	–	ASD
			–	–	Yes	EP
Fe			Dopaminergic dysfunctions	–	Yes	SZ
	AST/ALT		Liver toxicity, hepatic injury (Oxidative stress dysfunctions)	Positive correlations		
	Ferritin	*FTH*	Low Ferritin	Negative symptoms		
	Ferritin	*FTH*	Low Ferritin	Severe symptoms	–	ADHD
			Anemia	–	–	ASD, EP
Mn	SOD	*SOD*	MnSOD lower activity/Oxidative stress dysfunctions	–	Yes	SZ
	ALB/TP		Liver toxicity, hepatic injury (Oxidative stress dysfunctions)	Positive correlations		
	SOD	*SOD*	Oxidative stress dysfunctions	Hyperactive symptoms	Yes	ADHD
Se			Metabolic syndrome	–	–	SZ
Zn			Glutamatergic system, Inflammation, Neurodegeneration, Autoimmunity alterations	–	Yes	SZ
	ALB		Liver toxicity, hepatic injury (oxidative stress dysfunctions)	Positive correlations		
	SOD	*SOD*	Oxidative stress dysfunctions	Inattentive symptoms	Yes	ADHD
			Synaptic plasticity dysfunctions	Growth/mental retardation, Hyperactivity	–	ASD
		GRIN2A	GluN2A-Zn interaction (NMDARs)	–	Yes	EP

Note: CREA (creatine), UA (uric acid), SZ (Schizophrenia), ADHD (Attention Deficit Hyperactivity Disorder), FBG (fasting blood glucose), TG (triglycerides), TP (total protein), SOD (superoxide dismutase), CP (ceruloplasmin), EP (epilepsy), ASD (austism spectrum disorders), ALB (Albumin), ALT (alanina aminotransferasi), AST (aspartato aminotransferasi), (SOD) Superoxide dismutase, ATP7A/B (ATPase Copper Transporting Alpha/beta), GRIN2A (Glutamate Ionotropic Receptor NMDA Type Subunit 2A), Co (Cobalt), Cu (Copper), Fe (Iron), Mn (Manganese), Se (Selenium), Zn (Zinc).

4.4. Manganese

Several studies identified lower Mn concentrations in SZ [23,24,40,19], and thus lower activity of MnSOD (Superoxide Dismutase) and hepatic arginase. In addition, a positive correlation was observed between Mn levels and two liver function parameters (albumin, TP) in SZ [19], suggesting a role of Mn in the abnormal metabolism of arginase and liver functions in this pathology [41] (Table 2).

Mn was observed to be significantly reduced with anti-psychotic medications [38]. This suggests that antipsychotic drugs could chelate Mn, thus making it unavailable as an enzyme activator (Table 2).

4.5. Selenium

Serum Se has been reported to be associated with metabolic syndrome in SZ [26] (Table 2). Some studies observed a reduction in Se levels in drug-free, untreated and antipsychotic treated SZ patients [42,38,43] whereas Li et al. [33] observed higher levels.

4.6. Zinc

Joe et al. [44] conducted a meta-analysis of 10 studies, including a total pool of 658 SZ patients and 1008 controls, and showed that serum Zn concentration was significantly lower in patients. Zinc decrements were more pronounced among inpatients and newly diagnosed, drug naive patients. This study supports a disturbance of Zn homeostasis in SZ, probably acting on neurotransmitter dysfunction glutamatergic system, inflammation, neurodegeneration, and autoimmunity. A more recent paper, not included in the meta-analysis [19], demonstrated that in SZ, the Zn concentration was positively correlated with albumin, a metabolic parameter linked to liver function, in addition to be a transporter/exchanger of metals, particularly of Zn and Cu (Table 2).

While Cao et al. [19] and Joe et al. [44] studies support that Zn levels are not influenced by drug treatments, many other findings indicate that serum Zn concentration in SZ was decreased after antipsychotics treatment [45–47,27] (Table 2). Interestingly, Zn supplementation may be particularly relevant.

For all these trace elements the most recent meta-analysis [48] confirmed the results obtained from single studies described.

5. Role of essential trace elements as potential biomarkers in Attention Deficit Hyperactivity Disorder

ADHD is a neurobehavioral/neurodevelopmental disorder, characterized by inattention, hyperactivity, and impulsivity, resulting in substantial functional impairments (cognition and academic accomplishment, self-esteem, social relationships). The estimated prevalence of ADHD diagnosis in children ranges from 5 to 10 %.

5.1. Copper

Some studies reported lower levels [49,50], or no alterations [51] of Cu in subjects with ADHD. Yorbik et al. [52] showed that plasma Cu and Cp levels might influence event-related potentials (ERPs) in ADHD, thus indicating the existence of effects on information processing (Table 2).

5.2. Iron

Three meta-analysis investigated ferritin (peripheral marker of Fe status) levels in ADHD [53–55]. The more recent meta-analysis [56] showed that ADHD children (N = 1,560) have lower serum ferritin

levels as compared to controls (N = 4,691), and that children with iron deficiency (ID) were more likely to have ADHD and to suffer from more severe ADHD symptoms compared to those without ID (Table 2).

5.3. Manganese

A recent meta-analysis [57] (N ADHD = 175, N Controls = 999) supports higher peripheral levels in ADHD children than in controls. A link between Mn exposure and hyperactive behaviour was found (Table 2).

Interestingly, Mn concentrations were significantly reduced from baseline values following Methylphenidate (MPH) exposure [54] (Table 2).

5.4. Zinc

Some studies [58,59,51], confirmed by the most recent meta-analysis [54], reported lower Zn levels in ADHD, associated with inattentive subtype. Moreover, several researchers reported a link between Zn levels and the severity of ADHD symptoms, and the fact that Zn supplementation might be effective in decreasing these symptoms [54] (Table 2).

Significant findings were observed for oxidative stress and antioxidant proteins (among which SOD) [60].

6. Role of essential trace elements as potential biomarkers in Autism Spectrum disorder

ASD are a group of neural development disorders characterized by impairments in social interaction and communication, and by the presence of restricted and repetitive behaviours, and the prevalence of this disease continues to increase up to 1 in 88 children.

6.1. Cobalt, copper, iron, selenium, zinc

All these elements were analyzed in the most recent meta-analysis performed to date (N ADHD = 600, N Controls = 400) [61]. The results indicated peripheral higher levels of Cu (oxidative damage), Fe deficiency (anemia, emotional and behavioral problems), lower levels of Zn (autoimmune, resistant and recurrent infection, growth and mental retardation, hyperactivity) (Table 2). Cu overload is thought to cause Zn deficiency-synaptic dysfunction.

7. Role of essential trace elements as potential biomarkers in Epilepsy

Epilepsy is one of the earliest characterised neurological disease, characterized by recurrent unprovoked seizures. The endpoint of untreated intractable epilepsy is extensive hippocampal neuronal loss and reactive gliosis. An important role is played by oxidative stress.

7.1. Copper, manganese, selenium

Analyzing 40 studies, a meta-analysis reported no changes in Cu and Se levels [62]. Single successive works found decreased levels of Se [63] and Cu [64,65], but no alteration was found for Mn in epileptics [65] (Table 2).

The concentrations of Cu were altered in epilepsy patients who received antiepileptic drugs compared with untreated subjects [61] (Table 2).

7.2. Zinc

Some studies, including the meta-analysis [62], demonstrated changes in serum Zn in patients with epilepsy (higher), and during treatment with common anti-seizure drugs (lower). Diverse evidence supports that Zn administration may be helpful as an optimizing strategy for epilepsy, at least in those with decreased basal zinc supply/absorption [66]. Interestingly, a mutation in the *GRIN2A* gene (encoding the alpha-2 subunit GluNR2A) has been reported causing impaired GluN2A-Zn interaction in the GluN2A-NMDARs in idiopathic focal epilepsy [67].

8. Conclusions

To date, no biomarker has achieved the status of clinical utility as a diagnostic/treatment tool for the four NDDs pathologies (SZ, ADHD, ADS, Epilepsy).

This review highlights that: 1. several studies and meta-analyses are available on the crucial role of six essential trace metals in the four NDDs under study, even though, to our view, it is needed to extend knowledge about this topic. Mandatory is to increase studies in humans rather than in animal models, particularly for Epilepsy. 2. in light of the literature presented, based on meta-analyses, we suggest that Zn (glutamatergic neurotransmission, inflammation, neurodegeneration, autoimmunity alterations), could be a potential diagnostic biomarker associated to SZ that deserves further investigations. Moreover, considering the single association studies going in the same direction, increased Cu (catecholamine alterations, glucose intolerance, altered lipid metabolism/oxidative stress) and lower Fe (dopaminergic dysfunctions) levels were found associated with a specific negative symptomatology. Lower Mn (lipid metabolism/oxidative stress alterations), and lower Se (metabolic syndrome) were linked to SZ. From the meta-analyses in ADHD, it is evidenced that Fe (and ferritin in particular), Mn, and Zn (oxidative stress dysfunctions) could be potential diagnostic biomarkers, mainly associated to severe hyperactive or inattentive symptoms; as well as Cu, Fe, Zn in ADS and Zn in Epilepsy. 3. Fe, Zn and Mn levels seem to be influenced by antipsychotics treatment in SZ; Mn and Zn by MPH treatment in ADHD; Cu and Zn by antiepileptic drugs in Epilepsy. These trace metals could be thus potential biomarkers of treatment response. Some studies agree on the fact that a percentage of patients with altered levels of trace elements might benefit from supplementation. According to some authors [68,69] it is recommended to evaluate Cu and Zn levels in NDD patients especially in patients resistant to therapy as this may have a prognostic and therapeutic value. It is recommended also to use Zn supplementation during psychotropic therapy as it may improve response to therapy and/or decrease the dose that can minimize the side effects of these drugs. In addition, frequent psychiatric assessment is recommended for individuals chronically exposed to Cu.

A suitable study to measure and monitor trace elements in NDD should include the following collections: detailed medical history, information about previous drug treatment which was received, clinical and neuropsychological examination with specific scales and diagnostic instruments, serum/plasma samples after an overnight fast at the time of diagnosis (baseline visit). Measurement of trace elements with specific kits/tools. Some studies perform the measurement starting by the hair cutting from the occipital region to lengths of about $1.5-2$ cm using clean stainless-steel scissors. 6-month follow-up visits, collecting information about the clinical state, drug assumption and a blood drawn at fast to measure trace elements will be sufficient to monitor the association of trace elements with the clinical state and its progression.

Limitations. In the research of biomarkers, it is needed to establish the accuracy and discriminate values among patients affected by NDD as compared to healthy controls. As supported by Abruzzo et al. [70] and Perlis [71], the calculation of the Receiver Operating Characteristic (ROC) curves should become the gold standard for the identification of parameters that are sensitive and specific enough to support NDD diagnosis, with the aim to translate the biomarkers identification to clinical practice. A limitation of current review consists in the fact that only a small percentage of studies with small sample size that we discussed addressed this important issue, reporting the optimal cut off

values of levels of a biomarker as an indicator for the diagnosis of NDD with percentages of sensitivity and specificity [72–75]. For instance, Liu et al. [76] explored the associations between schizophrenia risk and serum levels of some trace elements, reporting that values for Cu (≤0.97 μg/mL), Se (≤72 ng/mL) and Mn (> 3.95 ng/mL) were associated with an increased risk of schizophrenia. In children with ASD, levels of Zn levels and Zn/Cu ratio were lower, while Cu levels was higher than in healthy controls. Using ROC curves, the authors suggested that a cut-off of 0.665 Zn/Cu had a sensitivity of 90 % and a specificity of 91.7 % (area under the curve 0.968, 95 % confidence interval, 0.943–0.993) [75]. Another small study, investigating 40 children affected by ASD, using ROC curves, suggested 0.81 Zn/Cu ratio as an optimal cut-off value with a sensitivity of 85 % and a specificity of 85 % (AUC 0.93) [74].

Another limitation is that the detection of peripheral concentrations of trace elements can be influenced by many environmental factors, such as for instance dietary habits, industrial exposure, geographical location that can be confounders of the results obtained. Moreover, concerning results reported on the topic of trace elements and drug treatments, potential pitfalls can derive from differences in drug dose and use of drug combination that can influence the results. Finally, it is not clear whether the peripheral changes in concentrations of trace elements are causal or an epiphenomenon of seizure activity.

9. Future directions

This growing literature is of value in the perspective of specific medicine that can enhance the results obtained to date by directing researches to focus on diagnostic subgroups within a specific NDD. The way to identifying biomarkers is still long. However, starting from the differences that are put into evidence by meta-analyses, a better understanding of the interaction network of genes, proteins, and biochemical processes linked to more accurate clinical profiles and the availability of more modern high-throughput computational technologies, will allow to identify a list of biomarkers of NDD subgroups, both for the optimization of diagnostic assessment and for the personalization of therapies. This could have implications in terms of therapy, responders or non-responders, in analogy with what happens with cancer in which biomarkers that identify only small percentage of patients who (for example) respond to a drug, is of great relevance.

This review represents the state of art of the literature available to date on the topic. Although further studies are needed, some of essential trace elements appear to be good candidates as potential biomarkers for NDDs. The effects of various drugs on trace element homeostasis could potentially be used to effectively guide successful development strategies in the future.

Author contributions

All authors contributed to the preparation of this review.

Funding

This research was supported by grants from the Italian Ministry of Health (Ricerca Corrente).

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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