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Evaluation of Biomarkers of Oxidative Stress in Attention-Deficit/Hyperactivity Disorder (ADHD)

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Abstract

Biomarkers of oxidative stress and ADHD in children and adolescents are critically reviewed. They are divided in two groups: biomarkers of oxidative stress (general, proteins, including enzymes and non-protein biomarkers) and biomarkers of specific oxidative damage. Observed associations between concentration levels and ADHD symptoms are nearly always contradictory, which is partly due to aetiological a phenotypic complexity of the disorder. Some trends could be observed: lower ferritin and zinc levels, lower total antioxidant status (TAS), higher total oxidant stress (TOS) and higher oxidative stress index (OSI) are associated with ADHD. Even when there is a correlation most authors claim that this relationship is not causative, as illustrated by placebo-controlled trials reporting conflicting evidence on efficacy of supplementation. Well-defined studies could shed more light on their significance in this disorder by observing changes in concentration levels of the various biomarkers and ADHD symptoms before and after treatment with therapeutics.

Keywords: ADHD; Biomarkers; Oxidative stress

Abbreviations: 4-HNE: 4-Hydroxy-2-Nonenal, 8-ISO: 8-Isoprostane, 8-OHdG: 8-Hydroxy 2'-Deoxyguanosine, 8-OHG: 8-Hydroxy Guanosine, ADD: Attention-Deficit Disorder, ADHD: Attention Deficit/Hyperactivity Disorder, ALA: Alpha Linolenic Acid, AOPP: Advanced Oxidation Protein Products, APA: American Psychiatric Association, ARES: Arylesterase, CAT: Catalase, CNS: Central Nervous System, DISC1: Dismocollin-1, GR: Glutathione Reductase, GSH: Reduced Glutathione, GSSG: Oxidized Glutathione, GSH-Px: Glutathione Peroxidase, GST: Glutathione-S-Transferase, MDA: Malondialdehyde, MetS: Metabolic Syndrome, ORAC: Oxygen Radical Absorbance Capacity, OSI: Oxidative Stress Index, PON1: Paraoxonase 1, SPON: Stimulated PON, SOD: Superoxide Dismutase, TAC: Total Antioxidant Capacity, TAS: Total Antioxidant Status, TBARS: Thiobarbituric Acid Reacting Substances, TOS: Total Oxidant Status, XO: Xanthine Oxidase

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is diagnosed on the basis of persistent and developmentally inappropriate levels of over activity, inattention and impulsivity [1]. ADHD is relatively common, affecting an estimated 5% to 12% of school-aged children, depending on definition and study [2]. The aetiology and pathology of this disorder is not completely understood, although genetic [3,4], interaction of genes and nutrition [5], epigenetic [6-8] and environmental factors, together with stress are mentioned [9]. Nutritional and dietary influences are reviewed [10,11], while restriction and elimination diets have been tried in ADHD treatment [12,13]. Supplements [14] and complementary medicines (herbal and nutritional products) [15] have been systematically reviewed. Numerous medical potential causes have been linked to ADHD in children: oxidative stress [16,17], metal toxicity [18,19], decreased methylation [20], mitochondrial dysfunction [21] and cerebral hypoperfusion [22]. An etiologic classification of attention-deficit/hyperactivity disorder has been reviewed [23,24]. For this review, a literature search was performed on biomarkers of oxidative stress and ADHD in children and adolescents. Although attention deficit disorder (ADD) is part of the ADHD spectrum, the search was limited to publications in which ADHD is explicitly mentioned.

Literature Review

A biomarker can be defined as "a characteristic that is objectively measured and evaluated as an indicator of biological and pathogenic processes or pharmacological responses to a therapeutic intervention" [25]. Biomarkers do not need to be exclusively linked to a particular disorder. For cancer (tumor markers) [26,27], vascular diseases [28], MetS [29], as well as many CNS disorders [30], including ADHD [31], various markers have been discussed. Oxidative stress represents a common etiological factor of diverse clinical conditions MetS [29,32], vascular diseases [28], hypertension [32], diabetes type 2 [32], as well as many CNS disorders [33], including ADHD [34] are mentioned in the literature. Therefore oxidative stress biomarkers can be related to various diseases. Sometimes genetic [3] and epigenetic markers [35] can be included in the broad group of "biomarkers".

Thome and co-workers [31] claimed that there are a lot of problems in developing ADHD biomarkers. Bradstreet and co-workers [36] reviewed biomarker-guided interventions in ADHD. They classified them as markers of 1) Oxidative stress; 2) Methylation and transsulfuration; 3) Immune dysregulation; 4) Mitochondrial dysfunction; 5) Heavy metal exposure, and 6) Cerebral dysfunction.

Scassellati et al. [37] reviewed biomarkers on this syndrome and classified them in groups, coming from: the monoaminergic neurotransmission systems, their enzymes and the metabolites; environmental risk factors (heavy metals); the hypothalamus-pituitary-adrenal axis pathway. Their observation that the concentration of brain-

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derived neurotrophic factor (BDNF) in ADHD was not different from those of controls [38], was contradictory to the increased levels of this factor in another study [39]. This illustrates that a lot of contradictory results are found in literature. In addition, the question remains whether the change in a biomarker is a cause or a response to the disease. More recently Bonvincini et al. [40] discussed common and specific genes and peripheral biomarkers in ADHD. Described genes belong primarily to the dopaminergic and neurodevelopmental systems. The authors reviewed oxidative stress markers (MDA, SOD, PON1, ARES, TAS, TOS and OSI) and second level markers (DISC1, microRNA and adiponectin). Additionally indicators of disturbed immunity are studied [41], including neopterin [42] and adenosine deaminase [43]. All this illustrates that ADHD is a complex, multifactorial disorder that arises from many risk factors, none of which are necessary or sufficient to cause the disorder.

Oxidative/nitrosative stress is defined as an imbalance between reactive oxygen/nitrogen species (ROS/RNS) and the organism's capacity to counteract their action [44]. Oxidative stress emerges from an enhanced ROS/RNS generation or from a decay of the antioxidant protective ability. This result in a reduced capacity of endogenous and exogenous systems to fight against the oxidative attack directed towards target biomolecules [45]. This imbalance could lead to detrimental effects. Because markers for oxidative stress are related to various diseases, they cannot be used as a specific diagnostic requirement of any exclusive disorder. It is medically reasonable to assume that the decrease of oxidative stress would be associated with amelioration of some features of these disorders, or at least prevent or slow their progression. In this review we have limited ourselves to markers of oxidative stress in ADHD of children and adolescents, which means that papers on the adult form of this disease are excluded [46-50].

The adult form can have other characteristics with related other findings on biomarkers. To illustrate this: malondialdehyde levels in adult patients were higher compared to controls [46,48], whereas for children lower levels were found in patients [51,52]. Also other factors (work, environmental pollution, alcohol abuse, smoking attitude) can result in enhanced oxidative stress. Division of markers into groups has limitations, since some overlap cannot be excluded and the risks of being subject to discussion always remain. Although the use of biomarkers in the diagnosis of ADHD appeared promising [53], only one review on markers of oxidative stress has been found [34]. Faraone and co-workers [53] concluded from their meta-analysis on oxidative stress and antioxidant status in medication naïve patients with ADHD that they have normal levels of antioxidant production. The response to oxidative stress however turned out to be insufficient, leading to oxidative damage of biomolecules such as cytoskeletal proteins, membrane lipids, and DNA. We have screened the literature using the terms "ADHD", "biomarkers of antioxidant status", "biomarkers of oxidative stress" and the various individual markers. References from 2000 onwards are used or some important previous references cited therein. We have tried to divide the biomarkers into two groups: biomarkers of oxidative stress on one hand and markers of specific oxidative damage on the other. The first group includes biomarkers of the oxidative balance, non-protein and protein biomarkers of oxidative stress. In the latter group the protein biomarkers can either be enzymes or have a non-enzymatic function. In the second group damage to biochemical molecules (DNA, RNA, proteins and lipids) are reviewed. Mostly plasma or serum is the monitored medium, but saliva, urine, as well as exhaled breath are included.

Discussion

Biomarkers of oxidative stress

Reactive oxygen (ROS) and reactive nitrogen species (RNS), such as superoxide, nitric oxide, peroxynitrite, and hydrogen peroxide are unstable molecules that can react with cells/molecules in the body. They are generated during normal cellular metabolism, mainly formed within the mitochondria. ROS and RNS can also be generated from ultraviolet light irradiation, environmental pollutants, and by neutrophils, eosinophils, and macrophages during inflammation via their influence on proteins, fatty acids and DNA, ROS and RNS have numerous essential physiological roles involved in the regulation of cellular function [54,55].

There is a balance between oxidative and anti-oxidative systems. Antioxidants remove ROS and RNS by scavenging radicals and decreasing their production. Examples of scavenger antioxidants are coenzyme Q10 (CoQ10), Vitamin C and E, and glutathione. ROS may also be neutralized by different antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and catalase (CAT). Some proteins including acute phase proteins such as albumin, transferrin, haptoglobin, and ceruloplasmin also function as antioxidants by binding ROS and RNS [56]. Anti-oxidants sometimes are divided into two groups: the endogenous antioxidants (SOD, CAT, GSH-Px, thiol-groups in proteins, metal-binding proteins, uric acid, bilirubin, reduced coenzyme Q, lipoid acid, endogenous Se) and exogenous ones (vitamin E, vitamin C, carotenoids, phenolic antioxidants, resveratrol, cinnamic acid, lecithins, acetylcysteine and exogenous Se). Also this division could be discussed. Considering the trace element Se, what is the most effective and should be monitored best: the endogenous or exogenous Se? Moreover, both are related to each other.

Biomarkers of oxidative balance (TAS, TOS, OSI)

Total oxidant status (TOS) and total antioxidant status (TAS) are valid and reliable methods to identify changes in oxidant and antioxidant parameters that may contribute to the aetiopathogenesis of a disease. The oxidative stress index (OSI, the ratio of TOS/TAS) reveals how much a current situation deviates from normal homeostasis [57].

Sometimes the expression total antioxidant capacity (TAC) is used, but this refers to an estimation of dietary total antioxidant capacity in which flavonoids and vitamin C and E are major contributors, via fruits and vegetables [58]. There are databases including the content of more than 40 individual antioxidants and the TAC per food item. These are: retinol, vitamin C, 4 forms of vitamin E (α-tocopherol, β-tocopherol, γ-tocopherol and δ-tocopherol), 6 forms of carotenoids (α-carotene, β-carotene, β-cryptoxanthin, lutein, lycopene, and zeaxanthin), 7 flavonoid subclasses (flavonols, flavones, flavanones, flavan-3-ols, anthocyanins, isoflavones, proanthocyanidins) and different others. TAC is measured by using the oxygen radical absorbance method (ORAC) [59]. Table 1 summarizes findings on the three most measured parameters (TAS, TOS and OSI). Findings are quite consistent, only the observed higher TAS values by Celik et al. [60] are unexpected.

Non-protein biomarkers of oxidative stress

a) NO: Higher NO levels were observed in plasma of patients compared to controls [61,62]. However, contradictory observations were found as also lower values [63] or no significant differences [64] were observed.

b) GSH/GSSG: Measuring total glutathione (Reduced: GSH,

Parameters	Medium	Difference compared to controls	References
TAS	Serum	↓	Sezen et al. [140]
	Plasma	↓	Chovanova et al. [17]
	Plasma	↓	Dvorakova et al. [20]
	Plasma	↓	Ruchi et al. [146]
	Plasma	↓	Ceylan et al. [43]
	Plasma	↓	Kul et al. [172]
	Plasma	↑	Celik et al. [60]
TOS	Serum	↑	Sezen et al. [140]
	Plasma	↑	Kul et al. [172]
	Plasma	↑	Guney et al. [71]
OSI	Serum	↑	Sezen et al. [140]
	Plasma	↑	Kul et al. [172]
	Plasma	↑	Guney et al. [71]
Note: TAS: Total Antioxidant Status, TOS: Total Oxidant Status, OSI: Oxidative Stress Index			

Table 1: Oxidative/anti-oxidative balance in paediatric ADHD.

along with oxidized: GSSG) and/or GSH will help to determine a patient's oxidation status. Our research group found statistically ($p \leq 0.001$) higher GSH-values in ADHD children compared to controls. A standardized polyphenolic extract from pine bark, Pycnogenol acts as a powerful antioxidant [65]. One month administration of this extract (1 mg/kg body weight/day) caused a significant decrease in GSSG and increase in GSH levels, as well as improvement of GSH/GSSG ratio in comparison to a group taking placebo [20,66].

c) Plasma thiol-levels: Thiols have an important role in coordinating the antioxidant defence system. They can undergo oxidation reactions mediated by ROS and other free radicals forming disulphide bonds [67]. These disulphide bonds are eventually reduced to thiol groups by antioxidants. In this way the thiol/disulphide homeostasis is maintained [68].

Total thiol levels in serum were significantly higher whereas the disulphide/thiol ratios were lower in children with ADHD compared to controls. Disulphide levels in males with ADHD were significantly higher than those of females. This can be due to the fact that boys may have another type of ADHD. The study suggests that thiol/disulphide homeostasis is abnormal in children with ADHD and can be used as a novel oxidative stress marker in these children [69]. Enhanced levels of protein thiols in saliva were also found in paediatric ADHD compared to the controls [70]. Oztop et al. [52] however did not find a significant difference in thiol levels in ADHD children compared to controls, while Guney et al. [71] proved to find lower plasma thiol levels in ADHD children. This could be considered as a consequence of the elevated oxidative stress. On the other side, higher thiol levels can be considered as a crucial antioxidant reaction in children with ADHD and might be interpreted as a consequent increase assisting in the activation of metabolism and to reduce the oxidative stress [69]. Selek et al. [47] indeed interpreted this finding as a rebound effect.

Anti-oxidative vitamins (A, C, D and E)

a) Vitamin C: Literature data on vitamin C and ADHD are scarce. Supplementation of 25 mg vitamin C, together with 200 mg alpha linolenic acid (ALA), twice a day and for 3 months, improved the outcome of ADHD [72].

b) Vitamin D: Vitamin D is involved in the control of serotonin synthesis and action [73]. An inverse association between umbilical cord 25-OH vitamin D [74] or maternally circulating vitamin D levels in pregnancy [75] and ADHD in their toddlers was found, suggesting a protective effect of prenatal vitamin D. Another study found no association between maternal vitamin D status and ADHD in the offspring [76]. Also Gustafsson et al. [77] found no difference in intrauterine vitamin D levels between children later developing ADHD and matched control children. But the authors agree that the statistical power of their study was too weak to detect an association. Lower levels of vitamin D have been found in ADHD children [78-87]. These lower levels of the 25-OH vitamin D in children with ADHD suggest that vitamin D level might be related to ADHD, but is not necessarily a cause [88]. Vitamin D supplementation was suggested as adjunctive therapy to methylphenidate for improving ADHD symptoms [89].

c) Vitamin E: Increased concentrations of γ-tocopherol were found in ADHD patients, together with reduced lipid peroxidation [51].

d) Vitamin A: Vitamin A has shown some antioxidant and neuroprotective effect [90], however this vitamin does not reveal abnormal concentrations in paediatric ADHD patients [51].

Co-factors (Fe, Zn, Cu, Mg, Se)

Iron (Fe) and zinc (Zn) are essential cofactors in the production of dopamine and norepinephrine and both play a pivotal role in oxidant/antioxidant mechanisms. Dysregulation of the Fe and Zn status could lead to increased susceptibility to oxidative damage, which is a reasonable hypothesis in the pathophysiology of ADHD.

a) Iron: Iron deficiency has been suggested as possibly contributing to the aetiology of ADHD in children [79,91] but this is also questioned [92,93]. Nevertheless, it is hypothesized that the treatment of iron deficiency or suboptimal levels might lead both to improvement of the severity of ADHD symptoms and to a decrease of the risk of cardiovascular events during treatment with ADHD drugs [94]. A systematic review of the literature intended to offer empirical evidence for a link between iron and ADHD [95,96]. Table 2 summarizes literature data on iron status in ADHD. Fe status was generally evaluated through serum ferritin levels (iron stores), although also serum iron levels or transferrin [97,98] were mentioned. Nearly all data indicate lower ferritin levels in ADHD patients. Only one publication claimed to find higher levels [99]. The discussion remains whether iron deficiency is causative of ADHD [92,93], or a consequence. It is e.g. possible that low iron stores result from a decreased appetite as a consequence of ADHD medication. It is also possible that patients with ADHD have a decreased ability to sit still during the meals and therefore have decreased nutritional intake of iron [92]. This can also be the case for other nutrients.

Patients receiving an iron supplement (5 mg/kg/day for 30 days) showed a significant increase in serum ferritin levels and a significant decrease of the parents' Connors Rating Scale scores [100]. A supplementation of 80 mg/day also improved ADHD symptoms [101,102]. After a systematic review there is a need for more evidence for the effect of iron supplementation (as well as for magnesium and zinc) in the treatment of ADHD among children [103]. Indeed, iron overload (measured by serum ferritin levels) can become a risk factor for oxidative damage and in this way a marker of oxidative stress [29].

b) Zinc: Zinc is a cofactor for enzymes involved in cell membrane stabilization and in the metabolism of neurotransmitters, melatonin [104], and prostaglandins. Zn also has indirect effects on dopamine metabolism (the dopamine transporter is regulated by Zn^{2+} [105] and has antioxidant functions [106]. Case-control trials in several geographical areas have demonstrated lower zinc levels in children

Parameters	Effect observed	Remarks	References
Ferritin	=	No Relationship With Symptoms	Menegassi et al. [174]
	=	-	Romanos et al. [183]
	=	-	Donfrancesco et al. [168]
	↑	-	Abu-Khadra et al. [163]
	↓	-	Antalis et al. [99]
	↓	Higher Connors Rating Scale Scores	Sever et al. [100]
	↓	Higher Conners Rating Scale Scores	Juneja et al. [169]
	↓	Contribution to ADHD	Konofal et al. [101]
	↓	No Causative Role	Millichap et al. [175]
	↓	Increased Risk of Restless Legs	Oner et al. [176]
	↓	-	Konofal et al. [171]
	↓	Related With Behavioral But Not With Cognitive Measures	Oner et al. [177]
	↓	Higher Behavioral Problems	Oner and Oner [178]
	↓	Related to Sleep Disturbances	Cortese et al. [166]
	↓	Higher Hyperactivity Symptoms	Oner et al. [111]
	↓	-	Mahmoud et al. [112]
	↓	Related to ADHD	Calarge et al. [95]
	↓	-	Lahat et al. [91]
	↓	Hyperactivity Reported by Parents	Oner et al. [179]
	↓	Compared to Healthy As Well As Psychiatric Controls	Cortese et al. [96]
	↓	Not Causative Role	Villagomez and Ramtekkar, [80]
	↓	Link with ADHD and Obesity	Cortese and Agriman [165]
	↓	Associated with ADHD	Bener et al. [79]
	↓	Correlated with Hyperactivity Scores	Percinel et al. [182]
	↓	Systematic Review	Wang et al. [185]
Transferrin	↓	Relationship with ADHD Symptoms	Kwon et al. [97]
Serum Fe	=	-	Wang et al. [185]
	↓	-	Bener et al. [79]

Note: = No different levels compared to controls, ↑- Higher levels compared to controls, ↓- Lower levels compared to controls

Table 2: Iron status in paediatric ADHD.

with ADHD compared to healthy controls [80,107-114]. Only one publication mentions higher hair zinc levels and ADHD [115]. However, this article would be more informative if this trend could be related to changed zinc levels in serum, since zinc in hair is a long-term parameter. Several meta-analyses also suggest a significant association between low zinc levels and a diagnosis of ADHD [37,106,116-118]. Neither of these observations however does prove that zinc deficiency causes ADHD nor that this disorder should be treated with zinc [106]. Randomized, placebo-controlled trials of zinc supplementation either as an adjuvant to psychostimulant treatment or as monotherapy have provided conflicting evidence of efficacy [10,28,117,119-124]. Evidence is insufficient to recommend zinc supplementation in areas where zinc deficiencies are rare. Also the dosing and the form of zinc supplementation varied widely between the trials, so an optimal dosing strategy is not apparent [14].

c) Copper: Only one publication on blood level of this trace element and ADHD could be traced [114]. Copper levels in ADHD children were higher than those in the control group, however, not significantly ($p > 0.05$).

d) Magnesium: Magnesium (Mg^{2+}) is an abundant cation in the intracellular compartment of humans and of great physiological importance [125]. Literature data on Mg levels in blood in ADHD patients revealed contradictory results. Higher [126], as well as lower levels [80,99,112,127] were found. Magnesium levels in saliva were significantly decreased in ADHD patients [70], as well as in hair [127]. Supplementation studies with Mg, mostly in combinations with n-3/n-6 fatty acids and zinc, resulted in a considerable reduction in symptoms [120].

e) Selenium: Selenium (Se) acts as a cofactor in the antioxidant enzyme glutathione peroxidase (GSH-Px) [128]. No significant differences in Se levels between controls and ADHD children were found [114]. However, low intake of Se was observed in ADHD groups compared to controls [129]. The restlessness of the children could be responsible for reduced meal times with resulting lower intake of various elements. An unexpected relatively high umbilical cord Se level was observed in children afterwards manifesting ADHD [130]. This observation should be interpreted with caution.

f) Uric acid: Uric acid is a strong reducing agent and hence a potent antioxidant. However it remains contradictory whether it induces or lowers oxidative stress, as acute elevation appears a protective factor, while chronic elevation is a risk for disease [131]. No publications on uric acid concentrations in ADHD children could be found.

g) Bilirubin: Bilirubin is an active scavenger of peroxyl radicals and lowers the mutagenic activity of oxidative species, polycyclic

aromatic hydrocarbons and heterocyclic amines [132,133]. However its role in development of ADHD is quite confusing [134]. Contrary to the scavenging character of the molecule, neonatal jaundice seems to increase the risk of ADHD [135], especially for those requiring phototherapy and longer treatment. Hyperbilirubineamia is associated with childhood symptoms of hyperactivity [136] possibly when serum bilirubin concentrations exceed protein-binding capacities, bilirubin crystals aggregate and precipitate in neurons [135], and causing behavioural problems. For the ADD form in the ADHD spectrum no association was found [137], contrary to results for the same type of disorder in Canada [138].

Proteins with influence on oxidative stress

Enzymes (PON1, GSH-Px, ARES, SOD, GST, GR, CAT, XO):

a) Paraoxonase 1: Paraoxonase 1 (PON1), which has antioxidant properties, is a multifunctional enzyme with paraoxonase (PON), diazoxonase and arylesterase (ARES) activities [139].

Lower PON activities were found in children with ADHD [43,140]. In contrast to these findings, Oztop et al. [52] did not report a significant association between ADHD and PON1. Guney et al. [71] did not observe lower levels of PON1, but after a short term follow up study post-treatment enzyme activity became significantly higher for PON1, as well as for salt- and activity-stimulated paraoxonase (SPON).

b) Glutathione peroxidase: The antioxidant activity of glutathione peroxidase (GSH-Px) was found to be significantly lower in ADHD patients than in controls [62,141]. Since selenium is a cofactor of this enzyme it should be suspected that this trace element also is lower in ADHD patients. However, this was not proven to occur [114].

c) Arylesterase: Some authors found a decreased activity of arylesterase (ARES) in ADHD children [140], while others did not [71].

d) Superoxide dismutase: Russo [142] claimed that the activity of this Cu/Zn dependent SOD is lower in ADHD children, particularly in those patients with high serum copper. Similar observations were published by Adham et al. [141]. No explanation therefore was given. After 8 weeks n-3 supplementation, Hariri et al. [143] found a significant increase in SOD activity in ADHD children. Another group did not find differences in SOD activity between patients and controls [62].

e) Glutathione transferase: Glutathione S-transferase (GST) is an antioxidant enzyme which plays a key role in cellular detoxification. Also here, contradictory findings were published on enzyme activity in plasma of ADHD children. Higher [60], as well as lower activity, compared to controls, were claimed [43,141]. No significant association between specific gene polymorphisms for this enzyme and the incidence of ADHD was observed [144].

f) Glutathione reductase: Glutathione reductase (GR) plays a major role in antioxidant defence as impaired GSH regeneration enhances oxidative damage [145]. After 8 weeks of n-3 fatty acid supplementation, Hariri et al. [143] found a significant increase in GR activity in plasma of ADHD children.

g) Catalase: The activity of this antioxidant enzyme was not significantly different in ADHD patients and controls [60,62]. Hariri et al. [143] supplemented n-3 fatty acids for 8 weeks to ADHD patients and found no difference compared to the beginning levels of CAT. Lower catalase activity in serum [141] and in saliva of an ADHD group was observed compared to the controls [146].

h) Xanthine oxidase: XO activity was significantly higher in serum of ADHD patients compared to controls [43].

i) Nitric oxide synthase: An enhanced nitric oxide synthase (NOS) activity was observed [43].

j) Non-enzymatic proteins: Transferrin and ferritin, but also lactoferrin, ceruloplasmin and even albumin have been confirmed as non-enzymatic antioxidants. They probably act by sequestrating transition metal ions responsible for the generation of the reactive oxygen radical species [147]. However no literature data on serum levels of lactoferrin, ceruloplasmin and albumin in ADHD could be traced. Ceruloplasmin levels in saliva of ADHD patients were not different from those of controls [70].

Biomarkers of specific oxidative damage

a) Proteins: Advanced oxidation protein products (AOPP) can be used as a marker of oxidative damage to proteins. Oztop et al. [52] did not find a significant difference between the concentrations of AOPP in children with ADHD versus healthy controls. Acrolein-lysine adduct is considered as a marker of lipid peroxidation and oxidative protein damage [148,149]. Urinary levels of this adduct appeared higher in ADHD children than control subjects [150]. Levels of butane, a marker of protein oxidation were unaltered in breath of ADHD patients, compared to controls [151]. 3-nitrotyrosine is an oxidative marker of protein damage as associated with bipolar disease [152]. However no publications could be traced linking the concentration with ADHD.

b) DNA: Measuring urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG) has become the most widely used technique to assess oxidative DNA-damage. There are several reasons why it is regarded by many laboratories as a valid biomarker of oxidative DNA damage [17,51]. 8-OHdG is formed in DNA by reactive species and its importance is reflected by its mutagenicity by inducing GC: TA transition, as well as by the presence of DNA repair mechanisms to remove 8-OHdG from DNA [153]. Quite contradictory Oztop et al. [52] found lower values of this biomarker in ADHD children.

c) RNA: A marker for oxidative damage to RNA is 8-oxoguanosine. Chovanova et al. [17] found that Pycnogenol® administration reduced oxidative damage in RNA as measured by reduced levels of 8oxoG 4 weeks after treatment.

Fatty acids

a) MDA: Malondialdehyde (MDA) is the breakdown product of the major chain reactions occurring after oxidation of polyunsaturated fatty acids and thus serves as a marker of oxidative stress [154,155]. Studies on levels of this biomarker in ADHD patients revealed contradictory findings: lower [51,52] as well as higher levels have been reported [62].

b) TBARS: The most widely used index of lipid peroxidation is the measurement of thiobarbituric acid reactive substances (TBARS), which includes MDA. However, the use of the TBARS test to assess oxidative stress status in human fluids is problematic for several reasons: a) aldehydes other than MDA may react with TBA; b) decomposition of lipid peroxides during the test itself may mask the actual MDA content before testing; c) the presence or absence of metal ions or other undefined radicals affects the rate of this decomposition, and d) most TBA-reactive material, including MDA, in human body fluids is not a specific product of lipid peroxidation and may produce false-positive results [156]. Other pitfalls in the measurement of TBARS are summarized by Hermans et al. [153]. Flax oil supplementation corresponding to 200 mg ALA content along with 25 mg vitamin C

twice a day for 3 months improves the outcome of ADHD, however resulted in higher post-supplementaion plasma TBARS levels [72].

c) 4-hydroxy-nonenal: Although 4-hydroxy-nonenal (4-HNE), a bioactive lipid peroxidation product [157], is claimed to be related to brain diseases [55], no studies were found, in which levels of 4-HNE were measured in ADHD patients.

d) Isoprostanes: Urinary concentration of isoprostanes is considered as a marker of lipid peroxidation [158]. However no publications on this marker and ADHD could be found.

e) Acrolein-lysine: Acrolein-lysine adduct is a marker of lipid peroxidation and oxidative protein damage [148,149]. It has been found to be elevated in neonates as a consequence of oxidative stress [159]. Urinary levels appeared to be higher in ADHD children than those of the control subjects [150].

f) Ethane: Breath ethane concentration is considered as a marker of systemic lipid peroxidation [160]. Its concentration significantly correlates with blood hydroperoxide concentrations and inversely correlated with that of vitamin E. Patients with ADHD had higher ethane levels in exhalant breath than healthy volunteers [151].

Conclusion

A problem in the development of oxidative stress biomarkers in ADHD is sample heterogeneity due to aetiological and phenotypic complexity and co-morbidities. Most likely, it is not feasible to identify one single, reliable, reproducible, non-invasive and easy to use biomarker with high sensitivity and specificity. The use of a combination of markers may help to reduce heterogeneity and to identify more homogeneous subtypes of ADHD. In addition, the determination of one or two markers of oxidative stress will not reflect the real redox status in an organism. The evaluation of total oxidative stress (TOS) and total anti-oxidant status (TAS) and their ratio as oxidative stress index OSI) could be more useful for identification of redox imbalance [57,161,162]. Due to the small number of studies and their variety, no definitive conclusions concerning involvement of oxidative stress in pathophysiology of ADHD can be drawn. The contradictory findings in literature may depend largely on the amount of diagnostic parameters and the treatment patients already received. Further on, the question arises whether a lower or higher level of a biomarker is causative for the disease or just a consequence. Moreover, oxidative stress can increase anti-oxidative response, further increasing the complexity of interpretation of oxidative stress related biomarkers. Hopefully, additionally well-defined studies could shed more light on changed levels of various biomarkers before and after treatment with therapeutics in ADHD [163-184].

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