Chapter 8

Personalized Management of Selected Neurological Disorders

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Additional information is available at the end of the chapter

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Abstract

Neurological disorders are medically complex diseases that affect the central and peripheral nervous systems. They can affect an entire neurological pathway or a single neuron. Some neurological problems can present years after a causative event. The World Health Organization reports that various types of neurological disorders affect millions of people around the world. So far, there are no therapies available to cure these disorders. Pharmacological and non-pharmacological interventions can at best relieve symptoms and perhaps delay the progression of the disease. However, there are a wide variety of helpful treatments for different disorders that may help an individual to learn better social skills and communication cues, in order to help them be able to interact socially, in a more natural fashion. For some neurological issues, the outlook can be quite good with treatment and adequate rehabilitation. Diet also plays an important role in the prevention of late-life cognitive decline. Deficits in cognition, low dietary quality and physical functioning, and cardio-metabolic risk factors are frequently reported in patients with neurological disorders. In this chapter we will briefly discuss research, as well as current opportunities and future prospects towards personalized medicine in relation to selected neurological disorders and diseases such as Down syndrome, neuronal ceroid lipofuscinoses (NCLs), and multiple sclerosis (MS).

Keywords: neurological disorders, free radicals, antioxidants, personalized medicine

1. Introduction

Genes are responsible for forming all of the neurons. However, they are certainly not the only factor determining how our brain develops and forms its inner connections. A combination of hereditary factors and environmental factors plays an important role in

determining a neuron's final location [1]. Studies confirm that an active lifestyle maintains brain function [2]; thus, new research aims to develop lifestyle behaviors and medications that could improve normal brain development as well as repair damaged brains. Many neurological disorders emerge during the early years of development and may be diagnosed at birth or later, and their causes include congenital, chromosomal, and gene abnormalities, infections, immune disorders, and environmental factors such as nutritional deficiencies and toxins. The effectiveness of self-management interventions for people with long-term neurological conditions, in particular, Down syndrome (DS), neuronal ceroid lipofuscinosis (NCL), Duchenne muscular dystrophy (DMD), and multiple sclerosis (MS), has been reported. The effectiveness of various antioxidants on several neurodegenerative diseases in clinical trials has increasingly demonstrated that reactive oxygen species (ROS) and oxidative damage are important factors in the processes involved. Imbalanced defense mechanism of antioxidants and overproduction of free radicals from environment to living system lead to serious penalty resulting in neurodegeneration [3]. The current need for better interventions is highlighted, particularly the importance of providing condition-specific information. As the overall life expectancy across the globe has increased, the global community is now facing new challenges of improving quality of life and healthcare; however, advancements in medical technology have benefits and improved healthcare [4, 5]. This chapter provides an overview of the evidence of current findings; research limitations and future directions of research efforts are discussed in some neurological conditions such as DS, DMD, NCL, and MS.

2. Free radicals in the brain

Unlike many other tissues, the brain is a highly aerobic and totally oxygen-dependent tissue. Oxygen reduction produces reactive radical intermediates, such as superoxide and hydroxyl radicals which are thought to be the major agents of oxygen toxicity [6, 7]. Hydrogen peroxide is formed through dismutation of superoxide anion catalyzed by Cu-Zn and Mn forms of superoxide dismutase (SOD), both found in the central nervous system. In addition to Cu-Zn SOD (SOD-1), the activity of which is increased in DS, and hydrogen peroxide (H_2O_2) is generated in association with D- and L-amino acid oxidase, monoamine oxidase, α-hydroxyacid oxidase, xanthine oxidase, and cytochrome P-450 system.

Unlike charged oxygen radicals, H_2O_2, being rather unreactive and stable, rapidly crosses cell membranes. Cellular damage is accomplished when H_2O_2 decomposes to the highly reactive hydroxyl radical in reactions catalyzed by iron (II) or copper (I). If the scavenging of H_2O_2 and the contemporaneous prevention of hydroxyl radical formation do not take place, the hydroxyl radical may attack, e.g., fatty acid side chains, and start a chain reaction of lipid peroxidation. Lipid peroxidation causes gradual loss of membrane fluidity and membrane potential and increases membrane permeability to ions [6, 7]. Abnormalities in the fatty acid composition found in fetal DS brain phospholipids suggest that from the early stage of ontogenesis, lipoperoxidation may have a pathological significance [8, 9]. Oxidative degradation and polymerization of lipids lead to the accumulation of lipofuscin, the age pigment. Current

evidence permits the interpretation that a high proportion of DS subjects later develop the neuropathological changes resembling Alzheimer's disease [10–12].

Considerable evidence has emerged in recent years implicating a role for oxygen free radicals in the initiation of cellular injury that leads to the development of several neurological disorders. The neonatal brain, with its high concentrations of unsaturated fatty acids (lipid content), high rate of oxygen consumption, and low concentrations of antioxidants, is particularly vulnerable to oxidative damage. Thus, increased oxidative stress has been implicated in various neurological disorders such as seizures, ischemia-reperfusion injury, and neurodegenerative diseases [13] such as Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease). Free radical damage has been implicated in the initiation and propagation of seizure activity as well as the accompanying seizure-induced neuronal damage [14]. Therefore, antioxidants could play an important role in modulating susceptibility to seizure activity and seizure-induced neuronal injury.

Radical attack may also destroy membrane-bound enzymes and receptors, e.g., the binding of serotonin is decreased. However, the brain tends to need radical reactions for the generation of physiological responses. Cellular redox adjustments generally regulate functional sulfhydryl groups of proteins. There is evidence supporting the suggestion that free radical intermediates are involved, e.g., in the coupling between depolarization of the plasma membrane Ca^{2+} fluxes and neurotransmitter release [15, 16]. It has also been hypothesized that the elimination of neurofilaments at nerve terminals is regulated by oxygen radicals and that a contact of a growing neurite with a neighboring neuron induces the production of oxygen radicals. Rapid elimination of oxygen radicals during synaptogenesis would result in a reduced number of synaptic connections [17]. Accordingly, transgenic mice bearing the human SOD gene develop abnormalities in neuromuscular junctions of the tongue which closely resemble those of DS patients [18]. However, these abnormalities may be explained by a decreased level of superoxide anion as well as by increased formation of highly active and toxic hydroxyl radicals and singlet oxygen.

The regulation of glutathione (GSH) level (GSH/GSSG) through pentose phosphate pathway producing nicotinamide adenine dinucleotide phosphate (NADPH), GSH reductase, and glutathione peroxidase (GSHPx) contributes to the overall redox state of cells in brain [19]. The brain tends to need radical reactions as well as to possess specific or high endogenous levels of free radical scavengers such as dopamine, norepinephrine, catechol estrogens, taurine, and carnosine [20] in neurons. Carnosine is involved with GABA activity in the brain, and brain tissue contains high levels of carnosine, which is capable of reducing the oxidative, nitrosative, and glycemic stress to which the brain is especially vulnerable [21–23]. Oxidation and glycation produce inflammation and also contribute to cross-linking of proteins, including the Alzheimer's disease protein called amyloid-beta [24]. A study by Takahashi [25] demonstrated that homocarnosine levels were high in patients who responded to antileptic drugs. The functional balance between various free radical scavenger systems in the brain seems reasonable. Significant positive correlations between catalase and SOD levels have been reported in tissues of normal subjects excluding erythrocytes. Factors concomitantly influencing the variation of the activities of SOD, catalase, and GSHPx have been reported. Enzymes

frequently called protective should rather be envisaged as being regulatory, controlling the levels of different states of oxygen reduction, phorbol esters, and strong superoxide producers through NADPH oxidase activation [26–29], inducing biosynthesis of polyamines [30, 31]. The role of polyamines is also associated with the architectural modeling of brain regions and generation of synaptic connections [32–34]. Thus effective scavenging of superoxide by excess SOD-1 may contribute even to the polyamine biosynthesis.

In addition to the complex enzyme systems, biochemical defenses include low molecular weight free radical scavengers and antioxidants. Lipid soluble vitamin E lowers the steady-state concentrations of many free radical species [35–39]. Ubiquinone may exert, similarly to vitamin E, a protective effect against lipid peroxidation [40]. The concentration of vitamin E in a fetal DS brain does not significantly differ from that of controls [41]. We have found the serum vitamin E concentrations of Down syndrome patients to be normal (1.01 + 0.35 vs. 1.13 + 0.39 mg/100 ml) [42]. In addition to conventional antioxidant systems, the brain has been found to contain specific or high endogenous levels of free radical scavengers such as dopamine, norepinephrine [43–45], catechol estrogens [20], carnosine [46], and taurine [47, 48]. The transport of taurine to platelets is impaired in DS [49]. Taurine and hypotaurine, found in high concentrations in the brain [50], could act as intracellular superoxide scavengers which would inhibit not only lipid peroxidation but also inactivation of SOD by both superoxide and H_2O_2 [51, 52]. The presence of 1–10 mM taurine protects cultured lymphoblastoid cells from the injurious effect of iron-ascorbate [48].

The role of dietary beta-carotene in the central nervous system is not elucidated. Beta-carotene acts as an antioxidant at low oxygen pressures [53–55]. Being converted to retinol or retinoic acid, it causes a marked decrease in superoxide generation. Through a still unknown mechanism, retinoic acid induces human neuroblastoma cell differentiation in vitro [56–58], and it also contributes to neural differentiation of embryonal carcinoma cells in vitro [59].

Serum β-carotene and vitamin A levels are generally normal in DS, although vitamin A levels lower than in normal subjects have also been reported. Relatively high carotene/vitamin A ratio suggests decreased efficiency in converting carotene to vitamin A. In addition the utilization of vitamin A in DS may be impaired at its site of action [60–62].

Thyroid hormones improve the cleaving of beta-carotene to vitamin A. This conversion to retinol is decreased in hypothyroidism. Thus, in hypothyroidism the vitamin A concentration decreases even when the dietary β-carotene remains the same or rises [63, 64].

3. Down syndrome

Down syndrome (DS), also known as trisomy 21, is a genetic disorder caused by the presence of all or part of a third copy of chromosome 21 [65]. It is one of the most common chromosome abnormalities in humans [66]. Globally, as of 2010, DS occurs in about 1 per 1000 births [67] and results in about 17,000 deaths [68].

In spite of the intensified antenatal diagnostics and termination of affected pregnancies, the prevalence of DS, first described in 1866, is still so high that it constitutes an important health-care problem. DS phenotype is readily recognized at birth. Karyotype analysis confirms the

diagnosis of DS associated with trisomy of chromosome 21. Since the further development of the child is predestined to be hampered by a multitude of clinical symptoms including mental retardation, premature aging, and immunological disorders such as hypothyroid states, attempts have been made to increase the understanding of the etiopathogenesis of the syndrome and to influence its progress.

The genetic imbalance due to an extra set of normal genes located in chromosome 21 means that the expression of these or actually of only some genes in the q arm leads to the disturbed development. Cumulative effects of increased amounts of primary gene products may be deleterious if no compensatory mechanisms exist. Genes of the q arm in chromosome 21, which may contribute to the DS pathology, include α/β interferon receptor, phosphoribosylglycinamide synthetase [69–72], cystathionine beta synthase [73], and cytoplasmic Cu-Zn superoxide dismutase (SOD-1) [74, 75].

DS, described in a karyotypically normal 18-month-old boy, has been explained by a microduplication of a chromosome 21 fragment (not exceeding 2000–3000 kilobase pairs) containing the SOD-1 gene [76, 77]. Further evidence of the involvement of additional SOD-1 gene in the neuropathological symptoms of DS has been derived from studies performed with transgenic cell lines and from mice carrying the human SOD gene [18, 78].

Consistent with the gene dosage effect, SOD-1 activity is increased in the cerebral cortex of DS fetuses as well as in erythrocytes, blood platelets, leukocytes, and fibroblasts of DS patients [79] (Thilakavathy et al. 2008). According to Sinet [75], elevated SOD-1 activity may constitute an oxygen free radical "stress." Usually SOD-1 protects cells from the harmful effects of oxygen radicals by catalyzing formation of H_2O_2 from O_2^- enzymes that remove excessive peroxides like catalase and glutathione peroxidase (GSHPx) [74]. NADPH is needed for the regeneration by glutathione reductase of glutathione (GSH), the utilization of which is increased via GSHPx as a defense against peroxide formation. Thus several enzymes with structural loci other than those of chromosome 21, including glutathione reductase, glutathione peroxidase, and glucose-6-phosphate dehydrogenase, show elevated activity in erythrocytes of DS patients [80, 81].

Some reports suggest that Both SOD GSHPx activities are increased in Down syndrome children [82]. It remains to be seen whether oxidative damage will still be related to the accumulation of aluminum silicates in the brain as well as to that of the senile plaques and tangles. Experiments have indicated that aluminum salts may not only accelerate Fe (II)-induced peroxidation of membrane lipids but do this especially in the brain [83]. Interestingly a high proportion of Down syndrome patients develop the neuropathological and clinical changes of AD suggesting a close pathogenetic relationship between these disorders. Thus the correction of antioxidant balance in AD by Se supplementation should be demonstrated by other means so as to direct it preventatively to those with a high risk of developing AD.

Balazs and Brooksbank [8] noticed that the adaptive response to elevated SOD-1 activity, i.e., increased GSHPx activity found in other tissues, is not detected in the fetal DS brain. The level of GSHPx activity in neural tissues seems to be as such too low to provide protection from peroxide-induced lesions [84]. Furthermore, if H_2O_2 production is high, catalase might be a superior scavenger, because restoration of glutathione becomes a limiting factor for the activity of GSHPx [85]. However, catalase level is normal in DS erythrocytes [72, 86],

and its activity is practically absent in the brain tissue [87]. Consequently brain cells may be extremely susceptible to oxygen free radicals.

3.1. The pathophysiology of Down syndrome and the role of the thyroid gland

Thyroid hormone has a regulatory function on mitosis and differentiation of neural cells; hence, it is intimately involved in normal brain maturation [88–91]. Experimentally trijodothyronine enhances neural outgrowth in vitro [92, 94]. Even subclinical hypothyreosis during the postnatal period may contribute to the delayed and incomplete maturation of the cerebral and cerebellar cortices.

Increased prevalence of thyroid dysfunction is associated with DS in infants as well as in older children and adults [95–98]. Hypothyroidism is reported in 17–50% of the DS patients studied depending on the age and sex distribution of the population [98]. The relatively high incidence of autoimmune thyroiditis suggests that impaired immune surveillance is the primary mechanism in hypothyroidism [99]. Pueschel and Pezullo [98] conducted a study which showed that approximately 28% of their 151 DS patients had elevated antimicrosomal antibodies, and a highly significant correlation of antimicrosomal antibodies to T4 and to TSH was found. Recent studies indicate that antimicrosomal antibodies are mainly, if not exclusively, against thyroid peroxidase [100].

Thyroid peroxidase is a membrane-bound enzyme associated with the endoplasmic reticulum and the apical membrane of the thyroid cell. lmmunoelectron microscopical observations of the thyroid microsomal antigen in the apical plasma membrane are compatible with the notion that microsomal antigen is identical with thyroid peroxidase [101–104].

SOD-1 system, which generates H_2O_2, is essential in the iodination and coupling reactions catalyzed by thyroid peroxidase [105–107]. However, an excess of H_2O_2 may inactivate the peroxidase complex [105–108]. The irreversible loss of catalytic activity, caused by H_2O_2 or by the reactive oxygen species generated, may result from oxidation of functionally important amino acid residues to carbonyl derivatives. This may also render the protein susceptible to proteolytic attack and to detachment of its cellular compartment. If so, the maintenance of the thyroid peroxidase function and its integrity would require correct steady-state production of H_2O_2 and strict control of its level. This requirement is mainly met with by GSHPx and catalase.

Antigenicity of the modified and disintegrated thyroid peroxidase should be recognized by helper lymphocytes only in the context of MHC Class 11 products coded by genes in the HLA-D region. This region normally expressed only by a restricted variety of cell types is found in autoimmune disorders in target cells. Thus an aberrant expression of HLA-DR antigen found on thyrocytes in Graves' and Hashimoto's disease indicates its potential importance in antigen presentation of thyroid autoimmune disorders [109, 110].

The presence and intensity of DR expression in Graves' thyroids correlate positively with the titer of microsomal antibodies. Curiously, in cultured thyroid cells, plant lectins are able to induce the expression of HLA-DR by a mechanism unrelated to the known mitogenic effects. On the other hand, the inducing effect of gamma-interferon (IFN-γ) could

have a physiological significance (IFN-α and IFN-β did not induce Class II expression in thyrocytes) [111–113]:

- Release of IFNs and lymphokines, best candidates for inducers, must be triggered by other factors [111–113].

On the basis of the gene dosage effect, we suggest possible mechanisms for the sensitization of DS thyroids to autoimmunization:

- Viral challenge including enhanced production of oxygen radicals due to macrophage and neutrophil activity may exert additional requirement for GSHPx and selenium. If these needs are not met with overproduction of oxygen radicals and constitutive excess of both LFA-1 and its beta-chain, it may hinder normal immune response [111–114].
- Excess H_2O_2 causes fragmentation of thyroid peroxidase which detaches from the cell membrane and turns into an autoantigen.
- Increased expression of IFN-α/IFN-P receptors, the gene of which is found in chromosome 21, may sensitize thyrocytes to the induction of HLA-DR antigen by γ-IFN [111–113].

3.2. The impact of early hearing loss on language

Down syndrome occurs in approximately 1 in 600–800 live births [115] and remains the most common genetic abnormality seen in most otolaryngology practices. Down syndrome has a number of clinical problems associated with it [116–118]. The symptoms of DS vary from person to person, and people with the syndrome may have different problems at different times of their lives [119]. Hearing loss will affect many people with Down syndrome at some point in their lives. It has been reported that children with Down syndrome are at particular risk of some degree of hearing impairment due to a number of physiological differences. The authors concluded that there are a range of middle ear problems that can be treated successfully if the children are taken for routine cleaning and examination from birth [120]. Hearing losses affect 40–80% of individuals with DS [121–124]. In young children, the most common cause is conductive loss due to episodes of ear infection and otitis media with effusion (OME).

To determine the prevalence of hearing loss in newborn with Down syndrome, Tedeschi et al. [125] reported that newborn with Down syndrome have a higher prevalence of congenital hearing loss than the total neonatal population (15 vs. 0.25%). Individuals with Down syndrome are prone to otolaryngologic anomalies that complicate the diagnosis and classification of hearing impairment [126]. In children, hearing loss can affect educational, language-related, and emotional development. Even mild hearing loss can affect a child's articulation. It is reported that as many as 80% of people with Down syndrome will have some problem with hearing [127]. A retrospective and cross-sectional analysis was performed to evaluate the prevalence of OME in children with DS for consecutive age categories between 6 months and 12 years [128]. The authors concluded that a high prevalence of OME was found at the age of 1 year (66.7%), with a second peak prevalence of 60% at 6–7 years. A declining trend was seen in older children [128].

As with children, adults with DS may experience hearing loss due to glue ear. Picciotti et al. [129] assessed auditory function in adults with DS to evaluate the prevalence of hearing loss. The authors concluded that hearing loss is common in adults with DS and shows a pattern compatible with precocious aging of the hearing system.

3.3. Hearing and spoken language

Disorders impairing a patient's communication abilities may involve voice, speech, language, hearing, and/or cognition [130]. The effect of hearing difficulties on spoken language development has been demonstrated in many studies of the speech and language skills of children and teenagers with Down syndrome [131, 132].

Most individuals with DS also experience speech and language impairments although the severity of these is variable [133, 134]. Researchers studying language development in DS have measured hearing either directly tested or using pure tone audiometry to establish hearing thresholds [135] or, indirectly, using speech discrimination tasks [136–138]. Therefore, it suggested that speech and language therapy should be provided when children are found to have ongoing hearing difficulties and that joint audiology and speech and language therapy clinics could be considered for preschool children [138].

4. Duchenne muscular dystrophy

Duchenne muscular dystrophy (DMD) is one of the most severe myopathies, usually obvious by the age of 5, and evolves progressively until it causes disablement and death, around the age of 20 [139]. In young boys, DMD is caused by deletions or point mutations in the pre-mRNA for dystrophin that result in out-of-frame transcripts and hence a nonfunctional truncated dystrophin protein [140]. It is recessively inherited, linked to sex, and the gene determining DMD has been mapped in the Xp-21 locus [141]. It has an incidence of 1/3000–1/3500 male births and 1/3 of the cases coming from new mutation. Some affected individuals may develop intellectual disturbance due to unknown mechanism, so far. The sister of an affected individual has a 50% chance of carrying the defective gene [141]. The result of the dystrophic locus on the gene is the absence of dystrophin, a rod-shaped protein that is part of the muscle cytoskeleton. Death commonly results from involvement of the respiratory muscles. Dystrophin is present in the muscle of normal individuals and has been rarely, or not at all, detected in patients with DMD [142, 143]. The genetic alteration produces abnormality in the membrane of the muscular fibers that consists of a disturbance in the calcium transport (Ca^{2+}), inside the muscular fibers, which is the base mechanism of cellular degeneration and necrosis. There is fiber necrosis and replacement of fibers by fat. A nucleotide degradation and decreased muscle ATP and ADP content have been reported. The ATP is necessary to drive the Na^{+}/K^{+} pump which maintains ionic gradients across the sarcolemma; resequester the Ca^{++} into the cisternae; and power contraction [144–146]. The production of ATP can be the result of anaerobic respiration, which breaks glucose down into ATP and lactic acid, or

aerobic respiration when ATP, carbon dioxide, and water are formed. A second immediate reserve of energy exists in the form of creatine phosphate, which can donate phosphate to ADP to form ATP, becoming itself a creatine. In the resting muscle, glucose is stored as glycogen, and in such a muscle aerobic respiration synthesizes ATP from glucose or fatty acids.

Muscle dystrophy and mitochondrial dysfunction give rise to an amplification of stress-induced cytosolic calcium signals and an amplification of stress-induced reactive oxygen species (ROS) production, and increased oxidative stress within the cell damages the sarcolemma and eventually results in the death of the cell. Muscle fibers undergo necrosis and are ultimately replaced with adipose and connective tissue. In recent years, synthetic splice-switching oligonucleotides (SSO) have been developed as new treatments for DMD whereby an SSO is targeted to the pre-mRNA and mediates splicing redirection to restore the reading frame of the dystrophin gene via exon skipping and thus to generate a shorter but functional dystrophin protein isoform [140, 147–155]. Several SSO chemistries have been developed for exon skipping in DMD and other neuromuscular diseases [156, 157], but of these only two SSO chemical types have been used in clinical trials, namely, 2′-O-methyl phosphorothioates (2′-OMe/PS) [158] and phosphorodiamidate morpholino oligonucleotides (PMO) [159, 160].

Therapy of DMD has been an elusive goal. Studies with isolated myocytes have shown that lipid peroxidation with an enhanced free radical production can be activated by increasing Ca concentration [161–163]. Thus, several kinds of antioxidants have been proposed as a treatment since increased levels of thiobarbituric acid (TBA) reactive material has been found in the muscles and blood of DMD males [164]. We have previously reported that the biological half-life of ^{75}Se in DMD patients was significantly shorter than in healthy controls [165]. Low oxygen saturation in the muscle tissue may stimulate the Il-6 production, a cytokine, which is produced by contracting muscles and released into the blood. The blood circulation of the older Duchenne patients is particularly disturbed. Pedersen et al. [166] have demonstrated that Il-6 affects the metabolic genes, induction of lipolysis, inhibition of insulin resistance, and stimulation of cortisol production. In addition, carbohydrate supplementation during exercise was shown to inhibit the release of Il-6 from contracting muscles. Thus carnitine supplementation is indicated to the Duchenne patients, to make sure that the energy supply will be good [167].

Shimomura et al. [168] observed that a group of trained animals, part of which were coenzyme Q_{10} (CoQ_{10})-treated, had to exercise for 30 min on treadmill, in downhill position. CoQ_{10}-treated animals had a higher level of CoQ_{10} in their muscles, and the early rise in creatine kinase and lactic dehydrogenase plasma levels, due to the exercise, was evident at a remarkably significant lower extent, in the treated ones. Similar observations were also made in humans [169, 170]. Therefore we have been treating the Duchenne patients with CoQ_{10}. In our earlier work, we gave DMD patients sodium selenite, 0.05–0.1 mg Se kg^{-1} BW day^{-1}; α-tocopherol, 10–20 mg kg^{-1} BW day^{-1}; vitamin B_{2}, 0.2 mg kg^{-1} BW day^{-1}; vitamin B_{6}, 5 mg kg^{-1} BW day^{-1}; carnitine, 10–20 mg kg^{-1} BW day^{-1}; and ubiquinone-$_{10}$ (CoQ_{10}), 3 mg kg^{-1} BW day^{-1} [171]. We reported two siblings of whom the elder one got practically no antioxidants and the younger one has antioxidant treatment starting at the age of 6 years. The first one was wheelchair bound at the age of 8 years and deceased at

the age of 17 years. However, at the age of 15 years, the younger brother was still able to walk without any assistance. At the age 19 years, he was to be a graduate student with the best scores of all seven subjects that he participated. At the age of 21 years, he was still able to swim a distance of 50 m without any assistance. At age of 30 years, he is still able to make computer art and to have art exhibitions of his own. There are also mothers who have made observations that the odor of lard characteristic of their DMD sons was cured during the antioxidant supplementation. Potential future developments therapy may be to produce functional amounts of dystrophin by skipping the mutated exon like what has been done in mdx dystrophic mouse [172–174].

5. Neuronal ceroid lipofuscinosis

Neuronal ceroid lipofuscinoses (NCLs) are clinically heterogeneous neurodegenerative lysosomal diseases [175–179]. NCLs are recessively inherited neurodegenerative lysosomal storage diseases. The neuronal ceroid lipofuscinoses are with a prevalence of 1 in 12,500 in some populations such as the USA and Northern Europe. Currently the classification is based on genetic defects, with 14 clinical subtypes and genetically separate neurodegenerative disorders that result from excessive accumulation of lipopigments (lipofuscin) in the body's tissues, and the most prevalent NCLs are CLN3 disease, classic juvenile and CLN2 disease, and classic late infantile [39, 176, 180–182]. Characteristics of the diseases are deposits of ceroid and lipofuscin pigments in the tissues, particularly in the neural tissue, visual failure, and progressive mental retardation; depending on the age of onset and clinical, electrophysiological, and neuropathological features, the NCLs can be subdivided into the infantile the late infantile, the juvenile and the adult type of NCL; however, the pathogenesis of NCL is still unknown.

5.1. Management of neuronal ceroid lipofuscinosis

Neuronal ceroid lipofuscinoses are a group of hereditary diseases caused by mutations in at least eight genes (CLN1-CLN8) [183, 184]. They are characterized by massive accumulation of autofluorescent lysosomal storage bodies in most cells and associated severe degeneration of the CNS [183]. There is no single, standard treatment for neuronal ceroid lipofuscinoses (NCLs), as there is currently no cure; however, a number of different treatments can be used to ease symptoms and encourage independence and better standards of general health [185]. Also there are certain medical problems that can affect someone with neuronal ceroid lipofuscinosis. However, a number of different treatments can be used to ease the symptoms and encourage independence and better standards of general health. These treatments are based on each individual's physical and intellectual needs as well as their personal strengths and limitations: enzyme replacement therapy, gene therapy, stem cells including tissue engineering, and medicine or metabolic therapy such as dietary restriction and immune biotherapy [186–190]. These modes of treatments have been used in many genetic diseases. Acetyl-L-carnitine (ALC) has been shown to be therapeutic in treatment of NCLs [191]. It was reported that ALC might rebalance the disorders

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underlying neuronal ceroid lipofuscinosis disease which are related to a disturbance in pH homeostasis [191].

The polyenic acid level with low levels of linoleic acid and an inverse relationship between GSHPx activity and the level of eicosatrienoic acid have been observed in juvenile neuronal ceroid lipofuscinosis (JNCL) [192]. The occurrence of the fluorescent pigments suggested the peroxidation of lipids in the etiology of NCL. It is likely that the diseased tissues peroxidized cause secondary damage more rapidly than normal tissues and cytotoxic end products of lipoperoxidation. On a weight basis, ceroid seen in JNCL patients binds five times more iron than the lipofuscin seen in normal elderly individuals. The increased levels of aluminum salts greatly enhance iron-dependent damage to membranes. Heiskala et al. [193] has confirmed the presence of complexable iron and copper in the CSF of patients with NCL and other neurological disorders, and when the pH value of the assay for iron was lowered, the NCL group had substantially more complexable iron in their CSFs. Interestingly aluminum has been observed in CSF and in ceroid lipofuscin pigments of the brain of NCL patients [194]. It is well established that damaged tissue release metals from protein-bound sites and these metals stimulate peroxidative damage to lipids and other biomolecules.

One of the most essential enzymes counteracting lipoperoxidation is the selenium-containing GSHPx. Two independent reports have demonstrated that erythrocyte GSHPx activity is decreased in JNCL patients [195]. This low GSHPx activity was reversed to normal level by selenium supplementation. The evaluation of sodium selenite absorption and losses before supplementation of JNCL patients has been studied by using total body counting for ^{75}Se detection. These studies showed that in three JNCL patients, about 55% of the administered ^{75}Se was eliminated during the first 11 days in the feces and about 10% in the urine [39]. Compared to healthy controls (42 and 7%, respectively), findings indicate a reduced absorption of selenium in JNCL patients contrary to a previous report. The low GSHPx activity in NCL patients may indeed reflect a low selenium intake most probably due to a disturbed absorption of selenium and secondary phenomena due to an inborn error of metabolism. Apart from the low selenium status, also very low vitamin E levels are found in the serum of advanced and hospitalized NCL patients. This can be explained by the recent finding of a pronounced reduction of apolipoprotein B as well as the whole fraction of very low-density lipoprotein (VLDL) in JNCL patients.

JNCL patients (genetically subgroups) have been given daily supplementation of sodium selenite (0.05–0.1 mg/Se/kg of BW), vitamin E (α-tocopherol acetate 0.014–0.05 g/kg BW), and vitamins B_2 (0.025–0.05 mg/kg BW) and B_6 (0.63–0.8 mg/kg BW). The benefits of the therapy are corroborated by the significant negative correlation of GSHPx activity with neurological dysfunction of motor performance, balance, coordination, and speech [196]. The mean age at death has been extended by 4 years as compared to that at the beginning of the century. As the best responders to antioxidant therapy show no neurological dysfunction at the age of over 20 years, there is no doubt that the life expectancy of JNCL patients receiving antioxidants, including selenium, will be significantly prolonged in the future [197]. Complications of the antioxidant therapy have been few and not severe. Six patients have experienced vomiting and

nausea when the serum concentration of selenium reached the level of 0.45 to 0.5 mM. Serum levels up to 4.0 mM were usually well tolerated, as well as when the sodium selenite was changed to ebselen (2-phenyl-1,2,-benzisoselenazol-3(2H)-one).

6. Multiple sclerosis

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system, where suspected autoimmune attack causes nerve demyelination and progressive neurodegeneration and should benefit from both anti-inflammatory and neuroprotective strategies [198]. MS affects an estimated 4.3 cases per 100,000 in Europe with a higher rate in Northern Europe [199]. Often it appears in individuals between 20 and 40 years of age and has a strong genetic component [200]. The disease course is benign in 10–15% of patients, and they do not need an assistive device for walking even after 20 years of MS [201, 202]. Low levels of polyenic acids are involved in the pathogenesis of both MS and JNCL. Earlier a decrease level of serum linoleate as well as unsaturated fatty acids of brain phospholipids in MS patients was shown [203, 204]. It has also been argued that supplementation with essential fatty acids may improve the clinical status of MS patients [205]. And as in NCL, the selenium may, by activating GSHPx (scavenger of organic peroxides), regulate the metabolic transformation of essential fatty acids and biotransformation of these to prostaglandins, thromboxanes, and leukotrienes [206]. Curiously decreased GSHPx activities in erythrocytes have been found in female but not in male MS patients [207]. A significant association between the two haplotypes of the dopamine D2 receptor gene (DRD2) and the age of onset and/or diagnosis of MS was reported [208].

Current treatments for MS mainly target inflammatory processes, and there has been scant progress in treatments that enhance neuronal or glial regeneration. Can we predict the risk of serious side effects? This asks for the development of biomarkers, clinical, genetic, imaging, or immunological, that allow for a better stratification of patients [209]. The need for tailored therapeutics is especially imperative, as the consequences of an ineffective medication might be irreversible dysfunction. However, it is obvious that treatment decisions in clinical practice must be made on an individual basis. This requires a personalized medicine approach in predicting disease activity in multiple sclerosis. Biomarkers that could predict disease course, treatment response, and risk of side effects would be highly appreciated. Despite extensive research over the last years, few biomarkers have made their way into clinical practice.

7. Advances in the development of novel antioxidant therapies

Earlier, through intervention efforts, patients with DS have received medical treatment and stimulation of sensory, motor, and cognitive areas [210]. In 1981, Harrell et al. [211] reported that the administration of a megavitamin mineral supplement to a heterogenous group of 16 mentally retarded children, 4 of which had DS, had led to encouraging results. However, controlled

double-blind studies on somewhat larger groups using similar megadoses of vitamins and minerals but no thyroid supplementation did not result in any beneficial effects [212–216]. However, these studies were devoid of a detailed theory of the mechanism of action, and the age distribution of the patients was disadvantageous in relation to possible targets in the developing brains.

Our primary survey and theory of antioxidant therapy in DS [42, 217] rest on the present concepts of the etiopathogenesis of DS [8, 79]. Earlier, selected antioxidants have been used, e.g., in the therapy of neuronal ceroid lipofuscinosis [218]. Prevention of free radical damage should be executed by agents focused on the tissue and cellular compartments and processes where the generation of free radicals is critical. In DS, elevated cytoplasmic SOD-1 activity causes free radical stress through H_2O_2. An excess of H_2O_2 may be activated in iron- or copper-catalyzed reactions to generate highly reactive hydroxyl radical (–OH) or singlet oxygen. The extent and nature of the damage depend on the precise site of the •OH production, which in turn depends on the intra- or extracellular location of the critical metal ions [7, 219].

However, GSHPx, which gives protection against elevated H_2O_2, is low in brains with intensive oxygen metabolism. Histochemical studies by Slivka and co-workers [220] are indicative of the relative absence of GSH in neuronal somata and locate GSH to non-neuronal elements and fibrous and terminal regions of neurons. Furthermore, in normal newborn infants, the activity of GSHPx is physiologically low [221, 222]. Just a reflection of this condition could be the low blood selenium level found in neonates [223]. Controversial results have been published on the level of selenium in plasma and erythrocytes of DS patients [79]. Peripherally decreased GSHPx activity may be corrected by selenium supplementation [224, 225]. Unlike catalase, benefit of optimal GSHPx activity is gained through its capability to reduce both H_2O_2 and organic hydroperoxides including lipid peroxides. The mean plasma selenium concentration in DS patients has been shown not to differ significantly from that of the control subjects although the GSHPx activity is 130% of the normal [226]. Neve and co-workers [227] reported normal erythrocyte but significantly decreased plasma selenium levels in 29 DS patients. These discrepancies may be explained by the differences in the population groups studied and by the distribution of the blood selenium pool. Only 10–15% of the erythrocyte selenium in man is reported to be incorporated into the GSHPx, whereas the corresponding value in rat is 75–85% [228].

We noticed in DS patients of different ages that the mean compensatory increase of erythrocyte GSHPx was lower than expected, 33.4 vs. 50%. The finding that the erythrocyte SOD/GSHPx ratio was higher than in healthy controls confirmed our belief of insufficient compensation [42, 217]. In DS the whole body retention of 5–8 kBq, ^{75}Se-sodium selenite, with 0.4 ug Se as carrier/kg BW, is estimated to be 53.3 ± 21.1%. Stable selenium supplementation increased ^{75}Se elimination indicating a saturated selenium pool in the body [229]. Selenium supplementation 0.025 mg Se/kg/d in the form of sodium selenite increased E-GSHPx activity by 28 (59.9% above normal). This was also demonstrated by the 23.9% decrease of SOD/GSHPx ratio ($P < 0.01$) [42, 217].

The consequences of selenium supplementation on the brain antioxidant balance, and thus its therapeutic value, are difficult to monitor. However, certain clinical, experimental, and in vitro observations may be indicative [230]. A highly positive correlation has been reported

between erythrocyte GSHPx values and IQ in DS [231]. The plasma selenium concentration and erythrocyte GSHPx activity were found to be higher in DS girls than in DS boys, which is consistent with the finding of significantly higher IQ scores for female than for male DS patients. The positive correlation of E-GSHPx activity between DS subjects and their siblings suggests the influence of environmental and/or additional genetic factors [26, 230].

Estimates of the amount of selenium in the rat brain indicate that the GSHPx may account for only ⅕ of the total selenium in the brain [232]. The finding that selenoproteins other than GSHPx are distributed mainly in the brain and endocrine organs raises a question of their physiological role. After the administration of very small amounts of selenium, severely depleted rats retained in the brain and in the reproductive and several endocrine organs (including thyroid) a dose which was 20–50 times the dose found in adequately fed control animals. This indicates the existence of regulatory mechanisms which ensure a sufficient level of selenium in critical organs, above all in the brain and the thyroid even during depletion [91, 233].

In concentrations of 6 x 10^{-7} M, selenite induces a 30-fold increase of GSHPx activity in neuroblast cells in vitro [234]. Earlier studies on the rat liver suggested that selenium regulates the level of GSHPx mRNA as well as GSHPx protein concentration and GSHPx activity [235]. Concentrations of 10^{-5} M exert obvious toxic effects on nerve fibers in vitro [236]. Trace elements, as "doping impurities" in organic material, could be key variables that regulate conductivity in biological semiconduction structures [237]. We suggest that the abnormally high levels of copper and iron and the low level of zinc ion in erythrocytes and blood mononuclear cells are reflections of disturbed oxygen radical metabolism in DS. However, increased concentration of copper can be explained as gene dosage evident by the increased activity of SOD-1 [238]. Except for the decreased iron content in erythrocytes, the results were in accordance with an earlier study [239]. Ferrous-ion (Fe II) and copper-ion (Cu I) react with H_2O_2 producing •OH radicals [240, 241]. Titanium in erythrocytes may indicate insufficient protection by GSHPx. If titanium is present as Ti (IV), stable compounds may be formed with hydrogen peroxides and probably with superoxide anions to give 1:1 adducts [238]. The low plasma zinc concentration in DS children has been recognized in earlier studies as well [242, 243]. The homeostasis of zinc is regulated by the intestine. The absorption of zinc seems to be decreased in DS, mean retention of zinc being 30% compared with 58% in healthy adults. Stable zinc supplementation in one DS patient did not increase the 65Zn elimination, indicating an unsaturated zinc pool [229].

Interestingly, the primarily high blood mononuclear cell levels of copper decreased, whereas the concentration of iron and zinc was not affected during selenium supplementation [244]. No significant alterations were observed in the erythrocyte concentrations of magnesium, calcium, iron, copper, zinc, sulfur, titanium, and manganese. Aluminum was not found in erythrocytes nor in neutrophils of DS patients [238].

8. Brain antioxidant homeostasis in relation to selenium and GSHPx

In nature the availability of selenium, as a trace element, may be limited. GSHPx activity has been shown to reflect selenium status in deficient and adequate states [245]. On the

other hand, protection against toxicity is likely to involve the alterations in GSH metabolism that occur in nutritional Se deficiency. A high concentration of erythrocyte glutathione in patients with neurological disorders has been reported [246–248]. However, regulatory mechanisms apparently exist which ensure that during periods of insufficient selenium intake, the content of the element is kept up above all in the brain and the reproductive and the endocrine organs.

Selenium seems to be somehow involved in the regulation of oxygen metabolism through its influence on a variety of enzymes. In concentrations of 6×10^{-7} to $\times 10^{-6}$ M, selenite induces a 30-fold increase of GSHPx activity in neuroblast cells in vitro. Other studies with the rat liver have suggested that Se status regulates the level of GSHPx mRNA as well as GSHPx protein concentration and GSHPx activity [235]. In concentrations of $0.7 - 2 \times 10^{-5}$ M, Se in the rat liver increases the activities of γ-glutamylcysteine synthetase, the first rate-limiting enzyme in GSH biosynthesis, and GSSG reductase, which catalyzes the reduction of GSSG to GSH [249]. In some species the induction of GSH S-transferase has been shown to occur as a result of Se deficiency. Hydrogen peroxide as the most stable and diffusible of the oxygen reduction intermediates may exert an influence on the expression of SOD, catalase, and GSHPx activities. The homeostasis in the oxidative metabolism and oxygen reduction may be distorted by different means either inherent or acquired. Depending on the spatial and temporal occurrence of the distortion, various neurological states are expressed. The developing brain is particularly susceptible to oxidative stress more so than the mature brain [250]. H_2O_2 accumulation has also been associated with increased injury in the superoxide dismutase-overexpressing neonatal murine brain, and greater cell death is seen when immature neurons are exposed to H_2O_2 than with mature neurons. Increased H_2O_2 accumulation may be the result of relative insufficiency of the endogenous enzyme GSHPx.

Under physiologic circumstances, the brain has efficient antioxidant defense mechanisms, including GSHPx, which converts potentially harmful H_2O_2 to oxygen and water at the expense of reduced GSH. Under oxidative stress, in the immature brain, endogenous levels of GSHPx may be inadequate for converting excess H_2O_2. Transgenic mice that overexpress GSHPx (hGPx-tg), when subjected to hypoxia-ischemia (HI), have less histologic brain injury than their WT littermates [19]. In addition, the cortex exhibits increased GSHPx enzyme activity at 24 h, whereas GSHPx activity remains unaltered in the WT brain. In addition, neurons cultured from the hGPx-tg brain are resistant to injury from exogenously applied H_2O_2 [251]. Neurons cultured from the hippocampus and cortex that are transfected (transfection describes the introduction of foreign material into eukaryotic cells) with genes for catalase and GSHPx also show protection from neurotoxic insults and a corresponding decrease in H_2O_2 accumulation [252]. These findings indicate that adequate GSHPx activity can ameliorate injury to the immature brain from oxidative stress due to H_2O_2.

It is well established that a previous stress to the brain can induce tolerance to subsequent injury, a phenomenon called personality change (PC). In neonatal rodents, protection against HI brain injury has been induced by PC with a period of hypoxia before the induction of HI [253]. The mechanisms of this protection have yet to be fully determined, but it has been established that a large number of genes are induced in response to hypoxia [254]. Many of these genes are regulated by the transcription factor hypoxia-inducible factor-1α (HIF-1α), perhaps most importantly

vascular endothelial growth factor (VEGF) and erythropoietin (EPO). VEGF is upregulated after focal ischemic injury in the neonatal rat, in parallel with the induction of HIF-1α [255].

9. Current opportunities and future prospects towards personalized medicine

Neurological disorders are diseases that affect the central and peripheral nervous systems. They can affect an entire neurological pathway or a single neuron; the neurodegeneration describes the loss of neuronal structure and function [256]. They are caused by genetic mutations present during embryo or fetal development, although they may be observed later in life [257–259]. The mutations may be inherited from a parent's genome, or they may be acquired in utero. The risk factors for the diseases are diverse, including age, genetics, lifestyle, etc. Inflammatory conditions represent a major causative factor in numerous medically significant disorders. It can result from a range of stimuli from outside or within the body. However, these stimuli trigger cells and physiological processes within a host environment. It is believed that environmental exposures increase the risk of developing the disease. Even in inherited cases, exposure to toxins or other environmental factors may influence when symptoms of the disease appear or how the disease progresses [258, 260, 261].

With an increase in life span and decrease in death rate, the prevalence of these chronic recurring condition are rising all over the world. Moreover, no direct therapy/treatment is available now, which can reverse or retard the pathophysiological processes permanently. The medication (drug) regimen needs to be well integrated with healthy diet and lifestyle to attain high-quality and longer lives [262]. Therefore, the complex physiopathological mechanisms must now be clarified, and the immunological and genetical causes to neurological diseases must be investigated. New research on gene changes linked and gene therapy to neurological disorders is helping scientists better understand the disease, in which DNA or RNA is used as the pharmacological agent, defined as gene therapy [263]. Both genetic and environmental factors are known to influence susceptibility to diseases. Therefore, environmental factors may also have a protective effect.

The role of free radicals is well established in etiopathogenesis of neurological disorders. Some of the known antioxidants, which can prevent oxidation chronic recurring condition, have been studied [38, 39]. Recent developments in basic research have confirmed the relationship between etiopathogenesis and supplementation therapy with vitamins and trace elements. Supplementation therapy studies should be conducted. We need more clinical experience and a longer follow-up period with our neurological disorder patients receiving antioxidant therapy to reach more final conclusions concerning efficacy in the control of optimal development. Studies are now looking at the possible effects of these compounds more closely to develop related compounds that are even more potent and might be used as dietary supplements. However, so far, most research suggests that a balanced diet is of greater benefit than taking these substances as dietary supplements.

10. Personalized medicine approaches

Neurological diseases cannot be managed by using one single approach. These disorders, like all chronic diseases, are a complex metabolic system that is related to the way a patient's genes interact with their individual environment. Therefore, precise and reliable testing methods are needed including patient biomarkers, age, and genetic history. Oxidative stress has been linked to dozens of chronic conditions [264, 265]. Identifying the cause of oxidative stress such as emotional stressors, poor diet, smoking, metal toxicity [266], chemical exposure, and pesticides can be of help [266, 267]. To balance free radicals may require lifestyle and diet modifications such as antioxidant supplementation [268, 269].

There is no doubt that the nervous system is involved in the etiopathogenesis of various pathological states and diseases. Interactions between the nervous, endocrine, and immune systems might represent the anatomical and functional basis for understanding the pathways and mechanisms that enable the brain to modulate the progression of disease. For example, an increasing number of pharmacogenetic association studies in DS are being reported [270, 273]. Personalized medicine is an evidence-based, individualized medicine that delivers the right care to the right patient at the right time and results in measurable improvements in outcomes and a reduction on healthcare costs. However, in order to make personalized medicine effective, genomic techniques must be standardized and integrated into health systems and clinical workflow. Though personalizing drug treatment on the basis of individual genotype rather than ethnicity may be more appropriate, differences in allele frequencies across continents should be considered when designing clinical trials of new drugs [270]. For example, new therapies for treating DS require quality of life measurement, such as the use of stem cells in order to develop treatments which may improve the intelligence of those affected with the syndrome [274]. Other methods being studied include the use of antioxidants, gamma secretase inhibition, adrenergic agonists, and memantine [275–279].

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