Amyatrophic Lateral Sclerosis: Treatment with Unconjugated Bilirubin

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How could the boots get on the table?
(What has that got to do with it?)

Abstract

The motto of this research article is a Hungarian proverb, and indicates an expression of indignant surprise: was this article written by two pediatricians (moreover, neonatologists)? That's easily understood by a popular English proverb: "you can't make an omelet without breaking a few eggs." Strictly speaking, the authors are beginning this review with the jaundice of the newborn infants, and would like to get a dreadful, age-related disease (amyatrophic lateral sclerosis - /ALS/). In addition, they are suggesting an unusual, and may be - onto first hearing - astonishing treatment (unconjugated bilirubin - /UCB/). Although the neonatal hyperbilirubinemia (NHBI) has been shown to be neurotoxic, studies performed during the past decades found that the bile pigment has a number of new and interesting biochemical and biological properties. If UCB is an effective antioxidant, metal chelating and anti-inflammatory agent, it should have a role in ameliorating the acute and chronic medical conditions. Several studies have reported that bilirubin associated with reduction of free radical generation and improves antioxidant status in patients suffering from atherosclerosis and cancer and a number of inflammatory, autoimmune and degenerative diseases. There is a potential role for UCB as an endogenous immunomodulatory agent, and it may protect mammals from copper poisoning.

Keywords: Amyatrophic Lateral Sclerosis; Neonatal jaundice; D-Penicillamine; Oxidative stress; Antioxidant effects of bilirubin; Copper-bilirubin complex

Abbreviation
ALS: Amyatrophic Lateral Sclerosis; BG: Basal Ganglia; BBB: Blood Brain Barrier; BIND: Bilirubin-Induced Neurologic Dysfunction; CNS: Central Nervous System; D-PA: D-Penicillamine; DNA - Deoxyribonucleic acid; OS: Oxidative stress; NHBI: Neonatal Hyperbilirubinemia; ND: Neurodegenerative Disease; ROS: Reactive oxygen species; RNS: Reactive nitrogen species; UCB: Unconjugated bilirubin

Introduction

The UCB at excessively high concentrations causes permanent neural damage in newborn infants, i.e. "chronic bilirubin encephalopathy" or kernicterus which is a well-described clinical syndrome of choreoathetoid movements, an auditory processing disturbance, impairment of upward vertical gaze, and dysplasia of the enamel of deciduous teeth [1,2]. NHBI is a common condition in the first week of postnatal life. Although generally innocuous, some neonates may develop very high levels of UCB. Subtle encephalopathy or Bilirubin-induced neurologic dysfunction (BIND) refers to individuals with subtle neurodegenerations (NDs) [3-6]. There is a tremendous variability in babies' vulnerability toward UCB: preterm birth, sepsis, hypoxia, hypoperfusion, hyperosmolality, acidosis, hypalbuminemia, hemolytic disease et cet. However, the UCB levels and neurological abnormalities are not strictly correlated [7], and the pathomechanisms of BIND have not been fully understood yet. Our concept addresses the medical necessity of chelation therapy (with D-Penicillamine - /D-PA/) in the neonatal period [8,9], as it is feasible that UCB molecule reveils particular affinity to copper stored in basal ganglia (BG) of the neonatal

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brain, where copper-bilirubin complex can be formed [10]. Copper dyshomeostasis and OS have also been concerned in NDs such as Alzheimer, Amyotrophic lateral sclerosis (ALS) or Menkes disease. These irreversible syndromes are related with a progressively aggravating lesions of neurons and injury of synaptic junctions in CNS. This review focuses on a ND (ALS) [11] which has multicausal etiology and pathomechanisms, including copper mediated damage or overproduction of reactive oxygen species (ROS) derived from other sources.

Oxidative stress

In a biological context, ROS have important roles in cell signaling and homeostasis. However, under conditions of OS, ROS production is very high, resulting in damage of membrane lipids, proteins, and nucleic acids that may become irreversible, even cause cell death. Oxidative damage is occurred in the age-related diseases as well in a variety of pathological settings. OS has been implicated in the pathophysiology of many neurological, particularly NDs, diseases. It can also contribute to the aging process. The strategy which limits oxidant-induced tissue damage, called antioxidant defense mechanisms, is a complex network of endogenous and exogenous systems for scavenging of reactive oxygen/nitrogen species (ROS/RNS). Binding of metal ions is also needed for up-regulation of exogenous/endogenous antioxidant defenses. In the CNS a high rate of oxidative metabolism takes place. At the same time, the brain is more vulnerable to OS compared to other tissues [12]. So, it seems reasonable that we need exogenous antioxidants which are effective in diminishing the OS [13]. ROS and RNS are two major types of compounds [14,15]. It is well-known that the blood-brain barrier (BBB) protects CNS maintaining brain homeostasis. At the same time BBB was destroyed by ROS. These observations suggest that ROS are key mediators of BBB breakdown and implicate antioxidants as potential neuroprotectants in various conditions [16].

Bilirubin as an antioxidant

UCB has been regarded until recently as a dangerous product of heme metabolism that can be toxic if accumulated at high concentrations, particularly in the brain (especially in the BG) of the newborn [3]. Studies on the toxic effects of NHBI historically involved infants with hemolytic disease. An increased incidence of kernicterus was found to be associated with UCB levels above 20 mg per dL in the presence of hemolysis. On the basis of this observation an aggressive treatment (exchange transfusion) was introduced into the therapy of all infants with significant hyperbilirubinemia (“vigintiphobia”) [17]. More recently, term infants without hemolysis have been found to tolerate higher UCB levels, and management guidelines now focus primarily on phototherapy as initial treatment (- Here we wish to notice that according to an up to date information [18] the hyperbilirubinemia does not influence DNA damage, whereas both conventional and intensive phototherapy are associated with DNA damage in term infants with high UCB levels -).

At low or, may be, moderate levels, however, UCB is a potent antioxidant that apparently protects individuals against common diseases related to OS. Bilirubin can serve as an endogenous scavenger of both ROS and RNS [19], which provides a possible explanation for a low incidence of cardiovascular diseases and, to a certain extent, neurodegeneration in patients with Gilbert-Meulengracht syndrome [15]. Research of the last 3 decades indicated that individuals with higher levels of UCB may experience various health benefits (in atherosclerosis, demyelinating neuropathies, cancer and certain heart diseases). Studies have found higher levels of bilirubin in old people who are living with higher functional independence [20-23]. The “classic” interpretation of bilirubin properties does not give sufficient answers to the following questions: how to call bilirubin: friend or foe? It is also true that there is no UCB concentration which certainly causes chronic bilirubin encephalopathy. In a Danish population-based study, the neonates with UCB levels of ≥ 25 mg/dL didn’t show any neurologic dysfunctions at 5 years of follow up [24]. According to our concept the key points of the explanation can be found regarding the BIND that it is a neurodegenerative disorder of immature brain, and caused by accumulation of free metals and UCB-Cu complex (as prooxidant) in the BG and other parts of CNS relevant to chronic bilirubin disorder. The main comorbidity is the hemolysis of neonatal blood red cells. During this process a great amount of heavy metals (mainly iron and copper) and Cu-UCB complex may circulate in the bloodstream, and can pass through the immature BBB, finding entrance into the CNS. In addition, ROS contribute to increased BBB permeability creating a dangerous vicious circle in the neonatal brain, especially in the BG [25]. UCB can act as an important cytoprotector of tissues that are poorly equipped with antioxidant defense systems, including myocardium and nervous tissue [26,27]. The UCB levels in jaundiced

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and non-jaundiced pups exposed to 95% O2 shows a negative correlation with lipid hydroperoxides at 3 days of exposure. Higher UCB concentrations resulted in lower lipid hydroperoxide levels [28]. In addition, UCB serves as a predictor of OS-mediated diseases [29,30].

To sum it up, high production of ROS/RNS from specific neurochemical reactions in the central nervous system (CNS) with aging is dangerous for the human brain. For this reason, along with inflammation, OS seems to be one of the main inducers of neurodegeneration, causing excitotoxicity, neuronal loss, and axonal damage, ultimately being now considered a key element in the onset and progression of several NDs, including ALS [31]. Population studies documented a reduced incidence of cardiovascular problems, of carcinoma in general and of colorectal carcinoma specifically in individuals with higher serum UCB [32]. In addition, other members of heme metabolism (biliverdin, conjugated bilirubin) also have similar beneficial effects [33,34].

Copper toxicity

Copper is present as an integral part of the active site of many enzymes and plays an important role in physiology. Too much copper, however, may damage various organs in the human organism, especially in the liver, kidneys and CNS [35]. As far as the copper atoms are concerned, its redox reactivity, i.e., the copper ion is acting as the oxidising agent (accepting electrons), leads to risks of damage to cell and tissues. Furthermore, copper induces the activation of apoptosis leading to neurodegeneration. This review will cover some aspects of the involvement of copper-mediated OS in age-related degenerative processes in CNS, with special focus on ALS [36]. Copper is implicated directly or indirectly in the pathogenesis of numerous neurological disorders, including aceruloplasminemia, Alzheimer, Huntington, Menkes, Creutzfeldt-Jakob, Parkinson and Wilson diseases, ALS and occipital horn syndrome. In the brain copper ion produces free radicals that causes mitochondrial damage, DNA breakage, and neuronal injury. The latter leads to loss of muscle strength and respiratory problems, and may be fatal [37,38]. Evidence suggests a direct pathogenic role for copper in this process. Gain-of-function mutations in the cytosolic copper enzyme Cu/Zn-superoxide dismutase result in motor neuron degeneration characteristic of ALS. The ALS is considered a model disorder for neurodegeneration involving deterioration of the anterior horn cells in the spinal cord [39-41].

There are several potential biomarkers of copper excess. Superfluous copper is deposited in the liver where high levels can cause injury. Interleukin-2, i.e., may be reliable biomarker of copper excess [42].

Complex formation of bilirubin with copper

Adhikari., et al. have shown that UCB may protect mammals from copper poisoning [10]. Treatment of human copper overload disorders is based on the chelating and cupriuretic effect of several agents [43] and the impairment of copper absorption induced by oral zinc therapy. Although we experience significant improvement in the hepatic injury if chelation therapy is started relatively early in the course of liver damage, many patients fail to have an adequate response to chelation therapy and eventually require liver transplantation to avoid death [44,45]. A similar lack of response to metal chelation has been demonstrated in advanced Indian childhood cirrhosis [46]. Copper forms complexes with bilirubin (H2BR). These complexes are able to scavenge ROS and RNS. There were studied a series of Cu2+ bilirubin complexes to ascertain the nature of the binding between Cu2+ and bile pigment. The complexes were prepared by dissolving protonated bilirubin in NaOH, and adding different ratios of aqueous CuC12 [47]. Chelating agent, such as D-PA reduces the amount of copper in the body, but it does not affect the increased levels of ROS caused by the copper. That is why intensive investigations are going to find a much better chelating agents [48]. Recent data indicate that bilirubin has several favourable effects [49,50]. For example, bilirubin is much stronger antioxidant than many other agents, including α-tocopherol (vitamin E), superoxide dismutase and catalase [51,52]. In addition, bilirubin also exhibits cytoprotective and neuroprotective properties [53,54].

Autoimmunity and neurodegeneration

Mutations in C9ORF72 are a common contributor to ALS, although yet the function of this gene is still poorly defined. Burberry., et al [55]. have demonstrated that mutations in mice developed features of autoimmunity. They further found that transplantation of normal bone marrow into animals ameliorated this phenotype, while transplantation of mutant bone marrow into normal animals has caused

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autoimmunity. The authors have concluded that the gene acted through hematopoietic cells to maintain normal immune function and suggested that investigations are warranted into whether disruptions in immunity contribute to disease in patients.

Bilirubin as a powerful immunomodulatory agent

It is excelling from written above that UCB has multiple biological activities, including immunomodulatory properties. *In vivo*, treatment with UCB effectively suppressed experimental autoimmune encephalomyelitis [56]. Kristin and Christopher recommended heme oxygenase, a rate limiting enzyme in heme degradation, for potential therapeutic applications [57]. Other authors found connection between UCB concentrations and multiple sclerosis [49], and showed that bilirubin influences the expression of Fc receptors in macrophages [58]. They hypothesized that the bile pigment was capable of regulating immune functions due to its high lipophilia and its direct interaction with cell membranes. UCB inhibits vascular cell adhesion molecule 1 (VCAM-1)-dependent cellular events suggesting that bile pigment blocks VCAM-1-dependent lymphocyte migration. These findings support a potential role for bilirubin as an endogenous immunomodulatory agent [59,60].

Conclusion

In our research review some less-known informations have been disclosed demonstrating the beneficial effects of UCB. As neonatologists we must meet this bile pigment each day, and are certainly doubtful about its harmless. We would like to draw colleagues’ attention to the bilirubin molecule which has a number of favourable properties, and which can be used curative in the age-related or neurodegenerative diseases. Of course, the contribution of pharmacochemical experts are essential to this promising project.

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