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Metal Mediated Bilirubin Encephalopathy: Treatment with D-Penicillamine

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Abstract

Introduction: Very wide-ranging studies have long been made on the possible biochemical transformations of un conjugated bilirubin (UCB) which is formed during the decomposition of hemoglobin. Particular attention has been paid to its photochemical and redox reactions but the relevant publications comprise only a very small proportion of those dealing with the molecular biochemistry of UCB and metal interactions.

Methods & subject: Based of the literature data and on our own experiences obtained in connection with 5-6000 newborn infants (only in our clinic) treated with D-Penicillamine (D-PA) during the last 40 years. In global perspective UCB has a special affinity for the basal ganglia (BG) because they are also target brain regions for divalent metal (Cu, Fe, Zn et cet.) accumulation. The immature and strikingly vulnerable neurons play important role in the pathogenesis of bilirubin induced neurological dysfunction (BIND). On the basis of abundant research data and hypotheses, according to our concept, the BIND is a neurodegenerative disease of immature brain caused by accumulation of free metals and UCB-Cu complex (as pro-oxidant) in the BG and other parts of central nervous system (CNS) relevant to BIND. During pregnancy, the estrogen levels rise, greatly increasing the retention of copper in the body. This metal will pass through the placenta into the unborn child. So many children are being born with toxic levels of copper and other heavy metals which were stored in the mother's body. The main comorbidity is the hemolysis. During this process, a great amount of heavy metals may circulate in free form in the bloodstream, and can pass through the blood brain barrier, finding entrance into the CNS and chelate complex with UCB.

Conclusion: It is important to note that there was no intolerance or short- or long-term toxicity of the medication, in spite of the fact that in the newborn period D-PA was used 10-20 times higher doses than those in adult.

Keywords: Bilirubin-induced neurologic dysfunction; Reactive oxygen species; Copper dyshomeostasis; Neurodegeneration; D-Penicillamine in the neonatal period.

Abbrevations: BG: Basal Ganglia; BIND: Bilirubin-induced Neurologic Dysfunction; CNS: Central Nervous System; Cp: Ceruloplasmin; D-PA: D-Penicillamine; MD - Metal Dyshomeostasis; ND: Neurodegenerative Disease; OS/NS: Oxidative/Nitrosative Stress; ROP: Retinopathy of Prematurity; ROS: Reactive Oxygen Species; TB: Total Bilirubin Level; UCB: Unconjugated Bilirubin; WD: Wilson Disease

Introduction

Our recently published case reports [1-3] and other healthy and highly educated patients of the long-term (28-42 years) follow-up suggest that D-Penicillamine (D-PA) therapy of newborn infants may have significant neuroprotective effects in cases jeopardized by bilirubin induced neurologic dysfunction (BIND) or retinopathy of prematurity (ROP). The first patient (43 ys) is now a member of a famous operahouse in Germany as an opera singer, the second one (16 ys) is excellent in music and matematics. In addition, it was our privilage to follow a number of children who are now adults, including sons and daughters of our relatives, colleaques, close friends. They are now highly educated persons working in health care (mostly as physicians), bank, computer and building industry, et cet.

UCB has long been considered as a cytotoxic waste product of heme catabolisms. However, during the last 3 decades a large body of evidence indicated that bilirubin has several beneficial properties [4]. It is much stronger antioxidant than many other agents, including vitamin E, superoxid dismutase and catalase [5-7]. In addition, UCB also exhibits cytoprotective and neuroprotective effects [8] and bilirubin an endogenous scavenger of nitric oxide (NO) and other reactive nitrogen species [9]. Morover, such an endogenous molecule is able to exert antiviral activity *in vitro* [10].

In our recently published review article [11] we have expounded that excessive metal (copper) accumulation in the nervous system may be toxic, inducing oxidative/nitrosative stress (OS/NS), disrupting mitochondrial function, and impairing the activity of numerous enzymes. Damage caused by copper excess may result in permanent injuries, including severe neurological/neurodegenerative disorders (NDs). The immature and strikingly vulnerable neurons play an important role in the pathogenesis of BIND as well. Our concept addresses the medical necessity of chelation therapy with D-PA in the neonatal period, as it is feasible that UCB molecule reviels particular affinity to copper stored in BG of the neonatal brain, where copper-bilirubin complex can be formed [12]. Copper dyshomeostasis and OS have also been concerned in NDs such as Alzheimer's, Amyotrophic lateral sclerosis or Menkes disease. These irreversible syndromes are related with a progressively aggravating lesions of neurons and injury of synaptic junctions in the CNS [13].

Pathological Basal Ganglia Activity [14]

The BG is a collection of large subcortical nuclear masses. It is agreed that core components comprise the caudate nucleus, the nucleus accumbens, the putamen, and the globus pallidus. The caudate nucleus and putamen together are sometimes called the striatum, and the putamen and globus pallidus are together sometimes described as the lentiform nucleus [15,16]. Functionally, the BG has considerable connections to the cerebral cortex, thalamus, and brain stem; so, anatomists consider portions of the thalamus as components of the BG [17]. A literature review was aimed at assisting us (as pediatricians) to provide further understanding with bilateral symmetrical BG and thalamic lesions on magnetic resonance imaging. The high-signal-intesity lesions on T2-weighted images can be caused by edema, gliosis, demyelinization, neuronal necrosis, or cystic degeneration both in Wilson's disease (WD) and BIND [18].

Role of Metals and Oxidative Stress in the Human Neurodegenerative Disorders

The brain (mostly the BG) accumulates among the highest levels of transition metals in the body for normal function, including redox-active copper. This high-redox metal load, in combination with the brain disproportionately active oxygen metabolism, makes this organ particularly susceptible to oxidative stress [19,20]. Metal ions such as calcium, zinc, iron and copper are key players in brain neurobiology; their homeostasis is altered in most ND conditions. The metal dyshomeostasis (MD) in the brain and related organs, and loss of the strict regulation is implicated in neurotoxic stress [21-24] and in a variety of NDs including BIND and prion mediated encephalopathies and other diseases [25-27]. Pathologic changes to the CNS in these disorders are always associated with a significant dyshomeostasis of tissue metals (particularly copper). Excess copper may combine with sulfhydryl, carboxyl, or amine groups, resulting in improper enzymatic activity or damage to cellular structure. Despite the ubiquitous presence of toxic copper within the brain, pathologic findings are limited primarily to the BG, thalamus, and brain stem. Histopathologic studies have shown abnormalities throughout this system in patients suffering from MD. These abnormalities include atrophy, spongy softening, cavitation, a general reduction of neurons, increased cellularity, and the presence of characteristic particles (Opalski, Lewy bodies). The pathologic changes are presumed to result from an increased amount of extracellular copper, which causes OS/NS and results in cell destruction [28]. Many diseases of the BG have some disorder of movement as their primary symptom, ranging from an excess of (abnormal) involuntary movements such as in chorea to a poverty and slowness of movement as in PD, Alzheimer disease and WD as illustrated in several clinical cases [29] and UCB encephalopathy [30] where a characteristic yellow staining can be observed in fresh or frozen sections of the brain obtained within 7-10 days after the initial bilirubin insult. If the affected infant survives the neonatal period and subsequently dies, the yellow staining may no longer be present, but the BG will display microscopic evidence of cell injury, neuronal loss, and glial replacement. Newborns, especially preterm infants, are particularly vulnerable to reactive oxygen species (ROS) because they exhibit accelerated production of free radical and limited antioxidant protection, which increases the susceptibility of rapidly growing tissues to damage. „Free radical-related diseases" of neonates promote cellular, tissue, and organ impairments. In 1988, Saugstad coined the phrase "oxygen radical disease in neonatology" to highlight the crucial role of ROS in a wide range of neonatal disorders [31]. There is now a large body of literature demonstrating that free or weakly bound iron and copper ions may exert their toxic action on BG. In a way, metals may provide the link between protein misfold and aggregation, oxidative stress and the cascade of biochemical alterations, eventually leading to neuronal cell death. Predominantly the cellular content of copper determines copper-induced toxicity in brain astrocytes [32].

Potential Molecular Mechanisms of Bilirubin-Induce Neurologic Dysfunction

The "classic" interpretation of bilirubin neurotoxicity does not give sufficient answers to the following questions: (1) How to call bilirubin: friend or foe? (2) If the bilirubin is really an "enemy", how does it induce its dangerous effects? Erythrocyte morphological changes have been seen with incubation of cells with different molar ratios of UCB. These changes occur as the bilirubin/human serum albumin molar ratio increases. This indicates that bilirubin can illicit toxicity in the erythrocyte membrane in a concentration and temperature-dependent manner, causing hemolysis [33]. The management dilemma for a clinician is that UCB is a beneficial antioxidant at low (and may be at moderatly higher) levels, but a neurotoxin at >20 mg/dL levels ("vigintophobia") [34], where it can impair the normal developmental maturation of the neonatal brain. Among the 23 elements with known physiological functions, 12 are metals (sodium, magnesium, potassium, calcium, vanadium, chromium, manganese, iron, cobalt, copper, zinc, and molybdenum) [35,36]. Copper is essential for the normal growth and development of human fetuses, infants, and children and it is crucial for the normal development of the brain [37] which has among the highest levels of copper, as well as iron and zinc, in the body. Copper is an interesting essential micronutrient. Deficiency and excess intake both induce a variety of clinical manifestations affecting mainly the hematopoietic system, the skeleton, the liver, and the brain. Although copper transport to the fetus

is high and liver storage is efficient, copper export from the hepatocytes to the bile and to blood ceruloplasmin (Cp) are reduced during this stage of life because of liver function immaturity. This leads to a high copper accumulation in the liver and brain, in a magnitude similar to that observed in WD. In fact, an obvious analogy can be observed between the newborns and patients with WD in the field of the copper "(dys)homeostasis". The increased liver and brain copper storage of the fetus may have a selective evolutionary advantage since it may prevent copper deficiency during the first months of life when the child receives a relatively low copper supply from breast milk [38]. In the neonatal period the ability of the liver to synthesize Cp is not fully developed and adult levels of the protein are not found in the blood till about three months of age. It is interesting therefore that the infant liver has a very much higher copper content than is found in the adult and a fall in concentration does not takes place until the ability to synthesize Cp has fully developed [39].

New Concept for Development of Bind

Very wide-ranging studies have long been made on the possible biochemical transformations of UCB, which is formed during the decomposition of haemoglobin. Particular attention has been paid to its photochemical and redox reactions [40] but the relevant publications comprise only a very small proportion of those dealing with the molecular biochemistry of UCB and metals interactions. UCB has a special affinity for the globus pallidus, the hippocampus, and the subthalamic nucleus because they are also target brain regions for divalent metal (Cu, Fe, Zn et cet.) accumulation [41]. Neurodegeneration: a return to immaturity [42]? This question certainly arouses the attention of neonatologists as the immature and strikingly vulnerable neurons play important role in the pathogenesis of BIND. The increased vulnerability of premature infants to brain damage may be due to a proneness of immature nerve cells to toxic stimulus [43]. The developing neurons undergo programmed cell death, a necessary phenomenon for proper nervous system development. Following the developmental period, neurons mature and restrict the apoptotic pathway to permit long-term survival. On the basis of above described abundant research data and hypotheses, according to our concept, the BIND is an ND of immature brain caused by accumulation of free metals and UCB-Cu complex (as prooxidant) in the BG and other parts of CNS relevant to BIND [12]. In strictly biological terms, at least 3 loci exist where UCB and copper can be "fusioned" in the neonatal period: (1) during hemolysis high UCB and copper level can be developed in the blood; (2) one albumin can bind one Cu++ in the primary binding site. At higher concentration of copper (if possible under certain conditions), loosely bound atoms, and can be very easily taken out by UCB. The bile pigment itself can displace loosely bound copper ions, which are electrostatically attached due to high negative charge on the surface of albumin; (3) in the basal ganglia [12,44]. The main comorbidity is the hemolysis of neonatal blood red cells. During this process a great amount of heavy metals (mainly iron and copper) may circulate in free form in the bloodstream, and can pass through the blood-brain-barrier (BBB), finding entrance into the CNS as well. Understanding the differences between neonatal and adult erythrocytes is critical in the evaluation of perinatal erythrocyte disorders. The reason for the reduced red blood cell survival observed in newborns is not known, although there are many biochemical differences between adult and neonatal red blood cells (RBCs) [45,46]. Increased oxidant sensitivity of newborn RBCs and relative instability of fetal hemoglobin have been considered as possible causes for this shortened lifespan. In a chinese study [47] the erythrocyte's copper content was significantly lower in the maternal blood than in the newborn cord blood. The compounds to be bound and transported by albumin are quite diverse and include bilirubin, fatty acids, metal ions and therapeutic agents. Free or loosely bound, redox-active transition metal ions are potentially extremely pro-oxidant, having the ability to catalyze the formation of damaging and aggressive ROS from much more innocuous organic and inorganic species.

Intriguing Points Concerning this Concept

An intriguing point raised in our review is the role of copper in BIND. Copper is a trace element with a very high denitrosylating activity; if present, copper increases NO release from low-molecular-weight S-nitrosothiols, which are considered the "stable" reservoir of "unstable" NO in cells. Copper shares this denitrosylating activity with bilirubin [48].

Along with NO and carbon monoxide (CO), hydrogen sulfide (H2S) is regarded as the third gasotransmitter and endogenous neuromodulator and plays multiple roles in the CNS under physiological and pathological states, especially in secondary neuronal injury [49]. D-PA is really an S-nitrosothiol molecule and it is well known that copper is srongly chelated by this drug [50]. At the same time, DPA is a hybrid drug in the neonatal period by its ability to modulate both oxidative stress and NO pathway. Tataranno et al. [51] have summarized the new body of knowledge about antioxidant drugs for neonatal brain injury. The oxidation of DPA in vivo may also important in the mode of action of the drug through simultaneous reduction of the reactive oxygen species (ROS). So, we can say that D-PA fulfills the criteria of a hybrid drug in the neonatal period by its ability to modulate both OS and NO pathway and can be a neuroprotective agent in the pathophysiology of neurologic dysfunction [52]. It is also obvious that a bilirubin lowering drug (DPA inhibits heme oxygenase (HO) in age related manner, ie. only in the neonatal period) [53] and a thiol containing agent such as D-PA can modulate both ROS and RNS [54]. Administration of very high doses of this drug in neonates, and the fact that we (and others) did not find any adverse effects during short- or long-term follow-up, are sufficient evidence for harmlessness of both D-PA-therapy and a higher generations of free radicals (OS or NS).

Mancuso et al. have published interesting observations [55] indicating an important action of bilirubin on redox signaling by neurotrophins, with either inhibitory or agonistic effects based on growth factor.

It is also unlikely that this effects would assert itself in the neonatal period because of: (1) DPA prevents the pathological increase of serum bilirubin levels; (2) The family of vascular endothelial growth factor (VEGF) and other growth factors (including neurotrophin) are polypeptides consisting of chains linked by disulfide bonds. One of the oldest and well-documented effects of DPA is the splitting of intramolecular or intermolecular disulfide bridges [56].

Through the control of peptide-disulfide regioisomer formation DPA can alter the biological profile of a native peptide by providing a local constraint or cleavage on the adjacent disulfide bond as well as on the global peptide conformation [57].

Further possibility that excessive free radical production, due to both OS and NS, could induce post-translational modifications to biliverdin reductase, the enzyme responsible for UCB synthesis [58,59].

To date the existence and role of this unpleasent phenomenon is still under debate and presenting and discussing the pros and cons on this topic. On the other hand biliverdin is an effective antioxidant as well [60].

Conclusions

The basic role of metal ions in neurological pathologies is generally accepted, — except for the case of BIND. Free copper ion in itself or binding to UCB and forming metal-bilirubin complex(es) involved in neurologic dysfunction, therefore they are important factors for whole brain damage processes in BIND. We hope that our theory will help answer some of the unsolved questions and concerns ocurred in the etiology and pathomechanisms of BIND. The beneficial neuropharmacological actions of metal-targeted (chelating) agents most likely arise from local metal redistribution rather than from massive metal removal [61]. The chelation therapy for non-metal overload indications continues to be investigated. Our present review address the medical necessity of the use of a chelating agent (D-PA) in the treatment of NHBI and ROP.

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