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Review

Iron Overload in the Organism as a Health Problem

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Abstract

Every intervention aiming to supplement a lacking nutrient in the body (or any application of medicine) should be accompanied by the question of whether any such intervention could bring about unsatisfactory changes. Many publications of medical research centres in England, Canada, the USA, Sweden and Germany aim to deal with the problem posed in the title. This paper, based on studied literature, presents some important aspects concerning epidemiology, experimental studies, and clinical observations on iron overload in the body, but only in cases of genetic conditioning - hereditary (primary) haemochromatosis - HH.

Keywords: iron overload, haemochromatosis, genetic conditioning.

Introduction

Thorough studies on iron overload in the body are comparatively recent. Only the eighties brought about the possibility of conducting relevant genetic studies indispensable in diagnosing hereditary haemochromatosis. Moreover, research has so far concentrated mainly on the effects of iron deficiency [5, 8, 14, 37, 38]. According to WHO records, about 2 million people suffer from serious illnesses connected with iron deficiency. However, the effects of iron overload are very seldom noted and are treated by scientists rather as a study of a case rather than a disease which should be taught about at pre/post diploma courses. Also, the clinical symptoms usually present in cases of inborn iron overload are very difficult to recognize for a family physician. The decided majority of HH cases were diagnosed retrospectively. In cases when etiopathogeneses of such diseases as myocardial injury, hepatic cirrhosis, neoplasms, atherosclerosis, diabetes and Parkinson's disease were difficult to establish, the specialistic studies were supplemented with measurements of iron levels and/or genetic studies, indicating the possibility of hereditary haemochromatosis.

The awareness that hereditary haemochromatosis manifests itself usually exclusively in elderly men will help to reduce the anxiety of those physicians who reasonably prevent the effects of iron deficiency, mostly in women and children, through fortifying their diets with iron preparations.

Causes of Iron Overload

Iron overload in the body can be caused by various reasons, which were used by clinicians to work out a following typology [12, 21, 24, 26, 31, 35, 42, 45]:

I. Increased iron absorption:
A. from the diet of normal iron content
   1) inborn haemochromatosis (primary)
   2) cure resistant inborn anaemia (not using iron in erythropoiesis)
   3) chronic degenerative liver diseases
   4) porphyria cutanea tarda
   5) inborn disorders of iron absorption and transport
B. from the diet of increased iron content
   1) permeation of iron from metal kitchen pots into food
   2) endemic malformations of skeleton (Far East), haemosiderosis - Kaschin-Beck's disease.
   3) iatrogenic overdos of iron.

II. Parenteral overdose of iron:
   A. post-transfusion increase of iron level
   B. increase of iron level as an effect of therapeutic injections.

III. Increase of iron level in newborns:
   A. inborn tyrosinaemia
   B. Zellweger's syndrome (cerebro-hepato-renal)
   C. inborn haemochromatosis in newborns.

IV. Focal iron storage:
   A. Spontaneous pulmonary haemosiderosis
   B. Hellervorden-Spat's syndrome (neurological disor-

ders caused by pathologic 4 iron deposition in the nervous system) C. renal haemosiderosis.

Etiopathogenesis of Hereditary Haemochromatosis

This is a genetically-conditioned disease. The hereditary haemochromatosis conditioning gene is localized in the short arm of chromosome IV. Simultaneously, the histocompatibility antigens HLA-A3, HLA-B7 and HLA-B14 are observed to occur. Both the ocurrence rate of that defect and the way it is inherited require a special comment. The subject literature defines those genetic anomalies as occurring in 5-10% of the population and concerning heterozygotic individuals, but they also occur in homozygotic individuals with the occurrence rate of 3-5 cases in 1000 [4, 6, 13, 16, 18, 27, 36, 48].

However, some researchers note that in the populations they studied such disease was a few times less frequent. The literature of the eighties tried to define gene characteristics, sometimes stating that it was recessive, other times that it was dominant. According to recent reports, the disease is known to be inherited autosomally and recessively [53]. Men are affected more often than women in an 8:1 ratio. Although this is a rare disease it seems proper to acquaint Polish physicians with the problem of iron overload in the body, especially that the reports on the subject seldom appear in Polish medical literature [39].

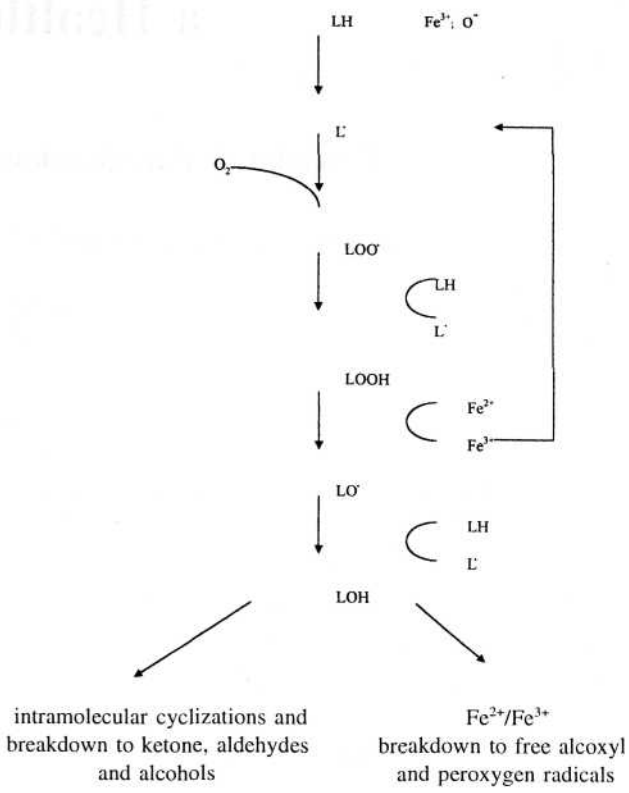
The nature of hereditary haemochromatosis is the excessive accumulation and storage of iron in cells. Such process causes both changes of the structure and functioning of the affected organs, in distinction with haemosiderosis - also causing excessive iron storage but without any changes of structure and functions [10]. In haemochromatosis detection the screening studies assay iron in serum, total iron bonding capability, and the percentage of transferrin saturation. Ferritin assay is conducted during a second phase test [3, 17, 22].

Pathologic symptoms of iron overload can be thus observed both on molecular and cellular levels and in tissues and organs. Clinicians identify hereditary haemochromatosis with the following non-specific pathological symptoms [1,2,15,41,43,46,49,50,54,55]:

- hepatic cirrhosis symptoms
- myocardial injury traits
- pancreas function disorders (resulting in, among others, diabetes)
- endocrine glands function disorders (mainly of the anterior lobe of the pituitary gland)
- degenerative diseases of connective tissue
- hyper pigmentation of skin
- degenerative changes in central nervous system.

From the amount of 3-5 g of iron present in the adult human body about 80% is involved in life supporting biochemical processes (erythropoiesis, O_2 transport, taking part in breathing cycles, the element of enzyme structure, etc.) The remaining amount is stored, among other places, in such protein complexes as ferritin or in scarcely mobilizable haemosiderin supplies. In discussing iron overload, transferrin and lactoferritin can be omitted as they do not take part in pathologic iron accumulation. In cases of pathologic absorption and/or storage of iron, the physiological standard can be highly exceeded (e.g. in liver, where the physiological iron level is lower than 200 µg Fe/g of tissue mass, in case of iron overload this value can increase to 3000-4000 µg Fe/g of tissue mass). The harmful (toxic) effects of increased amounts of iron are identified with the following hypothetical mechanisms:

1) Iron can act as a catalyst of reactions producing excessive amounts of free oxygen and non-oxygen radicals, according to the diagram [44]:



Among oxygen radicals the most important are the superoxygen radical ($O_2^{\cdot}$) and the hydroxyl radical ($OH^{\cdot}$) as well as the radicals of unsaturated fatty acids ($LO^{\cdot}$ $LOO^{\cdot}$). Some of these radicals are catalyzed in enzymatic oxidation reactions together with, among other things, peroxidases and catalases - the iron containing enzymes. According to the most recent reports, the presence of free ions of transient metals, like iron, strengthens the peroxidation process through increasing reactive oxygen forms and also through stimulating desintegration of hydroxyperoxides into the adequate alcoxyl and peroxyl radicals. The aldehydes created along with the disintegration of lipid peroxides are a great threat to the body. From among the aldehyde group, malonyldialdehyde is one of the most toxic [44]. Malonyldialdehyde and the intensity of oxidation processes have been proven to be closely connected. Therefore, malonyldialdehyde is recognized as a sensitive indicator of peroxidation processes. Malonyldialdehyde alone is very active towards biologically important substances, and that can disturb strategic biochemical body reactions (see diagram). It suffices to mention the results of great malonyldialdehyde activity towards lysine carrying two amino groups. Nucleinic acid inactivation can bring about some serious pathologic changes in the DNA and RNA structures [29].

1) In physiological cellular processes the appearance of

free oxygen radicals on a determined concentration level decides about many such important and favourable phenomena, e.g. bactericidal activity in the process of cellular immunity. However, the appearance of excessive concentration of free radicals initiated by the excess of unbound iron can result in cellular pathologies. For instance, free radical excess can disturb fatty acids synthesis which leads to creating the aldehydes mentioned above (malonyldialdehyde). This results in the damage of cell membranes, which in turn causes damage to basic cell structures. The effect of the destruction of the lysosome membrane is a release of digestive enzymes into a cell lumen, which brings about its malfunction or destruction. A similar effect is created by damaging the mitochondria and microsome membranes [9].

2) Another pathologic mechanism identified with ioni zed iron overload is the damage of nucleinic acid struc tures. Iron overload is assumed to be in a sense responsible for neoplasia [7, 20, 44, 47], as are some other metals (e.g. copper). The uncontrolled development of neoplastic tissue can be initiated by the free radicals excess acting mutagenically on nucleinic acids.

3) There are some hypotheses regarding harmful effects of iron overload, e.g. in the pathologically increased col lagen synthesis. Other hypotheses are based on excessive iron release from such albuminous complexes as haemosiderin and ferritin under the influence of ionizing radiation [9, 23].

There are also hypotheses about the disturbance of the natural level of magnetism characteristic in every living organism. However, those assumptions are not based on any reliable empirical material.

4) Many reports on etiopathogenetic studies of Parkin son's disease confirm that hyperactive microglia cells (an element of the brain's immunity system) activate a sequen ce of destructive reactions which result in destruction of the nervous system cells. However, this process is intensified by the iron released by nitrogen oxide and the radicals present [19, 34, 56].

The results of such disturbances at the cellular level can be observed as serious organ disorders. There are reports endeavouring to prove the dependence between detected iron overload and myocardial injury, hepatic cirrhosis, neoplasms, artherosclerosis, hypertension, rheumatic diseases, obesity, and central nervous system disturbances. The processes connected with anoxia of the heart muscle or other organs, as well as hypertension, are explained by the damage of blood vessels endothelium, in which there appears to be excessive lipid oxidation and protein structure disorders [3,7,9,25,28,51,52,56].

No conclusive evidence has been found regarding direct explanation of the connection between iron overload and obesity. Probably there is a sham connection between obesity and high iron levels in the body, because obesity is often a result of a high calorie diet, simultaneously rich in iron [20].

From among all pathologies resulting from iron overload, the hereditary haemochromatosis studies are the most advanced. Genetic research of the disease was conducted in patients showing total iron bonding capability (TIBC) within the range of 200-800 µg/l of serum and serum iron (SI) higher than 150 µg/dl. The hereditary haemochromatosis symptoms were observed almost exclusively in men in their third and fourth decades of life. The results of biochemical studies did not always confirm excessive iron storage in women, even if a genetic defect was found (homozygote). The results of genetically increased iron absorption were neutralized by blood loss processes such as menstruation, pregnancy, puerperium, lactation or miscarriage [50].

The authors of the pre-cited reports pay much attention to factors conducive to the appearance of the clinical symptoms of haemochromatosis; alcohol being mentioned as the most serious [11, 30, 32, 33]. Simultaneously, the social and economical status becomes increasingly important, as in highly developed countries it determines the quantity of haeme iron supplied in food, e.g. through high meat consumption.

Therefore, there appear suggestions of close supervision of diet fortification for people with iron defficiency anaemia so the fortified food and iron preparations would not be taken by persons with genetic haemochromatosis. Similar notices are directed towards clinicians ordering blood transfusions and routinely prescribing iron preparations. A few authors suggest that a thorough iron level examination of the body can be a sensitive indicator of approaching myocardial infarction. Such an examination should be routinely performed in cases of threatening infarctions [40,41].

The methodology of medical research demands that in every case of mass food fortification, any possible effects of such large-scale actions should be taken into account.

The problem can be summed up with the following conclusions:

1) Presented phenomena of hereditary haemochromato sis in full clinical picture are extremely rare. Polish medical literature describes only one case of hereditary haemoch romatosis. Relatively frequent appearances of genetic de fects in the general population are manifested clinically with repeatedly lower frequency, making only a fraction per cent. Considering iron overload as one of many health risk factors, this paper strives to encourage physicians to add iron level examination to other routinely performed laboratory analyses while diagnosing etiopathogeneses of such diseases as diabetes, hypertension or myocardial injury - especially in men in their third and fourth decades of life.

2) The current Polish methods of supplementing iron deficiency with pharmacological preparations are largely incorrect. The majority of physicians prescribe iron prepa rations without any monitoring of iron or absorption levels. This can lead to iatrogenic overdosage of iron or to the lack of an expected therapeutic effect, and can even deepen the existing body iron deficiency.

3) In Poland there is no threat of an increase in the frequency of incidents and intensity of clinical symptoms of hereditary haemochromatosis through excessive food for tification with iron preparations, which western authors caution against. With the exception of a few bakery centres producing iron fortified bread at present no iron prepara tions are added to food. The hereditary haemochromatosis symptoms were diagnosed nearly exclusively in highly de veloped countries, where meat plays a dominant role in nutrition structures. Such conclusion in context with the Polish nutrition model (with food low in iron) means that the estimated number of hereditary haemochromatoses will in all probability be much lower than in western countries, the origin of all the data presented here.

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