Diet therapies: bad communications and useless application in healthy individuals.

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Abstract

Among human diseases based on defect in metabolism of food components, there are cases for which no drug therapy is applicable and dietary restriction constitutes the unique therapy. Accumulation of metabolites or not metabolized compounds determines troubles at different levels, so that a toxic effect is due to a molecule that is innocuous for healthy people. Removal from diet of food containing the "individually-toxic" molecule is the only therapy for such patients. However, it can introduce adverse effects. Therefore, it is damaging the trend to use such diets also when not prescribed by doctors. Among pathologies requiring a "(food-component)-free diet", coeliac disease, galactosemias, phenylketonuria represent examples for which diet that excludes the dangerous food (or food component) is the main or the unique therapy, although drugs or alternatives begin to be in use or tested. Doctor's prescription of such diets as therapy must be rigorously applied by patients, by considering the toxic effects due to accumulation of not correctly metabolized compounds. Galactosemia disease is a family of genetic defects affecting one of the three enzymes involved into the metabolism of galactose. The error in galactose metabolism determines accumulation of galactose, with toxic effects for the patient. This is an inborn gene defect, so that newborns cannot assume food containing galactose; this includes mainly milk, although this is their natural form of nutrition: however, to remove galactose, the correct contribution of calcium and vitamin D is compromised. Alternative food has been defined for galactosemic infants, because the galactose-free diet is considered the only therapy. Similarly, no phenylalanine can be assumed by people affected by phenylketonuria, an autosomal recessive inborn error of metabolism due to deficiency of phenylalanine hydroxylase that prevent the correct phenylalanine metabolism. Removal of food containing phenylalanine implies difficulties in rigorous following the diet, and more relevant, it implies the removal of food containing proteins, with consequent loss of protein uptake and the needs to introduce other amino acids in different way. One of the most known diet is the gluten-free diet, required for celiac disease patients. Also in this case, removal of food containing a given component is required for specific patients; however, this alters the correct contribution of other nutrients that may be not present in alternative food. This means that there is no advantage, and maybe disadvantages to apply some "(food-component)-free diet" without a pathological state and a clear prescription as therapy.

In the following paragraphs we will discuss aspects related to some diet that requires the removal of specific food components.

Keywords: Metabolism, Diet, Protein.

Accepted on 15 February 2018

Galactosemia and the Galactose-Free Diet

Galactosemia (OMIM 230400) is an autosomal recessive disorder of galactose metabolism. The incidence of galactosemia is 1 in 30,000-60,000, therefore, it is classified as a rare disease. The most common form, or classical galactosemia, is caused by deficiency of galactose-1-phosphate uridyltransferase (GALT; OMIM 606999) activity. Other forms are cause by galactose epimerase deficiency (OMIM: 230350) and galactokinase deficiency (OMIM: 230200). Our resarch group has contributed to investigate molecular aspects of these forms [1-3] and we address readers to such publication of other literature references for details about this disease [4,5]. Early diagnosis or pre-natal diagnosis is crucial. Galactosemic newborns after milk introduction, may present symptoms as failure to thrive, poor feeding, diarrhea, renal failure, epatic failure. Without dietary treatment, these patients can also exhibit a progressive liver or kidney failure, sepsis or shock with consequent death in the neonatal life. Galactose-restricted diet usually resolves these acute symptoms, however, high percentage of galactosemic patients develop long-term complications. This is a specific reason to apply the galactose-free diet only in case of galactosemia diagnosis and doctor's prescription.

Phenylketonuria and the Phenylalanine-Free Diet

Phenylketonuria (PKU) is an autosomal recessive inborn error of metabolism described for the first time by Asbjørn Følling in 1934. PKU (OMIM 261600) and less severe hyperphenyalaninemia (HPA) constitute the most common inborn error of amino acid metabolism caused predominantly by mutations in the phenylalanine hydroxylase (PAH) gene. PAH gene encodes phenylalanine hydroxylase (PAH), a hepatic enzyme that requires the cofactor tetrahydrobiopterin (BH4), molecular oxygen and iron to convert Phenylalanine (Phe) into Tyrosine [6], a non-essential amino acid involved in the synthesis of a variety of biologically important molecules such as epinephrine, norepinephrine, dopamine, tyroid hormones and melanin pigment.

The position and nature of the mutation dictates its effect on the activity of the PAH enzyme, which determines the hyperphenylalaninaemia phenotype of the patient [7]. On the basis of blood Phe concentrations, PAH deficiency is classified into: classic PKU with little or no enzyme activity, mild PKU, and mild HPA partially inhibits enzyme activity. Therefore, a deficiency in PAH or its cofactor BH4, results in the accumulation of exceeding phenylalanine which is toxic for the organism [6]. High levels of Phe during brain development (infancy, childhood, adolescence) can cause, if untreated, severe and irreversible intellectual disability, autistic behaviours, motor deficits, eczematous rash, convulsion, microcephaly, growth failure. Furthermore, decreased or absent PAH activity can lead to deficiency of Tyr and its downstream products. The mechanisms by which high Phe levels result in intellectual impairment is not clear yet, but seems involve the hypomyelination and demyelination [8].

PKU is the most common inborn error of amino acid metabolism, though frequency varies widely in the world; 1:10,000 in Caucasians and with the highest incidence being in Northern Europe [6]. 1:2600 in Turkey; 1:100,000 in Japan [9]. In Australia, approximately 25 babies are diagnosed with PKU each year [Hafid and Christodoulou, 2015]. Finland has the lowest prevalence in Europe with 1:100 000. In the USA the prevalence is 1:15000. In Latin America it varies from about 1:50000 to 1:25000 births; prevalence is generally higher in southern Latin America than elsewhere in that region [7].

Actually, there is no therapy for PKU, however, the prevailing treatment is the Phe restricted intake through the diet, begins immediately after confirmation of hyperphenylalaninaemia in a neonate. Patients with PKU must undertake the phenylalanine-free formula [7]. So, foods rich in proteins such as meat, fish, eggs, standard bread, most cheeses, nuts, and seed and drinks containing aspartame, flour, soya, beer, or cream liqueurs are excluded from the diet. Low-protein natural foods such as potatoes, some vegetables and most cereals can be eaten but only in severely restricted amounts. Low-protein variants of some foods exist, such as low-protein bread and low-protein pasta. The required amount of daily protein is largely obtained from manufactured, commercially available phenylalanine-free protein substitutes. However, there are often issues associated with dietary therapy, including non-compliance due to poor palatability, and various social problems due to financial burden for the cost of special medical foods [6]. Additionally, potential nutritional deficiencies occur, especially concerning vitamin B12, vitamin D, calcium, iron, and long fatty acids that may result in neurological problems and bone density-related issues [10]. In this contest, it is needed to find alternative therapies for PKU that could be used safely and efficiently in all PKU patients. There have been continuous attempts at improve the quality of medical food including content, palatability and practical use of the products. Treatments that representing a good response in PKU patients are: intake of glycomacropeptides (GMP) and the use of large neutral amino acids (LNNA). GMP is a protein derived from cheese whey that is naturally low in Phe, and is rich in valine, isoleucine and threonine. This protein with the addition of essential amino acids tyrosine, tryptophan, arginine, cysteine and histidine can be a useful adjunct to the Phe restricted diet patients [6]. The concept behind LNNAs treatment is that they share with Phe the same amino acid transport system across the blood-brain barrier, creating a competitive inhibition of the transportation of LNNA with each other, large amounts of LNNA may block the transport of Phe in the brain and in this way, the high neurotoxic concentration in the brain is reduced. This treatment is applied in PKU patients which are off dietary therapy that have the high levels of Phe in the blood [10]. In patients with atypical PKU, that is due to mutations that cause defects in BH4 synthesis and recycling, the tetrahydrobiopterin therapy can be applied. This therapy consists in the assumption of sapropterin dihydrochloride (Kuvan, BioMarin Pharmaceutical, Novato, CA) a pharmaceutical form of BH4 [11]. Treatment with the cofactor BH4 or sapropterin in BH4 responsive PKU patients has proven successful in significantly increasing Phe tolerance allowing patients to alternate their diet and in some cases discontinuing the Phe free diet at all [6]. Unfortunately, for 90% of patients with classical PKU, BH4 therapy has no beneficial effects. Other therapies that involve gene therapy, enzyme therapy and probiotic therapy have been experimented on mice, so other studies are need in order to ascertain the safety of these approaches.

Gluten-Free Diet

There are different conditions for which doctors can prescribe the gluten-free diet. The most common is Celiac Disease (CD), an autoimmune disease which leads, in case of gluten assumption, to many gut damages, to impairs nutrients absorption and to many symptoms as anemia, bloating, diarrhea, nausea and constipation. Currently, adherence to a gluten-free diet is considered the first line and indeed only therapy for CD, which has been proven to relieve the symptoms in most cases and effectively prevent potential complications [12]. Although classified in the past years as a rare disease, CD has registered a great spread during these last years, also thanks to the development of new diagnostic methods; nowadays 1% of the European population is affected by this pathology (data AOECS) and in the USA the percentage is almost the same (CBS News reported). Actually, is possible to say that CD occurs in about 1% of the population worldwide, although most people with the condition are undiagnosed [13]. However, the last published data about the

gluten-free market and trade show that the global glutenfree retail market has grown from $1.7bn in 2012 to $3.5bn in 2016 and is forecast to grow to $4.7bn in 2020, according to Euromonitor, the consumer data group (Financial Time font). This high request cannot be explained by the assumption that the reason of all this business volume is due to a client portfolio composed only of Celiac patients. Actually, the gluten free-products are bought not only by people affected by coeliac disease but also by the so called “gluten sensitive”, it means those people who are intolerant to gluten, without having Celiac Disease or a wheat allergy (NCGS). These individuals may have similar gastrointestinal symptoms as the Celiac patients, but no damage to the intestinal tract nor will they develop complications associated with Celiac Disease. However, even if the number of the people affected by NCGS is growing because of their more efficient identification, and that this number is estimated to be greater than the number of Celiac patients, is still not possible to find an accurate percentage of this population. Another important little slice of gluten-free products consumers is composed by the individuals affected by Dermatitis Herpetiformis, Gluten Ataxia or Wheat Allergy. Dermatitis Herpetiformis (DH) or Duhring-Brocq disease is a chronic bullous disease characterized by intense itching and burning sensation in the erythematous papules and urticarial plaques, grouped vesicles with centrifuge growth, and tense blisters. It is an IgA-mediated cutaneous disease, in fact at the top of the dermal papilla of both affected and healthy skin it is possible to find in a granular pattern immunoglobulin A deposits. The same protein IgA1 with J chain is found in the small intestinal mucosa in patients with adult celiac disease, suggesting a strong association with DH. Moreover, specific antibodies such as antiendomysium, antireticulina, antigliadin and the epidermal and tissue transglutaminase subtypes, are common to both conditions, Celiac Disease and DH. Because of this, the chosen treatment is dapsone and a gluten-free diet [14]. A gluten-free diet is also necessary in people affected by Gluten Ataxia, an immune-mediated disease triggered by the ingestion of gluten, in genetically susceptible individuals [15]. This pathology affects cerebellum and therefore causes problems with muscle control and voluntary muscle movement. Differently from the celiac disease, wheat allergy is a food allergy. It is due to an undesirable response of the immune system against gluten or some other protein found in wheat as a disease-causing agent. Generally, food allergic reactions to wheat can give way to an array of clinical manifestations that can range from immediate to delayed, and their strictness can vary from mild to life-threatening. Typical immediate symptoms include erythema, pruritus, eczema, gastrointestinal reactions, oropharyngeal symptoms, urticaria, angioedema, AD, rhinitis, asthma, and anaphylaxis [16,17]. The protein content in wheat is 10%-12% and eliminating wheat from diet completely for celiac patient would mean the exclusion of a very good protein source. Gluten-free cereal foods are frequently rich in carbohydrates and fats and they are made using refined gluten-free flour or starch not enriched or fortified [18]. As a result, many gluten-free cereal foods do not contain the same levels of B-vitamins, iron and fiber as their gluten-containing counterparts [19]. Further studies have also demonstrated as there is a significantly lower contribution of folate from bread consumed by coeliac patients than from that consumed by the general population, whilst they ate bread to a similar extent, moreover, these studies have also underline as, in adult coeliac patients on a strict gluten-free diet for years, it is possible to observe the raise of total plasma homocysteine level. This last aspect not only is indicative of a poor vitamin status, but it may also imply an independent increased risk for cardiovascular disease in the same range as hypercholesterolemia and hypertension [20]. For these reasons, the gluten free diet must be applied only under doctor’s prescription.

Popularity of Diets and Related Risks

While galactose-free diet is not applied by healthy people, the low-protein intake and the gluten-free diet are more diffuse. PKU is a serious pathology that compels patients to intake low-protein foods, which implicates side effects on health due to nutritional deficiencies, as previously described, so requiring an adequate supplement of amino acids. Daily intake of amino acid, and in particular of essential amino acid, that the human organism can’t synthetize from other molecules, is necessary in order to avoid a general physical deterioration. For example, without proteins, the muscles loose mass and functionality, the glands work inefficiently, the production of hormones is compromised and more or less important endocrinological imbalances are established, the blood proteins decrease, the body prone infectious diseases, fertility is reduced. Unfortunately, some way of thinking imposes to exclude proteins, and animal proteins in particular, from daily diet also in healthy subjects, as lifestyle choice rather than for doctor’s prescription. While on-line proposal in the past years suggest that iper-proteic diets could help to lose body weight, nowadays a campaign against proteins for the human organism is being carried on, without scientific support. Some theories wrongly believe that the human organism is unable to assimilate the animal proteins, so they tend to eliminate such proteins from the diet. Instead, in order to live healthy the human organism has to intake in balanced quantities the macronutrients, i.e., carbohydrates, fatty and proteins, together with vitamins and minerals, in most cases conjugated to macronutrients. So healthy nutrition presupposes that proteins cannot be excluded from a balanced diet, unless doctor’s prescription.

Among the three examples we report here, the gluten-free diet is more known and, unfortunately, bad communications reach people without a correct awareness of the role of this diet. Even if there is a relevant percentage of people that for different pathologies must remove gluten from their diet, as mentioned before, these categories cannot be responsible of the exorbitant increasing of the glutenfree market. Actually, those who really drive the sales of gluten-free is the part of consumers, in constant increase, who choose gluten-free foods for a personal food style, regardless of intolerance to this protein. An American study has underlined as about 1.8 million Americans are affected by celiac disease, but also that on the flip side, about 1.6 million people in the U.S. are on a gluten-free diet even though they haven't been diagnosed with celiac disease [21]. This trend has not spare the Europe, the

Financial Time journal with an article of the 30 April 2017 on the basis of the European forecast and Euromonitor data, explains that "gluten-free foods have been consumed for years by people suffering from coeliac disease...however, demand has now widened beyond medical need as food intolerances have become more widely accepted and more people opt for "free-from" and "clean-label" products — a category that encompasses organic and GM-free foods — as a lifestyle choice". In the society of the followers and the influencers, one of the things which can have a huge impact, above all for the youngest generations, is of course the presence of celebrities who avoid gluten for non-medical reason and release public declaration about this topic exhorting to follow their example. An article of the daily newspaper the Guardian, titled "Grain drain: should everyone adopt a gluten free diet" underline exactly this aspect reporting the declaration of some international stars and trying to bring to the attention of the public opinion some important studies and scientific researches that explain why gluten-free for non-celiac patients is not synonymous of healthy. In conclusion, as the gluten-free diet is something that involves more people than we can imagine and is a topic of huge impact for several aspects whether economic or healthy, other "food-component"- free diet could become popular and applied without real motivations. The diet and nutrition cannot become a trendy affair, and should be strongly recommended to avoid dietary choices not correctly defined by experts.

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