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Advantages and disadvantages of glycomacropeptide therapy for phenylketonuria compared with traditional diet therapy

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Abstract. Phenylketonuria is an autosomal recessive disease for which there is no cure, which has a lasting adverse impact on patients' lives. At present, only two treatment methods have been widely used in clinical practice, one is traditional long-term low protein diet therapy, the other is glycomacropeptide therapy. However, the two methods have defects such as poor food palatability, poor patient compliance, and unclear immunity. Therefore, it is particularly important to explore the potential advantages and complementary advantages of the two widely used methods to improve patients' lives. This paper mainly applies the research method of literature review to explore and analyze the advantages and disadvantages of traditional diet therapy and glycomacropeptide therapy. The conclusion of this study is that in order to benefit the existing PKU patients to a greater extent and improve their quality of life and treatment effect, traditional diet therapy should be given priority, supplemented by glycomacropeptide therapy, and the two dietary plans should be implemented in parallel, so as to achieve better results. In addition, do not use the two treatment schemes in isolation.

Keywords: phenylketonuria, glycomacropeptide, phenylketonuria therapy, low protein diet.

1. Introduction

Phenylketonuria is a rare autosomal recessive disease. The pathogenic principle is phenylalanine hydroxylase (phenylalanine hydroxylase (PAH) deficiency or insufficient activity, or its coenzyme tetrahydrobiopterin (BH4) deficiency, leading to benzene that cannot be normally converted to tyrosine. The disease is caused by excessive accumulation of alanine (PHE) in the body [1], which can cause mental disorders such as mental retardation, backward language development, and somatic symptoms such as epilepsy and eczema. The quality of life and viability of patients were severely impaired. Therefore, for patients with phenylketonuria, one of the current mainstream treatment options is long-term low protein diet therapy, and the other is GLYCOMACROPEPTIDES (GMP) therapies. There are also other therapies such as tetrahydrobiopterin therapy, phenylalanine ammonialyse, PAL), large neutral amino acids, LNAA), gene therapy [2]. Because this disease is incurable, and other treatment schemes other than the mainstream scheme are still in the clinical trial stage or cannot be applied to all patients, such as the large neutral amino acid method, which is currently only recommended for adult patients, and the phenylalanine ammonia lyase method, which is still in the clinical trial stage, has not been widely used because it is easy to cause adverse reactions in patients after

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treatment. Therefore, there is still a large room for improvement and development of the two treatment schemes that can be promoted at present, so as to improve the quality of life of patients, reduce the cost and risk of treatment, and improve the compliance of the scheme. Through comparative study and literature review, this paper aims to analyze the advantages and disadvantages of long-term low protein diet therapy and glycomacropeptide therapy, and provide treatment suggestions for patients with phenylketonuria nowadays.

2. Pathogenesis of phenylketonuria

The pathogenesis of phenylketonuria is exemplified by classic phenylketonuria (PKU), which is caused by phenylalanine hydroxylation (phenylalanine hydroxylase (PAH) gene mutation. This gene is located on the long arm of chromosome 12. The gene is 79.28kb long, has 13 exons, and the mrna2681bp encodes a polypeptide composed of 451 amino acids. More than 600 mutations have been found, and more than 100 mutations have been found in Chinese. This enzyme is abundant in hepatocytes [3].
98% - 99% of PKU patients are due to hepatic phenylalanine hydroxylase (PAH) gene mutations, 1% - 2% of patients are due to tetrahydrobiopterin (BH4) deficiency, Lead to phenylalanine (PHE) metabolism disorder. Under normal conditions, Phe is converted to tyrosine under the action of liver PAH and the cofactor BH4. In any case, PAH or BH4 deficiency will lead to a large amount of Phe that cannot be hydroxylated to tyrosine, making Phe transaminate with a-ketoglutarate to produce Phenylpyruvate. A large amount of pyruvate accumulates in blood and tissues and is excreted in urine. The metabolites of Phe produce toxicity in central nervous system accumulation disease, which will produce irreversible nervous system damage without treatment. In addition, tetrahydrobiopterin deficiency (bh4d) is a special phenylketonuria not caused by abnormal PAH function. The pathogenic mechanism is different from that of classical type [4].

This therapy uses special medical formula food containing casein glycomacropeptide as a beneficial supplement to the daily diet of phenylketonuria patients.

3. Glycomacropeptide therapy

Casein glycomacropeptide (cGMP Caseinoglycomacep tide) is a bioactive peptide derived from bovine casein. In the process of cheese production, chymosin cuts off the PHE (105) -met (106) site of casein to form insoluble paracasein and soluble casein polypeptide (cmp:glycomacropeptide). The content of CMP in whey protein is second only to β- Lactoglobulin and α- Lactalbumin, which accounts for 15% - 25% of the total whey protein (whey protein accounts for 0.6% - 0.8% of the total milk protein), usually contains many sugar chain groups, so it is also known as glycopolypeptide; The glycopeptides from casein are collectively called casein glycomacropeptide (CMP) [5]. Since CMP contains almost no aromatic amino acids (amino acids that can not be degraded in patients with phenylketonuria), such as phenylalanine, but rich in isoleucine, threonine, isoleucine and other amino acids needed by the human body. Artificial foods containing CMP can be used as one of the ideal foods for patients with this disease, which can not only avoid the phenomenon of food intolerance, but also supplement the nutritional ingredients that are missing in their daily diet. At present, CMP food has been used in the daily treatment of patients.

Compared with traditional diet therapy, CMP has the following advantages. First, CMP special food has better palatability and richer variety. At present, American scholar kyungwha Lim and others have successfully developed a variety of snacks with good taste and a wide range of categories, such as strawberry chips, strawberry pudding, chocolate and orange drinks [6]. This kind of medical food is close to the taste of normal people's daily food, the quality of life of patients is significantly improved, and it is easier to follow medical diet therapy for a long time. In addition to taste, CMP is rich in complete protein, which meets about 70% of human daily needs, so it can give patients a higher sense of satiety. And through the prebiotic properties of glycomacropeptide itself, it can effectively improve the intestinal anti-inflammatory ability and strengthen bone. Studies have shown that diet containing glycomacropeptide reduces the acid load of patients' kidneys and reduces the metabolic pressure of patients. However, if glycomacropeptide therapy needs to be implemented on a large scale, there are

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several defects. The first is that CMP preparation technology is not yet mature and cannot be commercially produced on a large scale. At present, the mainstream preparation principle of CMP is to extract directly from whey, enzymatically hydrolyze casein, and finally produce casein glycomacropeptide. There are mainly the following production methods: chitosan adsorption method, precipitation method, aqueous two-phase system, enzyme crosslinking method, ultrafiltration method and ion exchange method [7]. However, the above methods all have the defects of low yield, low product purity and high production cost. For example, the main principle of CMP preparation by aqueous two-phase system method is to separate CMP from raw materials by electrostatic force in alkaline environment using the different selectivity of CMP between two water phases. This process consumes a large amount of water for industrialization, and industrial wastewater cannot be reused, thus causing serious waste of water resources. And after separation, the purity of the product is low and the yield is less. In addition, due to the chemical properties of CMP, such as cumbersome separation process and difficult purification, CMP research is relatively rare in China and slightly more in Europe and the United States. At present, only davisco Foods International in the United States, tatua co operative dairy in New Zealand, Arla foods ingredients in Denmark and a Japanese company can produce CMP products with a purity between 70% and 90% and realize industrial production. [8]. However, the production scale is still far from meeting the potential huge market demand. For the time being, there is no business in China that has realized the independent industrial production of CMP, and it needs to completely rely on foreign imports. The second defect is that this therapy is still immature, lacking clinical safety data for long-term consumption, and its immunity is not clear. If it needs to be used in the treatment of PKU patients on a large scale, there are still potential safety hazards.

4. Traditional dietary therapy

This method means to limit the intake of phenylalanine in patients' daily diet for a long time, so as to reduce the accumulation of phenylalanine in their body to relieve symptoms. In general, PKU long-term dietary therapy, the patient's food is divided into two kinds. One is natural low protein food. Most of the naturally occurring food materials contain high protein content in meat, eggs and milk, and low protein content in fruits and vegetables, so they contain less phenylalanine. This kind of food is cheap, widely sold and easy to obtain, accounting for the largest proportion in the daily diet of patients. Second, special low protein foods, including free amino acid formula powder made by mixing artificially purified amino acids other than phenylalanine and adding other necessary nutrients, and low phenylalanine foods processed by hydrolyzing natural protein, removing aromatic amino acids from the hydrolysate through adsorption, ultrafiltration and other processes, such as special low protein foods including low protein grains, bread, rice, cakes, cookies, flour Chocolate, energy bar, jelly, ice cream, dairy substitute, pasta and other types [9].

Traditional diet therapy has the main advantages of high social acceptance, popularity and low cost, and is currently the most common and effective PKU treatment. According to Huang Wenliang and others' experiments, among 73 children with PKU, their thinking ability, adaptability to the environment and learning ability have been improved after low phenylalanine diet therapy, and the detection rate of gastrointestinal adverse reactions such as diarrhea and vomiting was 10.8%, which was lower than 33.3% in the control group (another group of children without this therapy) [10].

However, there are also some aspects of traditional dietary therapy that need to be improved. The first is the limited variety of natural low protein foods and the poor taste of artificial special low protein foods, which reduce the quality of life of patients and lead to poor treatment compliance. The second is that the traditional diet therapy leads to the deficiency of some essential nutrients, resulting in malnutrition of patients, and the frequent occurrence of dysplasia in growing patients. For example, vitamins and minerals are generally deficient and unsaturated fatty acids are deficient. Hildegard and other researchers have proved that [11], patients with PKU may be deficient in vitamin B12, vitamin D, iron, zinc, selenium and other micronutrients [12]. Because unsaturated fatty acids mainly exist in high protein foods, such as meat, eggs, and milk, and patients with this disease should avoid ingesting such

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foods, most of them lack -3 polyunsaturated fatty acids. In addition, patients receiving low protein diet therapy have a lower ability to synthesize endogenous fatty acids than healthy people. Studies have proved that the concentration of n-3 unsaturated fatty acids (especially DHA content) in the plasma and serum of children with PKU is lower than that of normal children [13], so they are more prone to fatty acid deficiency.

5. Discussion

In conclusion, the two most mainstream methods for the treatment of phenylketonuria, traditional diet therapy and glycomacropeptide therapy, have certain advantages and disadvantages. For traditional dietary therapy, its main advantages are that patients generally accept it, the treatment cost is low, and the detection rate of digestive system adverse reactions is low. Its disadvantages are that the types of synthetic and natural low phenylalanine foods are limited, and the taste is poor, which leads to frequent phenomenon that patients are unwilling to comply with the treatment. In addition, due to the limited natural food categories available to PKU patients, some essential nutrients cannot be obtained from daily meals, resulting in malnutrition, dysplasia and other symptoms. For glycomacropeptide therapy, because CMP is rich in chemical components, it can supplement the nutrients missing from the daily diet of PKU patients without causing adverse reactions. Compared with traditional synthetic low Phenylpyruvate food, CMP special medical food has better taste, richer categories, is easy for patients to accept, significantly improves their quality of life, and improves patients' treatment compliance. However, at present, there are still technical obstacles in the industrial preparation of casein glycomacropeptide, resulting in low product yield, low purity and large-scale supply. In addition, the technology of CMP as a medical product is not yet mature, and its immunity has not been confirmed by experiments. Therefore, there are still potential safety hazards for large-scale clinical treatment. Therefore, in order to effectively improve the quality of life of patients with phenylketonuria and relieve their symptoms to the greatest extent, we should adhere to the traditional diet therapy combined with glycomacropeptide therapy, so that the two methods complement each other and complement each other, and the curative effect will be more comprehensive. This enlightens people that in the clinical practice of the treatment of existing PKU patients, the expectation of obtaining more comprehensive curative effect is not necessarily pinned on the invention of updated medical technology, but more need to consider the combination of existing multiple treatment schemes, and reasonable and flexible use on the basis of considering drug compatibility, so as to complement each other.

6. Conclusion

The conclusion of this study is that in order to maximize the benefits of existing PKU patients and improve the treatment effect and quality of life, traditional diet therapy should be given priority to, supplemented by glycomacropeptide therapy, so as to promote patients to avoid malnutrition and enjoy delicious formula food. In the process of exploration, the research method of this paper has certain limitations. Only using the literature review method, the arguments obtained are all from previous years' literature, lacking the scientificity of clinical research and experimental support conclusions. Moreover, some references were published too old, and the views and experimental conclusions involved may no longer be valid. In the future research on phenylketonuria therapy, the research center can be shifted to the combination and implementation of existing treatment methods to explore the possibility of multi therapy parallel.

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