AN INTRODUCTION TO NUTRITIONAL TREATMENT IN INBORN ERRORS OF METABOLISM – DIFFERENT DISORDERS, DIFFERENT APPROACHES

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Abstract. Treatment of metabolic disease aims to restore homeostasis, where possible. This can be achieved in a number of ways. For disorders of intermediary metabolism, treatment involves a thorough understanding of the disorder and the pathogenesis of the deleterious effects The various approaches indicated may involve substrate restriction, replacement of deficient products, removal of toxic metabolites or stimulation of residual enzymes. Newer therapies include enzyme replacement and gene therapy. Often, the cornerstone of treatment is dietary. Substrate restriction includes not only a diet low in the substrate indicated by the disorder, but also strict calorie support in times of illness to avoid catabolism. Useful levels of substrate restriction may require the use of supplements of "medical foods", for example amino acid mixtures. Provision of the deficient products is important in disorders affecting energy metabolism. To understand the problems involved in nutritional treatment it is helpful to consider examples of different types of disorders. In Maple syrup urine disease (MSUD), treatment with a very strict low-protein diet, supplemented by a branched-chain-free amino acid mixture is successful, but each intercurrent illness is hazardous, regimens for sick days vital, and strict lifelong treatment is needed. Treatment for phenylketonuria is similar in restricting a substrate but there is no tendency for systemic illness if the phenylalanine levels are too high. Disorders of the urea cycle are difficult dietary challenges because while a very low-protein diet is required, no specific amino acid needs to be avoided and there is a fine line between adequate protein intake and chronic catabolism. Fatty acid oxidation disorders affect energy production and can be detected by newborn screening using tandem mass spectrometry. For long-chain fatty acid disorders, long chain fats must largely be avoided and medium-chain fats must be substituted while strictly avoiding catabolism. Glycogen storage disorders require strict attention to providing carbohydrate, at all times including throughout the night. Many patients with inborn errors do not need any specific dietary therapy, (eg those with storage or neurodegenerative disorders), although all children benefit from an optimal diet, and sick children need this especially.

INTRODUCTION

The general aim in the treatment of metabolic disorders is to restore homeostasis by correcting the metabolic imbalance. This can be achieved in several ways including substrate restriction, replacement of deficient products, removal of toxic metabolites or blocking their production, stimulation or stabilization of residual enzyme activity and enzyme replacement therapy. More recently, gene therapy has begun to be achievable, but sometimes of course there is no useful therapy. This article discusses in an introductory way those aspects of management in which nutrition plays a major role.

The effects of an enzyme defect are well understood (Fig 1). In a normal pathway, a substrate is converted to a product or products by the action of an enzyme and perhaps a number of cofactors. If either the enzyme or cofactor is defective then there will be a build-up of substrates or further upstream compounds, a deficiency of immediate product or further downstream compounds, and alternative pathways may be activated, with an increase in products which are not normally present in significant quantity. Sometimes these products interfere with other reactions.

Dietary treatment is often a major factor in the management of disorders of intermediary metabolism as they are often susceptible to either substrate restriction, provision of deficient products, or a combination of these perhaps with the addition of pharmacological quantities of cofactor.

PHENYLKETONURIA AS A MODEL

The archetype inborn error of metabolism might be considered to be phenylketonuria. While the disorder was elucidated in 1934, the very first description of successful treatment was in a Lancet article in 1953 by Bickel, *et al.* In the early 1950's Professor Bickel was working in Birmingham, UK, and was interested in phenylketonuria. This preliminary communication in the Lancet described the influence of phenylalanine intake on phenylketonuria. He tried his experiment with a girl aged 2 who was severely affected. "She was an idiot and unable to stand, walk or talk; she showed no interest in her food or her surroundings, and spent her time groaning, crying and banging her head." After a good deal of trial and error a product was produced in which phenylananine had been removed from a casein hydrolysate. At first, phenylalanine deficiency was produced when the diet was used. Later, when a small amount of phenylalanine was added into the diet in the form of whole milk, biochemical findings were greatly improved and, more excitingly, this girl's behaviour changed. She stopped crying and banging her head, and she made motor progress, starting to walk for the first time. To make sure that the study was blinded to the observer (but in a way that would probably not now be considered ethical) phenylalanine at a normal level was reintroduced into her diet without her mother's knowledge. Within a short time she lost all the gains she had made in the previous 10 treated months. To prove the value of the special low-phenylalanine diet this experiment was repeated in the hospital with the full knowledge of the child's mother, and the same sorts of results were obtained and a treatment had been found for phenylketonuria.

Phenylketonuria is a good model for the general approach of substrate restriction. There is an elevated substrate, phenylalanine, and evidence that lowering the substrate produces clinical benefit. Whilst there are many papers which describe the clinical benefit of phenylalanine restriction there has been no randomised control trial of precisely this question. Smith *et al* in 1990 showed that the average phenylalanine concentration in a cohort of treated children born in the United Kingdom between 1972 to 1980 was closely correlated with a reduction in IQ score. The IQ fell progressively by about 4 points for each four weeks' delay in starting treatment, and for each 300 μmol/L rise in mean phenylalanine concentration. If the phenylalanine level had been maintained at 360 mmol/L or below, the IQ score was similar to the population norms whereas at an average phenylalanine concentration of approximately 900 mmol/L the mean IQ scores were

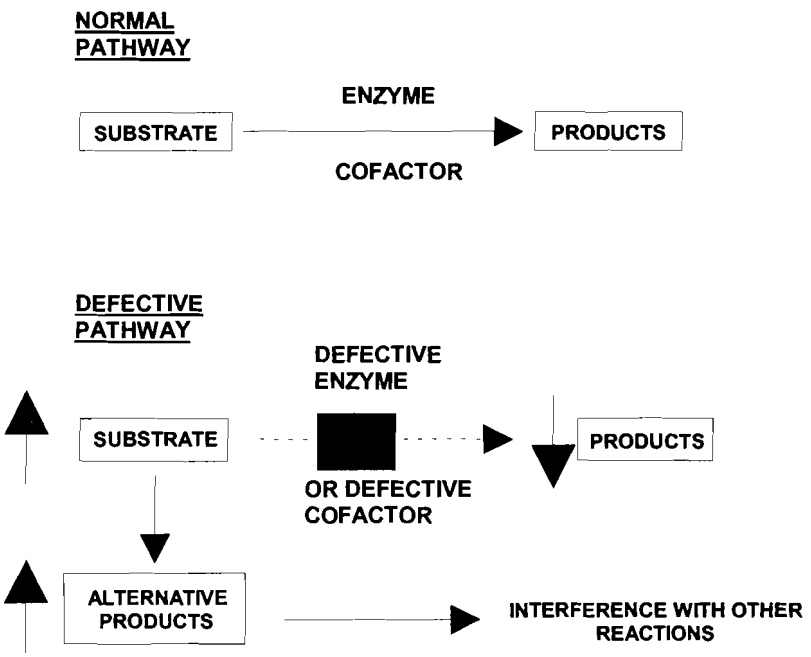

Fig 1. Effects of an enzyme defect.

more than 1.5 standard deviations below the population. In order to lower phenylalanine, a low protein diet and an "unbalanced" supplement containing a normal spectrum of all amino acids except for phenylalanine must be provided. A low-protein diet alone will not ensure sufficient lowering of phenylalanine levels, as it will cause catabolism. Early treatment of phenylketonuria ran into just the troubles described in the preliminary communication of Professor Bickel. Children were inclined to become phenylalanine deficient or have other vitamin and mineral deficiencies which produced various complications including rashes and other skin disorders. These can be prevented by measuring blood phenylalanine regularly, and modifying the diet according to the blood phenylalanine level.

Phenylketonuria is caused by deficiency in the enzyme phenylalanine hydroxylase. If we continue with the model in relation to elevated levels of phenylalanine we find that some proportion of patients have a disorder not of phenylalanine hydroxylase but of the pterin cofactor, tetrahydrobiopterin. Several different disorders produce a BH4 deficiency and in this case the treatment is different, in part because the cofactor is also a cofactor for other enzyme activities. Replacement of neurotransmitters and of BH4 itself as a medication often negates the need for any nutritional alteration.

The model of substrate restriction in the treatment of inborn errors of metabolism provided by phenylketonuria can be applied to several other disorders including homocystinuria due the cystathionine synthase deficiency and tyrosinemia type 2 (tyrosine amino transferase deficiency). Another example is maple syrup urine disease. Here the restriction is of the branched chain amino acids leucine, isoleucine and valine. The difference between maple syrup urine disease and phenylketonuria from a treatment point of view is that high levels of the affected amino acids can, in the case of MSUD, cause life-threatening decompensations. Thus treatment must be meticulous every single day and emergency treatments and sick-day regimens are of particular importance.

UREA CYCLE DISORDERS AND ORGANIC ACIDEMIAS

Substrate restriction is more difficult in the urea cycle disorders, and in certain organic acidemias because there is an overall need to reduce protein, but usually no indication to reduce intake of any individual amino acid. In urea cycle defects, there is loss of ability to excrete sufficient excess nitrogen, which leads to an accumulation of glutamine and ammonia. The results may be cerebral edema, coma, brain damage and death. Here the nutritional treatment is reduction of the substrate, nitrogen, by means of a low protein diet, but including enough of all essential amino acids. Non-protein calorie support is essential and additional strategies include the provision of product – either arginine or citrulline or both, and medication with "ammonia sinks" compounds which enable the excretion in the urine of additional nitrogen. In these cases the challenge for the nutritionist is great, and there is a fine line between decompensation caused by too much nitrogen, and catabolism caused by too little. The problems are many. These patients need a generally low protein diet and while specific amino acid supplements are not relevant, some of the protein, perhaps half, can be given as essential amino acids, which is a nitrogen-sparing strategy. Such patients often have very poor appetite and there is considerable danger of a chronic catabolic state. Special regimens for days when the patient is sick are vitally important.

PRODUCT SUPPLEMENTATION

Product supplementation is often important. In some of the amino acid disorders already mentioned, this is part of the overall treatment strategy. Additional tyrosine is given in the amino acid supplement to phenylketonuric patients, additional cystine probably required by homocystinuric patients, and as already mentioned, additional citrulline and arginine required by the different urea cycle disorders. Product supplementation however is the **main** nutritional strategy in several disorders. Obvious examples include the glycogen storage diseases. Provision of glucose as complex carbohydrate is the mainstay of treatment as in these disorders glycogen cannot be released from the liver to supplement circulating glucose. Supplementation is required around the clock, and nighttime feeding is needed. This is often best achieved using uncooked cornstarch, because the release of glucose is slow, and it may be possible to maintain a normal level of blood glucose for 6 hours or more after a dose of 1.0 to 2.0 g/kg body weight of uncooked cornstarch in water. Avoidance of simple sugars is also necessary, and daytime use of more palatable slow-release carbohydrates is also used in a complex dietary regimen.

FATTY ACID OXIDATION DISORDERS

Another group of disorders which depend heavily for their management on nutritional therapy are the fatty acid oxidation defects. The most common of these is a disease of medium chain fat oxidation, medium chain acyl coA dehydrogenase (MCAD) deficiency. Here, catabolic stress may cause hepatic encephalopathy. Strictly speaking, diet is not necessary, but a strategy for avoiding fasting,

(which prevents the body's needing to use the deficient product, ketones) is important, and the nutritionist here can provide valuable advice. In the group of disorders of long chain fatty oxidation, nutritional therapy is much more complex. There must be substrate restriction – severe restriction of long chain fats, which comprise virtually all the fats in a natural diet – and product supplementation with medium chain fats, and then careful attention to the intake of essential fatty acids. Here, of course, avoidance of catabolism is also a key feature.

SUMMARY

Diet therapy is a major part in the management of many inherited metabolic disorders. Understanding the biochemistry is vital for the intelligent application of nutritional strategies, and avoidance of catabolism is a key feature at all stages of treatment. The partnership between the nutritionist and the metabolic physician is essential for the good care of patients with disorders in intermediary metabolism.

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