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Metabolic Mistakes

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METABOLIC MISTAKES

From a dissertation given by M. Higgins, B.Sc.

For many physicians the inborn errors of metabolism represent a somewhat esoteric group, unlikely to be encountered in clinical practice. Many more diseases have been added to the list of "inborn errors" in the last few years and these diseases can no longer be considered as rarities.

The concept of "inborn errors of metabolism" was introduced by Sir Archibald Garrod in 1908, when he suggested that four metabolic disorders:

albinism
alcaphenuria
cystinuria
pentosuria

had certain features in common.

These features were four in number.

1. The onset of symptoms or signs could be traced to the first few weeks of life.

2. A familial tendency was noted in many cases.

3. These diseases were relatively benign in nature.

4. In many cases the disease showed itself in the progeny of consanguineous marriages.

Before consideration of the clinical aspects of some of these diseases it is valuable to discuss the genetic principles involved in inheritance of disease and its expression within individuals.

Classically genetic defects are transmitted by one of three modes of inheritance.

Namely, as (1) autosomal dominants; (2) autosomal recessives; (3) sex-linked characters.

In dominant inheritance most of the individuals affected are heterozygous for the abnormality. Occasionally however, two affected individuals will mate and produce an offspring who is homozygous for the trait concerned. Such an individual usually has a more severe form of the disease than either of his affected parents.

A recessive gene will only be expressed in individuals who are homozygous for the condition.

As a general rule the following findings suggest a recessive mode of inheritance.

1. The great majority of the affected persons are the offspring of parents who are normal in outward appearance.

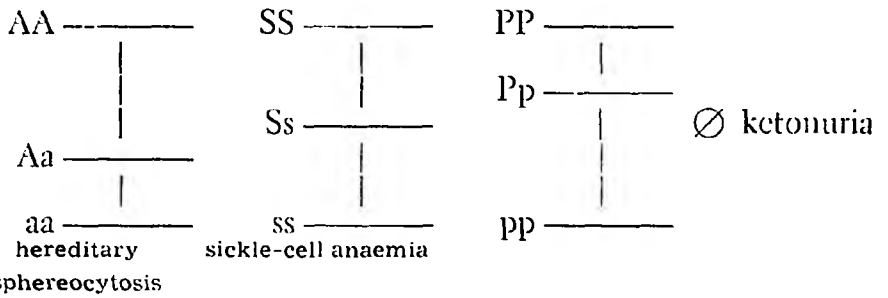
2. The condition tends to affect the siblings in a family, but does not usually affect parents or offspring unless there is intermarriage between close blood relatives.

3. There is an undue proportion of consanguineous marriages among the parents of affected persons. Thus consanguinity occurs in about 80 per cent. of the parents of phenyl-ketonuries, which is considerably higher than the one per cent. seen in the population as a whole.

The classical example of a condition transmitted by sex-linked inheritance is that of haemophilia. Since haemophilia is a recessive trait the offspring, if female will show no clinical disease, but can transmit the abnormality to her male offspring who will display all the stigmata of the disease.

FACTORS AFFECTING EXPRESSION OF GENES

I. It should be emphasised that genetic conditions are seldom completely "dominant" or completely "recessive". This is best illustrated by the following examples :—



In hereditary spherocytosis the heterozygote has anaemia, spherocytosis, increased red cell fragility and all the characteristics of the clinical disease. The homozygote with the two abnormal genes (aa) occurs rarely, but upon investigation of such an individual, his condition is little different from that of the heterozygote — except that the haemolytic process may be a little more severe. Yet, although clinically similar, the genetic make-up is quite different and the condition is regarded as being transmitted as a "dominant".

In sickle cell anaemia the heterozygote (Ss) has about 40 per cent HbS + 60 per cent HbA in the blood. This places it as intermediate between the affected homozygote (ss) and the normal (SS). Such conditions may be regarded as being neither completely dominant nor completely recessive.

Finally in ∅ ketonuria the heterozygote Pp is almost normal in every way. Such patients may have some difficulty in handling large amounts of ∅ alanine as compared with the normal individual (PP).

Thus genetic conditions only appear to be dominant or recessive, depending upon how well one can distinguish between the heterozygote and the normal and the heterozygote and the homozygote with two abnormal genes.

II. While genes are regularly transmitted they are not always expressed in an individual. Thus in some conditions an abnormal trait may "skip" a generation, and only careful study will show some minor degree of the abnormality in the "skipped" generation.

III. A trait which is truly inherited need not necessarily be present at birth but may appear later in life (despite Garrod's original comments upon the nature of inborn errors). The most tragic example of such a disease is probably that of Huntingdon's chorea in which the individual develops marked mental deterioration with involuntary movements etc. at the age of 30 - 40 years.

EXPRESSION OF THE INBORN ERRORS OF METABOLISM

It is not possible to discuss here the mechanism of protein synthesis and gene reproduction. Let us consider, however, a known example of the primary effect of a gene upon a specific molecule within the body.

This may be illustrated by considering sickle-cell anaemia. As mentioned earlier it is known that in this disease two forms of haemoglobin are present

in the blood of affected individuals — HbA + HbS. Now the exact gene responsible for the presence of HbS cannot be identified as yet.

However, on analysis of the globulin moiety of both HbA + HbS it can be shown that there is a difference of one amino acid only, i.e.

HbA - Hist - Val - Leu - Leu - Thre - Pro - Glu - Glu

HbS - Hist - Val - Leu - Leu - Thre - Pro - Val - Glu

This simple difference has far reaching effects on the I.E.P. and hence the solubility of HbS is much less than the solubility of HbA, with the resultant tendency to haemolysis of red cells containing HbS and the stigmata of sickle-cell anaemia.

So far only protein molecules appear to be involved in the primary gene effects of the hereditary disorders.

CLASSIFICATION OF INBORN ERRORS

It is convenient now to classify inborn errors as to the way in which they express disturbances in protein molecules. Three main types may be distinguished according to Hsia.

1. Disturbances in the structure of the protein molecules whereby there appears to be a change in the actual shape or arrangement of the molecules themselves.

2. Disturbances of synthesis of the protein molecule whereby an enzyme is not properly made, or may be entirely absent.

3. Disturbances in the function of the protein molecule, where an enzyme is either absent or not functioning properly.

It is obvious that any classification is highly tentative and until we have more information regarding the "gene effect" then no definite and accurate classification will be possible. Space allows only of the description of a few of these diseases and we may now consider some of those disturbances due to enzyme defects or malfunction.

These represent for most of us the "classical" inborn errors of metabolism and best known among these are the defects in the metabolic pathways of the aromatic amino-acids.

The normal pathways of phenyl-alanine and tyrosine metabolism are shown in Fig. 1 and the site of enzyme defects by Roman numerals.

I. ∅ ketonuria is a hereditary condition, characterised by mental retardation and the presence of phenyl-pyruvic acid in the urine. Nearly 400 cases have been reported since the first cases were described by Folling in 1934.

Clinically, the children found to be suffering from this disorder are noted for their unusually attractive features in infancy. Unlike many mental defectives they show only a slight reduction in stature and head size. Many of the children have blonde hair, blue eyes and a fair skin. A few show a tendency towards developing eczema.

Neurologically no change in muscle here can be demonstrated, but there is an accenuation of both the deep and superficial tendon reflexes. The majority of patients have an I.Q. of 30 or less.

PATHOGENESIS

As indicated ∅ alanine is normally converted to tyrosine by the enzyme ∅ alanine hydroxylase.

Mitoma et al. have shown that two protein fractions are involved in this reaction; a labile fraction I, which is present only in the liver; and a more stable fraction II, which is present also in the kidney and heart. The system requires DPNH and the overall reaction appears to occur in one step with no intermediates.

Recent studies have shown that in ∅ ketonuria fraction II is present in the tissues in normal amounts and that the disease occurs because of a deficiency of fraction I in this enzyme system.

An excessive accumulation of ∅ alanine in the blood and CSF thus results.

This has three effects.

1. Excess ∅ alanine is converted by a transaminase to ∅ pyruvic acid which is converted to

∅ acetic acid
∅ lactic acid
∅ actetyl glutamine

and excreted in the urine.

2. The excess ∅ alanine also inhibits the normal pathways of tyrosine metabolism. There is a fall in melanin production, and this is responsible for the light pigment in the skin and hair of such patients. There is also a disturbance in adrenaline production, since ∅ ketonuries have unusually low blood adrenaline levels.

3. The amino acid excess may also be responsible in some way for the CNS damage, which is characterised by mental retardation, epileptic seizures and abnormal E.E.G. changes.

Diagnosis can now be established early in life by the simple screening procedure using phenistix (effectively, acidified ferric chloride).

Treatment is based upon a diet free of ∅ alanine consisting of a protein hydrolysate.

Associated with ∅ ketonuria as a disorder of the aromatic aminoacids is tyrosinosis, first described in 1932 by Medes.

In the patient described, there was a continuous excretion of P-OH-∅ pyruvic acid, but no other clinical signs. Recently, Felix and his co-workers have made similar observations on two patients with liver disease. The mode of transmission of tyrosinosis is completely unknown and the disease itself is extremely rare. In 26,000 reducing urines tested not one gave a positive reaction to Millon's test.

Tyrosinosis appears to be due to a congenital absence of the liver enzyme P-OH-∅ pyruvic oxidase, which requires glutathione and either vitamin C or dichloro-phenol-indophenol as cofactors. If the protein intake increases or dietary tryosine is increased the amount of P-OH ∅ pyruvate in the urine will increase. The following substances also appear in the urine.

Tyrosine
∅ lactic acid
3.4 D.O.P.A.

On the other hand if homogentisic acid is fed to the patient P-OH-∅ pyruvate does not appear in the urine i.e. the block is at site II in Fig. (1).

No treatment is required for this condition.

The third condition associated with the aromatic amino-acids is that of Alcaptonuria, which is characterised by the excretion of homogentisic acid in the urine.

Apart from the discolouration of the urine, there are no clinical manifestations until the second or third decade, when ochronosis begins to appear. This consists of ochre-like pigments in various parts of the body.

The deposits are particularly prominent in the sclera on either side of the corneal limbus, in the ears and nasal cartilages, and in the superficial tendons of the hand.

By the time such patients reach middle age they usually complain of pain and stiffness in the large joints, owing to a deforming arthritis. X-ray examination shows the presence of thin, densely calcified intervertebral discs.

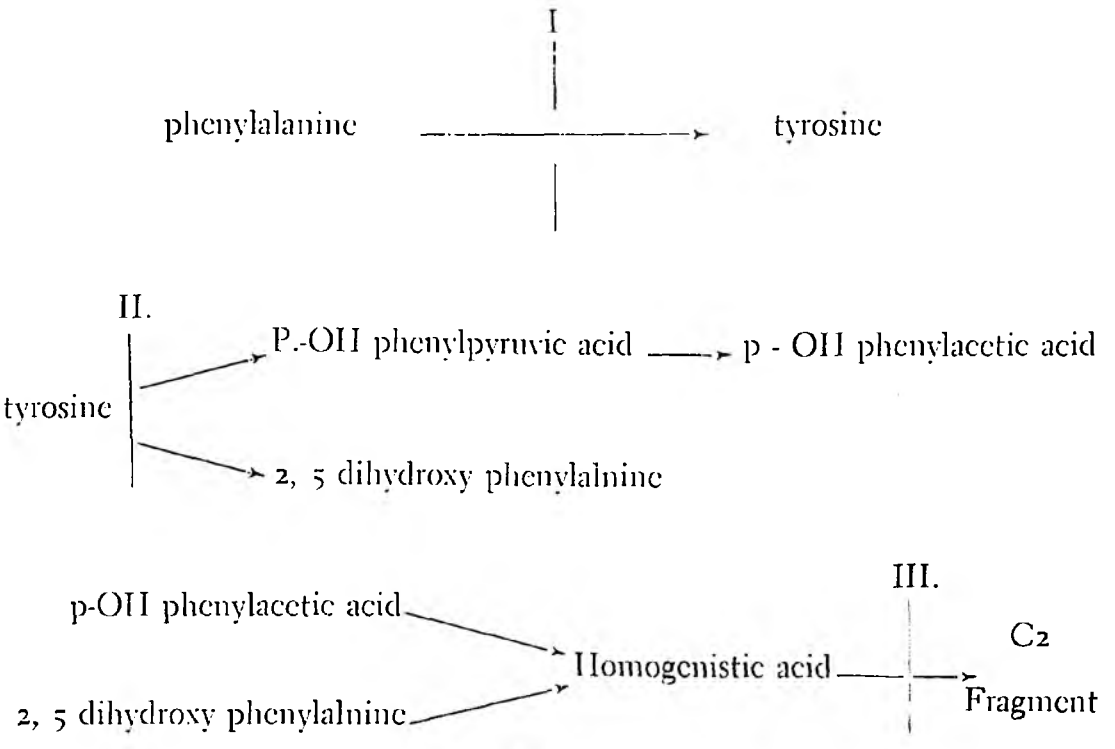


Fig 1.

In most cases alcaptonuria is transmitted as an autosomal recessive trait, but in some instances it appears to be transmitted as a simple dominant. In these families the affected individuals must be regarded as heterozygous for the condition.

It would thus appear that there are two types of alcaptonuria, which are not related to each other. As yet it is not known whether the two types are alleles or at different loci on the same chromosome.

As the feeding of homogentistic acid to alcaptonurics results in almost quantitative recovery of that substance from the urine, it is postulated that the block exists as shown at site III in Fig (1). This has recently been confirmed in a patient with alcaptonuria.

The treatment of this condition is confined to the symptomatic treatment of the arthritis.

Albinism, as the name implies, is characterised by a complete absence of pigment in the skin, eyes and hair. The pupils appear to be red and the iris is pink or bluish from reflected light.

Astigmatism
Photophobia (are present in varying degrees)
Nystagmus

The hair is fine and white or very pale yellow in colour. The condition is transmitted as a simple recessive, as is shown by the fact that 20 - 30 per cent. result from marriages between cousins.

The pathogenesis of albinism appears to be due to the absence of the enzyme tyrosinase from the melanocytes of the skin.

These pigment-producing cells have been shown to be present in normal amounts in such patients, but the enzyme's absence ensures no melanin is produced.

The action of tyrosinase is :

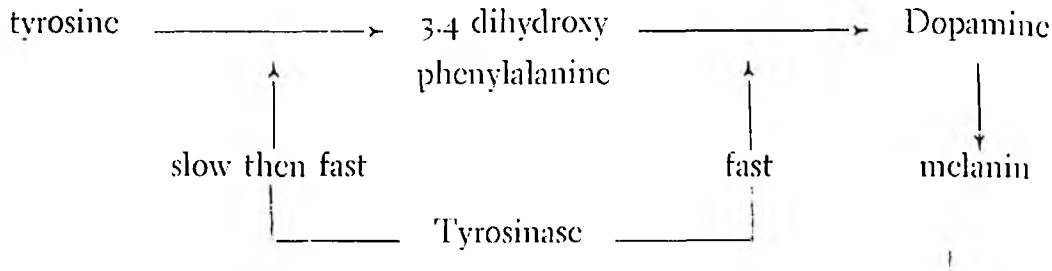


Fig. 2.

Tryosine is not converted to DOPA in the absence of Tyrosinase and absence of the enzyme results in a complete block.

Clinical examination is usually sufficient for diagnosis and treatment consists of prevention of exposure to sunlight and proper protection of the eyes by dark glasses.

The classification of diseases used in this artcile was taken from "Inborn errors of metabolism" by Hsia published by Year Book Medical Publishers Inc.