PHENYLKETONURIA: REPORT AND DISCUSSION OF THREE CASES

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During more recent years biochemical methods of investigation have enabled us to gain a deeper insight into the nature of certain types of defective mental development. This work signifies a comparatively new approach towards a better understanding and even a possible solution of some of the many hidden problems of mental retardation. In this manner a few cases of defective mental development have been crystallized out of the large group of primary amentia and have been found to be associated with or even caused by errors of metabolism of a specific nutrient or substrate. Work on these novel lines continues and will no doubt throw more light on conditions of mental defect.

In accordance with the major metabolic substrate involved, these disorders have been classified under the following headings:[1,2]

1. Errors of protein metabolism represented by phenylketonuria, H-disease, and hepatolenticular degeneration (Wilson's disease).

2. Errors of carbohydrate metabolism represented by galactosaemia, idiopathic hypoglycaemia, and gargoylism.

3. Errors of fat metabolism represented by the group of familial amaurotic idiocies, Niemann-Pick's disease, and Gaucher's disease.

4. Disturbances of hormone synthesis represented by familial sporadic cretinism with goitre.

5. Cases of probable defective metabolism such as idiopathic hypercalcaemia of the infant, Lowe's disease, pitressin-resistive diabetes insipidus, and congenital familial non-haemolytic jaundice.

On none of these types of mental deficiency accompanied or caused by metabolic anomalies has more attention been focussed than on phenylketonuria, probably because of its easy mode of diagnosis by a simple urine test, because of the hope it holds forth of responding to treatment, and because it is the most frequent and best defined representative of this group of metabolic syndromes.

About 7 years ago, Dr. E. H. Welsh, then a member of the medical staff of the Alexandra Institution for the Feebleminded, and Sister van Zyl, now assistant matron at the institution, conducted a preliminary investigation into the existence of phenylketonuria among the inmates, and found only one case. Recently I undertook a systematic search for this condition among 888 patients of the same institution (including 707 White cases of mental deficiency and 181 non-White mentally disordered patients with psychoses such as schizophrenia, manic depressive and epileptic psychoses and dementia paralytica); 3 cases of phenylketonuria were found among the 707 mentally defective patients, and none among the psychotic patients. A possible 4th case was the clinically suspected familial case who had been a patient here for many years until her death 8 years ago.

As far as I know only one case of phenylketonuria has hitherto been recorded in the South African medical literature (Braude[3]).

CASE RECORDS

First Case

The strange fact that the urine of this patient, the very first of all the 888 urines examined for this investigation, should have been positive for phenylketonuria, is not entirely due to coincidence, for he is one of a group of 4 patients whom, for certain physical features present in them, I had selected as likely cases of this condition.

He was admitted to this institution as a certified mentally defective patient on 23 June 1946 at the age of 3 years. His weight was then 36 lb. (normal average 31¼ lb.), his height 41 inches (normal average 35 inches), and his state of nourishment good; he was well developed and all his tendon reflexes were within normal limits, but his gait was described as slightly uncertain. His WR was negative.

Unfortunately a proper history of his case has been unprocurable. As far as can be ascertained there is no mental abnormality among members of his family. The first note in his case-sheet, dated 24 June 1946, is instructive: 'His appearance is not unpleasant, he is quite well formed, has fair hair and blue eyes and lacks any of those signs characteristic of special forms of amentia. He is clearly mentally backward for a child of his age, is emotionally unstable and cries and screams on very slight provocation; his vocabulary is limited to 'Papa' and 'Mama'. He has outbursts of uncontrollable, violent temper, when he mutilates himself and hurts others within reach. He is almost completely helpless and nearly everything must be done for him.' On admission, and for 13 years thereafter his condition had been diagnosed as primary amentia, simple type, idiocy (according to the classification of Tredgold sr.). The examiner was obviously puzzled by the patient's pleasant appearance, blue eyes and fair hair. Until fairly recently no attention had been paid to phenylketonuria at this institution, and the possibility that this patient was a phenylketonuric had therefore not been considered or even vaguely contemplated. During the 13 years of his hospitalization his mental condition has remained stationary, and his conduct as unruly as ever. His intestines were repeatedly infested with round worms, and he often had most obstinate attacks of microscopically confirmed amoebic dysentery.

At present he is 16 years old, his weight 81 lb. (normal average 123¾ lb.), and his height 60 inches (normal average 65¾ inches). Even the senior nursing staff are impressed by his white skin, blue eyes and fair hair. Brown marks, the size of a sixpence to a shilling, which he has in his skin on the back of his hands and on his legs, are attributed to blisters; in his case-sheet notes he is described as 'rather subject to sunburn'. He has healthy and normally spaced and aligned teeth. The tendon reflexes of his upper extremities are brisk, those of his lower extremities very brisk. He has moderate talipes varus. As the result of the deformity of his feet, and probably also of the increased tendon reflexes of his lower extremities, his gait is slightly impaired and suggestive of spasticity. His posture has a tendency to flexion. He is so constantly restless, that he is on the move nearly all the time, either running about wildly and aimlessly or performing the same movements over and over again in rhythmic fashion, such as rocking his trunk backwards and forwards when in a sitting position, bouncing a big rubber ball and each time with remarkable skill jumping high to catch it without fail, or suddenly spinning his body round its long axis, etc. He is a typical example of phenylketonuria.

Second and Third Cases

As these two cases, both females, are also fairly typical instances, and their full description would in some respects be just a repetition of the preceding, only the essential points of their condition will be mentioned. There is nothing in their case-histories to throw light on a possible cause of their disorders. They are both certified mental defectives, the one with an intelligence level of feeblemindedness (IQ 67), the other an idiot with IQ 22. They both have been in this institution for many years.

The case of feeblemindedness, now 47 years of age, is a quiet, reserved, very good and pleasant, hard-working person, who spends much of her time attending to the helpless low-grade patients. She has an attractive appearance, with fair hair, blue eyes and a delicate skin. Her late sister, an imbecile, probably also a phenylketonuric, was a patient here.

The other patient of our series is a very restless, resistive, apprehensive, highly tensed, helpless idiot. She too has fair hair, very blue eyes and a delicate skin. As a baby she had bad eczema of the face, and her father is hypersensitive to sun-rays. She is a very healthy, strapping, pretty girl. Her mother's urine reacts normally to the ferric-chloride test.

All 3 of our cases had until quite recently been classified as instances of simple primary amentia only, without further specification, until by the application of the ferric-chloride test to their urines, they were found to be typical phenylketonurics.

DISCUSSION

The diagnosis of simple primary amentia which constitutes about 70% of all cases of mental deficiency and which sometimes is arrived at only by a process of exclusion did not always satisfy. It was felt that in some of these cases there must be another factor involved, apart from the genetically determined abnormality of the germ plasm. Continued investigations shed some light on this problem, when in 1934 Følling, a Norwegian biochemist, found that the urines of certain low-grade cases of mental deficiency developed a green colour on the addition of ferric-chloride solution. This reaction is caused by the presence of phenylpyruvic acid, which is the breakdown product of the amino-acid phenylalanine, and normally is not present in the urine. Følling named those cases in which the urine behaved in this manner 'imbecilitas phenylpyruvica'.

His observations were soon confirmed by others, and Penrose named the condition phenylketonuria; it is also known as phenylpyruvic amentia or oligophrenia. Phenylketonuria is a variety of simple primary amentia associated with or, as some believe, actually caused by an error of protein metabolism. The disorder is produced by a recessively inherited inability, possibly of the liver, to supply a sufficiency

of the enzyme that is necessary for the oxidation of the amino-acid phenylalanine, which in the normal person is almost entirely converted into tyrosine. In the phenylketonuric the blocking of this process results in the accumulation in the blood, tissues and cerebrospinal fluid, of phenylalanine and its products of incomplete inoxidation such as phenylpyruvic acid, phenyllactic acid, phenylacetic acid and others, which are considered to have a toxic effect on the functions of organs such as the brain. Others again believe that phenylketonuria is caused by the inability of the tissues to utilize certain metabolites.

Phenylketonuria usually presents no special clinical manifestations by which it can be distinguished from the ordinary simple variety of primary amentia. Occasionally, however, its diagnosis can be suspected by the presence of an assemblage of fairly characteristic physical features, sometimes, it is claimed, aided by an aromatic odour given off by its victims and their urine; but the presence of phenylketonuria can be conclusively determined only by the application of chemical tests to the urine and blood.

The test generally used, because it is so simple, easily performed and at the same time highly sensitive, is to add about 10 drops of a 5% solution of ferric chloride to about 5 c.c. of urine acidified with a few drops of dilute sulphuric acid; if the urine develops a light apple-green colour which rapidly turns deep-green, then the diagnosis of phenylketonuria is confirmed. In cases where a sample of urine is unobtainable, as with babies, we make use of the diaper test,[4] in which a drop of a 5% ferric-chloride solution is placed on the urine-soaked diaper; the test is positive for phenylketonuria if a grey-green or blue-green spot appears, and negative if the spot is yellow. In this investigation the diaper test was modified by first applying a drop of dilute sulphuric acid and then on top of it the drop of ferric-chloride solution. The results of these tests were all so convincingly negative that, in spite of recently raised doubts about the reliability of the test, there did not exist the slightest reason to question the findings in the 41 cases on which it was done in the investigation.

Apparently, by means of the phenylalanine tolerance test and the phenylalanine-tyrosine ratio, one is able to detect heterozygous carriers.[5]

As phenylketonuria and its abnormal constituents of the urine are present at birth,[6] and as it is one of the few instances of mental deficiency where medical treatment actually holds forth some hope—but only if it is tackled thoroughly and early enough—and as its diagnosis can be confirmed so easily by means of the ferric-chloride urine test, it is most important to perform this test on the urine of every newborn child as soon as possible after its birth. It should be repeated several times at intervals of a few weeks to check the findings of the previous urine tests and to control the effect of dietary treatment if this has been instituted; and also because there have been instances where phenylpyruvic acid has not been persistently present in the urine, although in most cases it is excreted constantly.[17] Recent investigations conducted on affected siblings of known cases of phenylketonuria appear to indicate that the blood level of phenylalanine begins to rise between the 2nd and 6th week of life, and therefore it is recommended that the urine should be tested for phenylketones at the age of 3 weeks and again at 6 weeks, and treatment started at about the same time, if positive.[8,9]

If the result of the urine test is in any way doubtful, the case should be referred to a biochemical laboratory for a confirmatory test with dinitrophenylhydrazine, and preferably also a quantitative estimate made of the phenylpyruvic acid in the urine and of the phenylalanine in the serum.

Levy and Perry[9] found the incidence of phenylketonuria to be 0·693% among the intellectually retarded they had examined.[10] Jervis found a total of 161 cases among 20,300 defectives in various institutions of the USA.[11] Phenylketonuria occurs about once in 25,000 births.[2] As stated above, at the Alexandra Institution 3 cases of this condition were traced among the 707 mentally defective inmates (0·43%) and none among the 181 non-White mentally disordered patients.

Evidence of hereditary origin is present only in one of the cases of phenylketonuria; her late sister, a certified mental defective of imbecile level of intelligence was an inmate of the same institution and, although the pathognomonic ferric-chloride urine test had not been performed, yet sufficient clinical evidence was present (such as blond hair, blue eyes, fair delicate skin and athetoid movements) to make her condition suggestive of phenylketonuria.

The grade of intelligence of phenylketonuria is usually not higher than that of imbecility (in about 70% of the cases) or idiocy (in about 30% of the cases),[10] although more recently a few instances, probably not exceeding 0·1%,[12] with an intelligence approaching the normal range, have been reported.[12-15] Among the cases traced here, one is feeble-minded (IQ 64) and the other two are idiots (IQ 22 and 4 respectively).

In phenylketonuria there seems to exist a connection or correlation between the degree of metabolic error, i.e. the total daily output of phenylpyruvic acid, and the severity of mental defect.[12]

A fairly well defined constitutional body make-up was found in a large number of patients afflicted with phenylketonuria, in some instances sufficiently pronounced to suggest its diagnosis. About 77% have blue eyes, fair hair and hyperactive tendon reflexes.[9] Our 3 cases are all characterized by this dilution of the colour of their eyes, hair and skin and by neurological manifestations like brisk tendon reflexes. One case displayed spasmodic contractions of the head; another had athetoid movements. All these neurological manifestations are attributable to lesions of the extrapyramidal system.[10] They all have pleasant, attractive facial features. With the exception of deformed feet in one instance, all 3 cases of our series are physically well developed and very healthy.

In none of them has there been any evidence of mental deterioration during many years. Investigations seem to indicate that the intelligence of most phenylketonurics deteriorates rapidly during the first months of life, so that at about 12 months a state of imbecility or idiocy is usually reached, and thereafter mental deterioration is only very slow.[9]

As mentioned above, phenylketonuria is one of the very few conditions of mental deficiency—the others are those associated with cretinism, galactosaemia and ideopathic hypoglycaemia, with the very remote possibility also of mongolism, —which, as recent investigations have shown, actually hold forth hope of being amenable to treatment if carried out efficiently and early enough to forestall irreversible damage to the brain. The treatment is to put the patient on a

phenylalanine- and tryptophan-restricted diet. In a few cases of phenylketonuria which were recently treated in this manner very pleasing results were obtained. A list of references to this dietary treatment is given at the end of this article.

That in addition to the knowledge, although still very fragmentary, which we have of the prevention of certain types of mental deficiency, we can now actually apply medical treatment, with hopeful results, to a few varieties of defective mental development, is a remarkable achievement, particularly in view of the firmly fixed attitude of defeatism and negativism hitherto generally adopted. This new development, which is still a faint glimmer on the distant horizon, is bound to stimulate continued and still more intensified efforts in this direction.

SUMMARY

Three cases of phenylketonuria are described and discussed.

OPSOMMING

Drie gevalle van fenielketonuria word beskryf en bespreek.

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