

PHENYLALANINAEMIA OR CLASSICAL PHENYLKETONURIA (PKU) ?

In the past screening programmes for PKU were carried out in mental institutions on a selected population with brain damage. FÖLLING's ferric chloride test was used to demonstrate phenylpyruvic acid in the urine, but was only effective when the phenylalanine blood concentration exceeded 15 mg⁰/₀, thus introducing a second selective factor into the screening. In recent years more sensitive and specific screening tests have been developed, such as GUTHRIE's and MCCAMAN's and ROBIN's permitting phenylalanine estimations from 1mg⁰/₀ upwards in a few drops of blood. These new screening techniques have been used to test millions of newborns for PKU. In this wider and less selected sample various "phenylalaninaemias" (syn. hyperphenylalaninaemia) have been discovered, due to unknown causes, thus raising a number of diagnostic problems.

The original description of PKU was based on older children and adults who generally exhibited severe mental retardation, phenylalaninaemia of over 20 mg⁰/₀ and an excessive excretion of phenylalanine, phenylpyruvic acid and other phenolic compounds in the urine. Family investigations revealed siblings with similar clinical manifestations, though some "atypical" cases with milder oligophrenia and/or biochemical changes were also discovered and were classified as "for-

mes mineures" or "formes frustes" of the same disease. Especially confusing were the rare cases whose intelligence was normal, but with phenylalaninaemia below or well above 20 mg⁰/₀ and urinary phenolic compounds missing or just as elevated as in their severely retarded siblings with classical PKU. On the other hand patients of preschool and school age of very low intelligence have been described, whose phenylalanine blood levels were below 20 mg⁰/₀ and whose ferric chloride reaction was repeatedly or constantly negative, and who had siblings with classical PKU.

The discrepancy between clinical and biochemical symptoms in certain patients with PKU has been known for many years and has remained unexplained. It has become a matter of great practical concern since mass screening of newborns has been started in many countries. Has every infant with raised phenylalanine blood levels classical PKU and should it be put on a phenylalanine-restricted diet without delay to prevent brain damage? In this issue MENKES and HOLZMAN describe the GUTHRIE test results of some 55 000 infants in Maryland of whom 37 had phenylalanine blood levels above 4 mg⁰/₀ (normal range 1—2 mg⁰/₀). Earlier guesses concerning the incidence of PKU in the population were derived from screening in institutions (as described above) and were by their

very nature imprecise, their wide range of 1:17 000 — 1:50 000 being due to small, unrepresentative samples, to the test methods, to the definition of PKU, to racial differences, etc. Nevertheless, the detection of 37 cases of phenylalaninaemia in 55 000 infants is obviously too high to be solely accounted for by classical PKU. Some other causes must contribute to this high incidence of newborn phenylalaninaemia which justifies a "differential diagnosis" as suggested in the subtitle of MENKE's paper.

But here the trouble starts and is in fact still greater than in older age groups. Infants with PKU are mentally normal at birth and may not show any definite signs of brain damage until months or even years have passed. So mental retardation, cardinal symptom of classical PKU, has no value in the differential diagnosis of neonatal phenylalaninaemia. Differentiation must, if at all possible, be based on biochemical criteria.

The biochemical differences between classical PKU and the transient form of phenylalaninaemia occurring in premature and occasionally in mature infants are soon established. The transient form is due to delayed enzyme maturation and needs no therapy if the phenylalaninaemia is mild and of short duration. MENKE's Typ II-phenylalaninaemia (his Tables I and II) is probably due to a phenylalanine transaminase defect in addition to the hydroxylase defect. The absence of phenylpyruvic aciduria despite phenylalaninaemia above 20 mg% favours such

an explanation and justifies the biochemical differentiation from PKU, though actual enzyme measurements are still lacking. It is quite another question as to whether Type II really needs no dietary treatment if phenylalanine blood levels range persistently above 10 or even 20 mg%. The fact that the few patients known with this form have so far developed normally is suggestive has not yet proved anything definite. Recent work by AGRAWAL et al. and earlier observations by LINNEWEH et al. and by WAISMAN and HARLOW suggest that phenylalaninaemia per se may well inhibit myelin synthesis, reduce the uptake of other essential aminoacids into nerve cells and result in mental retardation, at least in experimental animals, such as monkeys.

The most problematic aspect of MENKE's differential diagnosis is his distinction between the relatively common Type IV - phenylalaninaemia and true PKU. He, like other authors, considers the diagnosis of PKU as established only when the phenylalanine blood level of untreated infants is above 20 mg%, when phenylpyruvic and oHO-phenylacetic acids are excreted in excess, and when phenylalanine loading tests during dietary treatment reproduce these abnormalities without raising the blood tyrosine concentration. By contrast, Type IV - phenylalaninaemia is defined as having phenylalanine blood levels below 20mg% on a normal diet, a usually negative ferric chloride test and a persistent, moderate phenylala-

ninaemia throughout life. MENKES states that up to now "almost all" patients with this condition are of normal intelligence despite unrestricted phenylalanine intake. Consequently, infants are only placed on a restricted diet if their blood phenylalanine levels were 20 mg⁰/₀ or higher on more than one occasion. This practice is in agreement with that of other authors such as BERMAN et al. (1969).

In the present state of our knowledge it is difficult to agree to this procedure. It is not yet possible to decide which infant with moderate phenylalaninaemia has true PKU and which not, or which infant needs the phenylalanine-restricted diet and which not. The suggested danger level of "20 mg⁰/₀ phenylalanine or higher" seems too arbitrarily chosen and does not take into account the observation of lower blood levels in mentally defective children and adults diagnosed as PKUs. GUTHRIE has recently presented results of phenylalanine blood tests performed in mental institutions in Austria, Germany, New York and Scotland. Of 26 393 patients 235 had blood levels above 6 mg⁰/₀, 24⁰/₀ of which ranged between 6—20 mg⁰/₀ phenylalanine. LUND and WAMBERG came to very similar conclusions in Denmark: of 111 untreated, mentally retarded patients with PKU 24 showed phenylalanine blood levels between 6—19 mg⁰/₀.

Thus phenylalaninaemia below 20 mg⁰/₀ seems to exist in mentally retarded patients in the same frequency as in newborn infants: of 1 million

newborns tested in a collaborative screening programme in USA 116 had phenylalanine blood levels above 6 mg⁰/₀, 37⁰/₀ of which ranged between 6—20 mg⁰/₀. This distribution of moderate phenylalaninaemia in infants and retarded individuals is in striking contrast to the findings in "normal" adults (soldiers, pregnant and non-pregnant women, blood typing specimens, etc.), again collected by GUTHRIE from various sources: only 3 of the 392 800 normal adults had blood phenylalanine elevations above 6 mg⁰/₀, all 3 being cases of PKU with mental retardation, phenylalaninaemia above 20 mg⁰/₀ and positive ferric chloride reaction in their urine.

If Type IV-phenylalaninaemia below 20 mg⁰/₀ persists according to MENKES throughout life without leading to intellectual impairment, it should be found in normal adults just as often as in infants. The fact that this is not so, but that it is detected in mental institutions nearly as often as in infancy, suggests that it is either not a persistent condition or one which after all finally leads to brain damage. In view of these recent observations and others not quoted here an earlier plea is repeated as regards the practical management of any infant with phenylalaninaemia: until there is unequivocal proof that persistent blood phenylalanine levels above 8 mg⁰/₀ do not damage the infantile brain, any infant with such levels should be treated with a phenylalanine-restricted diet to protect it from potential danger. The arbitrary level of

8 mg⁰/₀ is, of course, again open to criticism; future experience will show if this level is too low to cause brain damage or too high to prevent it.

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