Historical perspective: tyrosine and maternal phenylketonuria, welcome news¹,²

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The paper by Rohr et al (1) in this issue is a welcome addition to the growing number of studies that have recognized the importance of a tyrosine deficiency in the causation of mental retardation in phenylketonuria (PKU). Deficient tyrosine formation was first recognized in PKU patients because of their light hair pigmentation, which was due to a deficiency in melanin (a polymer of tyrosine). Penrose and Quastel (2) normalized hair color in PKU patients by feeding them tyrosine, but this had no effect on the patients' mental retardation.

The justification theory (3; Table 1), also cited by Rohr et al (1), proposed that mental retardation in PKU is caused in utero because of poor availability of tyrosine during gestation resulting from a lack of its synthesis by the fetus coupled with a poor supply by the heterozygous mother. Rohr et al do not agree with this theory, citing much evidence in support of the common belief that children with PKU are born with normal brain function, are poisoned by accumulated phenylalanine, and are rescued from impeding mental retardation by diminishing their dietary intake of phenylalanine as soon as possible. Let us examine the evidence for these beliefs.

The notion that PKU patients have normal brain function at birth is based on many measurements of the intelligence quotient (IQ) in patients diagnosed with PKU generally before 1 y of age. These data showed a falling IQ with age, ≈30 points in the first year of life. This finding was interpreted as proving that intellectual function was normal at birth and was diminished by exposure to excess phenylalanine. Psychologists have long interpreted falling IQs in the early years of retarded children, seen dramatically in institutions, as being due to lack of stimulation. IQ tests measure mental age, which is the amount the subject “knows” divided by the amount that the “normal” child “knows” at the same age, multiplied by 100. If the mental age does not increase as rapidly as is normal, the IQ will fall. Normal brain function in PKU patients at birth has never been proven and a falling IQ could indicate poor intellectual stimulation of a mildly retarded child.

There is no question, however, that PKU children consuming low-phenylalanine diets have IQs that are nearly normal. Unfortunately, this does not prove that low phenylalanine concentrations prevent mental retardation because no controls were used in studies of stimulation of these children. Hsia et al (4) conducted the only blind study (ie, the caretaker was unaware of the amount of phenylalanine in the diet) in PKU patients. There was no significant effect on IQ in the test or control group, except in two patients who were treated at home.

The clinics that supplied and monitored uncontrolled treatments had a charged atmosphere of enthusiasm in which there was continuous encouragement and advice to parents on how to formulate and administer the abnormal diet that their children required as well as help with the psychologic problems it engendered. There was also frequent IQ testing. The warnings of dire consequences, whether explicit or implicit, for failure to maintain low phenylalanine concentrations in their children from the first weeks of life surely caused parents to pay much more attention to their children than healthy babies get from their parents. Nothing like this educational approach had ever been used in untreated children with PKU who were nevertheless considered as untreated examples. The major effects seen after the first use of a low-phenylalanine diet were on behavior and not on mental age. On the basis of seriously flawed work, a nationwide campaign to detect and treat PKU began (5).

Even though the measured IQs of treated PKU patients were almost normal, it was troubling that well-treated patients were unable to learn as well as their schoolmates in school, and many of them were kept in special education classes for most of their childhood. There was a poor correlation between blood phenylalanine concentrations and the IQ of patients. It seemed as if the mere act of placing patients on the diet was enough to affect the IQ.

Why the renewed interest in tyrosine? As time went by, children born to treated women with PKU were found to be severely mentally retarded, even though they showed no signs of PKU. Control of phenylalanine concentrations in pregnant women consuming low-phenylalanine diets, even zero-phenylalanine diets in some cases, did not prevent mental damage to their fetuses. Apparenently stimulated by the predictions of the justification theory (3; Table 1), Komrower et al (6) treated several pregnant PKU patients with tyrosine, fairly successfully. A serious effort is now developing to supplement these patients with tyrosine. Before continuing to use a zero-phenylalanine diet, physicians should refer to the study by Bessman et al (7), which reports the effects of such a diet on pregnant rats. Blood concentrations of phenylalanine and tyrosine in the dams were in the normal range, as were phenylalanine concentrations in their pups, but tyrosine

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concentrations in the pups decreased dramatically. Perhaps this is why the justification theory further predicted slightly less mental retardation in maternal PKU (heterozygous fetus of a homozygous mother) than found by others. The theory did not take into consideration that the mother may have been consuming a zero-phenylalanine diet.

The justification theory further predicted, as observed by Fuller et al (8), that some mental damage occurs to a heterozygous fetus of a heterozygous mother. Ford and Berman (9) showed that in siblings with PKU, the heterozygotes (identified by phenylalanine-tyrosine conversion tests) had significantly lower IQs than their siblings who had normal results on conversion tests. Similar results were reported subsequently by another group (10). This finding could not be explained by phenylalanine toxicity.

Fisch et al (11) reported a higher than normal incidence of intrauterine growth abnormalities in PKU in early as well as late stages of gestation, supporting the view that the problem with PKU is gestational (7). Mental retardation in PKU can best be explained by a gestational deficiency of tyrosine, tyrosine being critical to the growth and function of the brain. Normal brain development depends, inter alia, on the genetically determined ability of both mother and fetus to make tyrosine.

The renewed interest in tyrosine may improve dietary regimens for pregnant patients with PKU. It is hoped that PKU therapists will understand that the psychologic effects of a low-phenylalanine diet are not due to lower blood phenylalanine concentrations but represent an educational effect resulting from the intense attention that parents pay to their children with PKU, which is necessary to administer the low-phenylalanine diet. The effects of current treatment programs are variable because they emphasize the diet to the parents and not its educational effects. The history of PKU leads us to the conclusion that a formal education program, started when PKU is first diagnosed, should produce the most favorable results.

REFERENCES


TABLE 1
Relative risk of mental retardation caused by gestational deficiency of a nonessential amino acid

<table>
<thead>
<tr>
<th>Genetic classification</th>
<th>Relative risk of retardation</th>
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<tr>
<td>Fetus</td>
<td>Mother</td>
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<tr>
<td>Low-protein diet</td>
<td>High-protein diet</td>
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<td>Heterozygous</td>
<td>Normal</td>
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* Data from reference 3. A high maternal amino acid intake (protein) may ameliorate the concurrent maternal-fetal insufficiency.