SERUM TRYPTOPHAN TO LARGE NEUTRAL AMINO ACID RATIO AND URINARY TRYPTOPHAN IN THREE PATIENTS WITH PHENYLKETONURIA IN A FAMILY

A Clinical and Biochemical Study

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ABSTRACT

In this work clinical and biochemical findings are presented in three untreated children with phenylketonuria in a family. Their clinical pictures were not typical for classical phenylketonuria. As a result, diagnosis was missed. It has been shown that patterns of large neutral amino acids in serum and urine were somewhat different. Significantly lower serum TRP/LNAA ratio was observed in all patients with phenylketonuria, compared to the control group. These findings suggest that there was subnormal tryptophan availability in the central nervous system leading to its decreased metabolism through the serotonin and kynurenine pathways. These results may explain decreased children's growth and their mental deficiency.

1. INTRODUCTION

In his historic report, Følling (1934) described ten mentally defective subjects who excreted large amounts of phenylpyruvic acid. He termed their condition imbecillitas phenylpyruvica. In the clinical picture, Følling (1934) also stressed the high incidence of dermatitis and spasticity. Phenylketonuria (PKU) is an inborn error of metabolism with different biochemical and clinical characteristics. The disease is inherited as an autosomal-recessive disorder. The inborn enzymatic defect in PKU is inability to hydroxylate phenylalanine (PHE) to tyrosine. The phenylalanine-hydroxylation reaction is complex (Scriver and Clow, 1980). This reaction is controlled by several genes (Scriver...
and Clow, 1980; Annenkov, 1982). Tryptophan (TRP) and tyrosine (TYR) metabolism is disturbed secondary in untreated patients with PKU (Yarbro and Anderson, 1966). It has been found that intestinal transport of TRP and TYR is impaired in PKU, because intestinal absorption of these two essential amino acids is inhibited by the high PHE levels. Peak plasma TRP response following oral TRP loads is reduced. Some biochemical in PKU have been attributed to competitive inhibition by PHE and its metabolites some of the relevant enzymes. In accordance with these observations, serum levels of TRP, serotonin (5-HT), and TYR are decreased. Blood and urinary dopamine, adrenaline and noradrenaline are also decreased. Urinary kynurenic acid, xanthurenic acid, N'-methylnicotinamide, and 5-hydroxyindol-3-ylacetic acid (5-HIAA) are decreased (Nejfax and Saposnikov, 1965). Perry (1962) reported that urinary excretion of serotonin and tryptamine considerably diminished in untreated phenylketonurics. It has been suggested that impaired 5-HT synthesis may contribute to mental deficiency in patients with PKU (Pare et al., 1957). Phenylketonuria due to a deficiency of tetrahydrobiopterin is also associated with impaired amine synthesis, but here, the amine changes are much less affected by blood concentrations of PHE (Smith et al., 1987). Patients with a PKU variant, called hyperphenylalaninemia, have less pronounced PHE levels of only 150 to 800 μmol/l (Ledley et al., 1986). Recently, a case of sclerodermiform PKU was reported (Szczepanski et al., 1995). The variety of cutaneous lesions observed during different periods of the disease depend upon the extent of the disturbance of TRP metabolism and upon inadequate maintenance of the PHE deprived diet. In this work, we will describe clinical characteristics and point out some different findings in 3 patients with PKU in a family.

2. PATIENTS

In our clinic, we have diagnosed three untreated children with PKU in a family. The ferric chloride and 2,4-Dinitrophenylhydrazine test results in the urine were positive. Serum and urinary PHE levels were significantly increased. Their clinical pictures were not typical for classical PKU. They have light-brown hair and brown eyes. The skin was pale. The children’s growth was below normal compared to children of the same age. Hypotrophy of the thorax and both upper and lower limbs were found. Other somatic findings could not be found. Prominent symptoms and signs of PKU patients are severe psychomotor retardation, but some differences among them were found. The children could not control the sphincters and took any food without help. They have never had convulsions. Treatment consisted of Encephabol (piritioksin), Vitamin B₆ (pyridoxine) and Lucidril. All the children in this family were born at home.

2.1. Case 1

The eldest patient was a girl, aged 10 years. She had been a full-term infant born after an uneventful pregnancy. At birth, she cried immediately. The body weight was normal. The psychomotor development began to stagnate at the 7th month of life. She began to stand at 6 years. A few years later, she could move some steps. Her vocabulary consisted of two or three words which could only be understood by her parents. Neuro-