Abnormal Regulation of Pyridoxal 5'-Phosphate in Reye's Syndrome

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Seeking to determine the effect of liver disease associated with Reye's syndrome on the regulation of plasma pyridoxal 5'-phosphate, we measured this compound in plasma from 11 patients with biopsy-proven Reye's syndrome. Its concentrations in plasma are significantly higher [37.5 (SD 6.13) µg/L] at the onset of the disease than after treatment [8.50 (SD 2.9) µg/L] or in a group of hospitalized patients with no evidence of liver disease [8.4 (SD 1.5) µg/L]. The concentration of pyridoxal 5'-phosphate in plasma at the time the patients entered the hospital correlated significantly with their activities of serum alanine aminotransferase.

Additional Keyphrases: liver disease · vitamin B₆ · pediatric chemistry

Similarities between Reye's syndrome and fulminant hepatic failure suggest that these illnesses may share many biochemical features. Increased concentration of amino acids, ammonia, and tyramine in plasma are characteristic of both Reye's syndrome and other diseases involving hepatic dysfunction (1–6).

Pyridoxal 5'-phosphate (PLP), the biologically active form of vitamin B₆ compounds, is essential to human health, being involved in various key biochemical processes associated with nitrogen metabolism (7). Liver disease may influence plasma PLP because the liver is a primary source of plasma PLP (8) and may also be involved in its degradation (9). Rossouw et al. (10) demonstrated that plasma PLP was markedly increased in patients with fulminant hepatic failure, whereas Mitchell et al. (11) noted its deficiency in patients with chronic liver disease.

Stimulated by these observations, we carried out the present study to assess, for the first time, the effects of liver injury in Reye's syndrome on the regulation of plasma PLP. Because we have recently developed a specific and sensitive radioenzymatic assay for the direct measurement of plasma PLP (12), we can now measure PLP in venous plasma of patients with Reye's syndrome on admission to the hospital and following treatment. For a comparative evaluation, a group of hospitalized children with no evidence of liver disease served as a control population.

Materials and Methods

Patients. We evaluated 11 patients with Reye's syndrome (white, ages one to 14 years, five girls and six boys). All had clinical and histologic features consistent with the diagnosis of the disease, including (a) acute onset of central nervous system disturbance as evidenced by profound alteration of behavior and (or) state of consciousness, (b) hepatic dysfunction as demonstrated by increases of serum alanine aminotransferase and ammonia, and (c) massive microvesicular fatty infiltration of the liver at biopsy. These children were treated in the intensive-care unit of Henrietta Egleston Hospital for Children in Atlanta, GA, by an established protocol of continuous infusions of hypertonic glucose and intermittent bolus infusions of mannitol. Plasma PLP was also measured in eight hospitalized patients having no clinical or laboratory evidence of liver disease; these served as controls. This investigation was approved by the Emory University Human Investigation Committee.

Analysis. Blood (2 mL) was drawn into evacuated glass tubes (Venloject; Kimble-Terumo, Elkon, MD), containing sodium EDTA. The specimens were promptly chilled to 0 °C and centrifuged (500 × g, 10 min). The plasma was then removed and quickly frozen at −80 °C until analysis within two weeks. For assay we diluted the plasma 20-fold in potassium acetate buffer (0.1 mol/L, pH 5.5) containing 5 µg of Na₂EDTA per liter; 0.2-mL samples were used. We measured the PLP in the sample by our radioenzymatic technique (12). Alanine aminotransferase in serum was measured according to standard laboratory techniques (SMA-12 profile, normal range 0–40 U/L).

Statistical analysis: The results obtained in each series of experiments were expressed as the arithmetic mean and standard deviation (SD). The sample means were compared by Student's t-test for paired data when appropriate. Values of p < 0.05 were considered to indicate significant differences.

Results

Plasma PLP was measured in patients with Reye's syndrome at admission to the hospital and after treatment. Concentrations in plasma are significantly (p < 0.002) higher in all of these patients [37.5 (SD 6.13) µg/L] at the onset of the disease than in a group of hospitalized patients without hepatic disorders [8.4 (SD 1.5) µg/L]. Even though there were some fluctuations in plasma concentrations of PLP (Figure 1) after recovery from the disease and release from the hospital, the mean concentration in plasma [8.50 (SD 2.91) µg/L] decreased to values not significantly different from those of hospitalized patients with no evidence of liver disease. The concentration of PLP in plasma at the time the patient entered the hospital correlated significantly with the activity of alanine aminotransferase in serum (Figure 2).

Discussion

In the present report, we noted a severe disturbance in the regulation of PLP in patients with Reye's syndrome, demonstrated by a marked increase in the concentration of PLP in plasma at the time of admission to the hospital.

In all likelihood, the underlying abnormality in PLP is a result of hepatic dysfunction. In Reye's syndrome, this could be triggered by numerous precipitating factors, including viruses (13), drugs (14), agricultural hepatotoxin (15), and short-chain fatty acids (16). The high plasma concentrations of PLP in patients with Reye's syndrome could arise from its increased release from the liver as a result of the massive hepatocyte injury. This would be in keeping with the work of Rossouw et al. (10) and Frank et al. (17), who showed low hepatic concentrations of PLP in patients with fulminant hepatic failure and in rats after carbon tetrachloride-in-

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The low plasma concentrations of PLP observed after treatment presumably reflect the reversible process of hepatic injury, but may also represent the decreased hepatic stores of PLP in these patients. Consequently, a possible deficiency of PLP would be expected to exacerbate the hepatic metabolism of amino acids.

Therefore, measurement of plasma PLP may represent not only a sensitive and specific assessment of hepatic injury but also an important indicator for evaluation of the nutritional status of the patients after recovery from Reye's syndrome.

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References