Frequency of hypoglycemia in children with adrenal insufficiency

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Abstract

The frequency of hypoglycemia in 165 children with primary adrenal insufficiency, 118 of whom had Congenital Adrenal Hyperplasia and 47 Addison's Disease, was 18%. Half of the hypoglycemic episodes occurred in the neonatal period. Hypoglycemia was isolated in 13 children, revealing the disease in 4 newborns with Congenital Adrenal Hypoplasia and in a boy with 11β Hydroxylase deficiency.

Basal plasma cortisol levels were significantly lower in those of subjects who experienced hypoglycemia (47.1 ± 28.6 ng/ml vs. 106.0 ± 86.6 ng/ml, p < 0.001). A significant correlation (p < 0.001) was found between the plasma concentration of glucose and cortisol at time of hypoglycemia.

Key words

Hypoglycemia, Cortisol deficiency, Primary adrenal insufficiency, Congenital Adrenal Hyperplasia, Addison's Disease.

Introduction

Although cortisol deficiency decreases the level of fasting plasma glucose (Pagliara et al. 1973; Senior et al. 1979), the frequency of hypoglycemia due to adrenal insufficiency appears to be low in childhood (Sauls et al. 1974). This can be due to the rare occurrence of hypoglycemia in young patients with Congenital Adrenal Hyperplasia (Wilkins 1965; Zuppinger 1975) or Addison's Disease (D'Albora et al. 1976; Bovier-Lapierre et al. 1974; David 1974) as well as to the paucity of the adrenal diseases themselves.

We report here the frequency of hypoglycemia in a large number of children with impaired cortisol production by Congenital Adrenal Hyperplasia (CAH) and Addison's Disease (AD).

Subjects and Methods

The frequency of hypoglycemia and the main clinical and biological characteristics of the hypoglycemic episodes were evaluated in 165 children aged 1 day to 13.5 years with impaired cortisol secretion secondary to CAH or AD.

118 children (53 boys and 65 girls) had CAH. 21 Hydroxylase deficiency was recognized in 96 of them, 39 boys and 57 girls, (17 Hydroxyprogesterone: mean ± sd 251 ± 249 ng/ml, range 23 - 1500 ng/ml), a salt losing syndrome being present initially in 56 children. 15 children had 11β Hydroxylase deficiency (11 Deoxy cortisol 251 ± 120 ng/ml, 120 - 370 ng/ml), 6 others 3β Hydroxysteroid dehydrogenase deficiency (Dehydroepiandrosterone 43 ± 58 ng/ml, 7.6 - 160 ng/ml), and one boy 20 - 22 Desmolase deficiency. Basal plasma cortisol was normal or low in all of them (126 ± 100 ng/ml, 20 - 500 ng/ml).

AD was diagnosed in 47 children (41 boys and 6 girls) based on classical clinical symptoms, mainly melanodermia, and hormonal findings: low plasma cortisol concentrations (52.5 ± 38.2 ng/ml, 20 - 140 ng/ml), with elevated basal Adrenocorticotropic Hormone (ACTH) plasma levels (1047 ± 814 pg/ml, 120 - 3300 pg/ml), and no cortisol increase after exogenous ACTH stimulation (76.9 ± 57.5 ng/ml, 20 - 240 ng/ml). AD was secondary to Congenital Adrenal Hypoplasia in 6 infants, to Adrenoleukodystrophy in 21 children and Idiopathic in 19 children.

Hypoglycemia was defined by the occurrence of loss of consciousness and seizures with plasma glucose concentration below 40 mg/dl. Plasma glucose was measured using a glucose-oxidase method (Hugget et al. 1957) and plasma cortisol by an Immunoenzymatic assay (Ogiharat et al. 1977). Adrenal steroids were measured by specific radio-immunological assay (Chaussain et al. 1974).
Data in the text are expressed as mean ± sd, and range. Unpaired Student's t test was used for the comparison of the hypoglycemic versus the normoglycemic groups. Correlation between plasma glucose and cortisol concentrations at time of hypoglycemia was determined by the Pearson Correlation Coefficient.

**Results**

Whole population: Hypoglycemic episodes occurred in 30 out of 165 patients (18%): 15 times in the first month and 20 times in the first year of life. Hypoglycemia occurred before therapy in 24 children and during substitutive therapy in 6. Hypoglycemia was isolated in 13 children, revealing the disease in 5 newborns, and associated to low plasma sodium in 17. Hypoglycemia occurred in two situations: in the neonatal period (15/30) or later in life (15/30), always preceded by 4 - 10 hours of fasting and gastrointestinal troubles, mainly vomits, and viral infections.

Basal plasma cortisol levels were significantly lower in hypoglycemic subjects (41.7 ± 28.6 ng/ml) than in the others (106.0 ± 86.6 ng/ml, p < 0.001). In hypoglycemic patients a significant correlation was found between plasma concentrations of glucose (25.5 ± 8.0 mg/dl) and cortisol (39.2 ± 27.2 ng/ml) at time of hypoglycemic episodes (figure).

![Graph](image-url)

**Figure I**: Correlation between plasma glucose and plasma cortisol at time of hypoglycemia (AD ●, CAH ○).

\[ y = 19.07 + 2.28 x, \quad r = 0.671, \quad p < 0.001. \]
Patients with CAH: Hypoglycemia was documented in 14/118 patients with CAH (12%), 10 times in the first month and 14 times in the first year of life. Hypoglycemia occurred before therapy in 8 patients and under substitutive therapy in 6. Hypoglycemia was either isolated (6/14) or associated with a low plasma sodium (8/14). In the patient with 11β Hydroxylase deficiency, immediate postnatal hypoglycemia led to the diagnosis, macrogenitosomia being noted later.

The mean level of basal plasma cortisol was lower in hypoglycemic subjects (42.5 ± 25.0 ng/ml vs. 143.0 ± 12.5 ng/ml, p < 0.05).

Patients with AD: 16/47 patients with AD (34%) developed hypoglycemic episodes: 5 in the neonatal period, 6 in the first year of life and in the others cases between 2 and 10 years of age. In all cases hypoglycemia occurred before substitutive therapy, but recurred in 2 cases under treatment.

Among the 16 patients with hypoglycemia and AD, 5 had Congenital Adrenal Hypoplasia, 3 Adrenoleukodystrophy and 8 Idiopathic. Hypoglycemia was isolated in 7 patients, associated with a low plasma sodium in the others. Hypoglycemia was the primary abnormal finding in 4 newborns with Congenital Adrenal Hypoplasia.

In this group also basal plasma cortisol were significantly lower in hypoglycemic subjects (27.3 ± 15.8 ng/ml) than in the others (64.7 ± 40.0 ng/ml, p < 0.02).

Discussion

In the present series of 165 infants and children with primary adrenal insufficiency, hypoglycemia occurred in 18% of cases with varying frequencies according to the etiology of the adrenal disease. Hypoglycemia was more frequent (34%) in young patients with AD. Its frequency is much lower in CAH, the 12% observed representing a slightly higher percentage than reported by Wilkins (1965) and Zuppinger (1975). The difference between AD and CAH in terms of hypoglycemia relates probably to the fact that the glucocorticoid deficiency is more complete in patients with AD. The relation of causality between the plasma level of cortisol and the degree of hypoglycemia is suggested by the close correlation of their respective values in the present study.

However, since many normoglycemic patients in this series had very low cortisol levels, the severity of the glucocorticoid deficiency is not the only factor responsible for the occurrence of hypoglycemia. It is generally accepted that hypoglycemia in these patients is due to impaired gluconeogenesis (Zuppinger 1975), and occurs when liver glucogen stores are depleted, suggesting the importance of nutritional factors. As a consequence the risk of hypoglycemia in cortisol deficient children increased drastically in the present series when anorexia or vomiting occurs.

Another distinctive feature of the studied group in the high proportion (50%) of newly born infants, who are characterized by a remarkably high cerebral demand of glucose (Bier et al. 1977). Hypoglycemia in the neonatal period can thus be an early symptom of adrenal disease, as reported for Congenital Adrenal Hypoplasia (David et al. 1974).

References:


