

6-1968

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Recommended Citation

Bickham, Richard E.; Silvestre, Dora; and Mellinger, Raymond C. (1968) "Addison's Disease in Half-Siblings," *Henry Ford Hospital Medical Journal* : Vol. 16 : No. 2 , 157-162.

Available at: <https://scholarlycommons.henryford.com/hfhmedjournal/vol16/iss2/8>

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In this only reported incidence of Addison's disease in half-siblings, the adrenal failure is postulated to be a sex-linked recessive character. Adrenocortical antibodies were not detected.—Ed.

Addison's Disease in Half-Siblings

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and Raymond C. Mellinger, M.D.,***

Considerable evidence supports the concept that an autoimmune mechanism is responsible for the pathogenesis of nontuberculous adrenocortical insufficiency.¹ Although rare, familial cases of Addison's disease occur, with the age of onset of clinical manifestations varying from the neonatal period to adulthood. The etiology of the familial disorder has been considered to be genetic in origin,² but an autoimmune process has also been demonstrated in familial cases.³

The present report concerns Addison's disease occurring in two boys having the same mother but different fathers. The condition was proved by assay of urinary adrenal steroids before and after stimulation with corticotropin and by complete remission of the symptoms with adrenal hormone replacement. No abnormal steroid metabolites were detected in the urine. Study of the serum of both patients and their mother failed to demonstrate adrenocortical antibodies.

Methods

Urinary 17-ketosteroids were determined by the method of Sobel⁴ and 17-ketogenic steroids by the method of Metcalf.⁵ Urinary 17-hydroxycorticosteroids were measured by a modified Porter-Silber technique⁶ and pregnanetriol by the method of Bongiovanni and Clayton.⁷ Tests for the presence of antibodies to the adrenal cortex, thyroid and parathyroid glands were performed in the laboratory of Dr. Robert M. Blizzard, associate professor of pediatrics, Johns Hopkins University School of Medicine. The indirect Coons method¹ was employed for antibodies to adrenal and parathyroid while both the fixed and the unfixed Coons methods were used for thyroid antibodies. Other laboratory tests were done by standard procedures, the blood of the infant being tested by micromethods although the high potassium values were verified by macromethods.

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Case Reports

Case #1

This child, a white male of three years and four months, was admitted to the Henry Ford Hospital because of failure to gain weight during the previous two years. A few months before admission he had developed brown pigmentation of the neck, hands, back and abdomen and for six weeks had been troubled by increasing irritability, frequent urination and persistent vomiting. The child had been born at term, weighing 7 lbs. 13 oz., following an uncomplicated pregnancy and delivery. Since infancy he had been troubled by chronic eczema, and for six months had experienced recurrent attacks of asthma. His father is said to have had hypothyroidism, asthma and rheumatic fever and the maternal grandmother had had breast carcinoma and tuberculosis, although there had been no contact between the grandmother and the patient. There was one normal younger half-sibling. Another half-sibling born subsequent to this hospitalization required treatment of adrenocortical insufficiency in the neonatal period (case #2).

The patient was thin, weak and apathetic. He weighed 26 lbs. 12 oz. and was 36¼ inches tall. The skin was deeply pigmented over the neck, hands, back and abdomen. There was an eczematous rash in the antecubital fossae. He refused food, becoming progressively weaker and more dehydrated until corticosteroids were given nine days after admission.

An extensive laboratory study was performed. Histoplasmin and tuberculin (PPD) skin tests were negative. X-ray examination of the esophagus, stomach, small bowel, urinary tract, chest, hands (for bone age) and skull were all normal. The electroencephalogram was normal. Routine blood, urine and stool examinations, the protein-bound iodine, Vitamin A absorption test, serum transaminase and bilirubin were all within normal limits. Initial serum urea nitrogen was 33, creatinine 1.4, calcium 8.1, and inorganic phosphate 6.0 mg/100 ml, while serum sodium was 122, potassium 5.8, chloride 85 and CO₂ content 18.6 MEq/L. Sweat chloride was 53 mEq/L. Absolute eosinophil count was 317, and four hours after intramuscular injection of 90 units of corticotropin gel, 267/cu mm. Urinary level of 17-ketogenic steroids and 17-ketosteroids, which were very low, failed to increase after corticotropin stimulation (Table I). Immunologic studies failed to disclose adrenocortical, parathyroid or thyroid antibodies in the serum.

The child was given 0.1 mg of fluorhydrocortisone per day and 5 mg of hydrocortisone three times a day. Clinical improvement was prompt and sustained. Serum urea nitrogen fell to 19 and creatinine to 0.7 mg/100 ml while serum sodium rose to 135 and potassium fell to 4.3 mEq/L. Serum calcium was rechecked repeatedly with values of 8.4, 8.8, 9.2, 8.8 and 9.8 mg/100 ml, while serum phosphorus varied from 4.4 to 6.0 mg/100 ml. Six weeks after his hospitalization the patient was free of symptoms, the serum electrolyte values were all normal, serum calcium was 9.4 and phosphorus 4.9 mg/100 ml. In the next year, the boy grew 4.5 inches and gained six pounds. The skin pigmentation disappeared. When last examined at age seven he was physically normal taking 20 mg of hydrocortisone and 0.1 mg fluorhydrocortisone daily.

Table I ACTH Stimulation Test (Case #1)

Test Day	Creatinine mg/24 hr	17-KGS mg/24 hr	17-KS mg/24 hr
Control	118	2.4	0.3
ACTH (40 U b.i.d.)	148	3.5	0.8

Case #2

Four months after the Case 1 study, this 14-day-old white male infant was admitted to the hospital because of a 17-ounce weight loss since birth. The infant was a half-sibling of patient #1 having the same mother but a different father. He had weighed 8 lb. 13 oz. at term delivery after an uncomplicated pregnancy but from birth had refused to take more than one to two ounces of formula every four hours. There was no increased irritability, somnolence, vomiting, or diarrhea.

At the time of admission the baby was markedly dehydrated and lethargic. The skin was dry and flaky with decreased turgor but there was no increased pigmentation. The anterior fontanel was soft and slightly depressed. Except for generalized weakness, the remainder of the examination was not remarkable.

The initial hemoglobin was 18 gm/100 ml, WBC 12,800/cu mm with three percent eosinophils. Serum sodium was 124, potassium 8.9, chloride 93, and CO₂ content 13.9

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mEq/L. Alkaline phosphatase was 4.7 Bodanski units, serum calcium was 8.9, inorganic phosphate 5.8, and BUN 20 mg/100 ml. A 24-hour urine sample contained 13 mEq of sodium and 7.4 mEq of potassium.

The child had several episodes of vomiting but upper gastrointestinal and chest x-rays were normal. The serum potassium rose to 10.6 mEq/L on the third hospital day. Because of the family history, his grave condition and the markedly abnormal serum electrolytes, the child was given hydrocortisone and desoxycorticosterone acetate. Improvement was prompt and striking. A corticotropin stimulation test was subsequently performed while the patient was receiving 0.1 mg of fluorohydrocortisone daily and 0.25 mg of dexamethasone twice a day. The 24-hour urinary excretion of 17-hydroxycorticosteroids, 17-ketogenic steroids and 17-ketosteroids was very low and increased only slightly with intensive corticotropin stimulation. However, significant levels of 17-hydroxycorticosteroids and 17-ketogenic steroids were excreted when hydrocortisone was administered. There was no abnormal excretion of pregnanetriol before or after corticotropin (Table II). As in the case of the older boy, tests for antibodies to the adrenal, thyroid and parathyroid glands were all negative. Six weeks after his hospitalization the baby appeared entirely normal, receiving fluorohydrocortisone 0.15 mg and hydrocortisone 15 mg daily. The electrolyte values were normal and the weight had increased from 7 lb. 12 oz. to 10 lb. 4 oz. In the subsequent three and a half years he has continued normal growth and development with daily corticosteroid therapy.

Table II ACTH Stimulation Test* (Case #2)

Test Day	Creatinine mg/24 hr	17-OHCS mg/24 hr	17-KGS mg/24 hr	17-KS mg/24 hr	Pregnanetriol mg/24 hr
Control 11/2	63	0.5	0.8	0.4	0.1
Control 11/3	40	0.6	0.4	0.6	0.1
ACTH (20 U b.i.d.) 11/4	54	0.5	1.0	0.4	—
ACTH (20 U b.i.d.) 11/5	69	1.1	2.3	0.3	0.15
Hydrocortisone** 11/9	39	3.9	10.1	0.3	—
Hydrocortisone 11/10	41	6.3	11.3	0.2	—

*Patient was given 0.1 mg of fluorohydrocortisone per day and 0.25 mg of dexamethasone twice a day from 10/31 to 11/6.

**Patient was given 0.05 mg of fluorohydrocortisone per day and 10 mg of hydrocortisone every eight hours from 11/6/64 to 11/10/64.

Although the third male child of this family, (half-sibling to patient #1 and full brother of patient #2) is now five years old and has always been free of clinical evidence of Addison's disease, adrenal steroid secretion and response to ACTH were determined when he was two years old. The results shown in Table III were interpreted as normal. Similarly, the mother of all three children was proved to have normal adrenal function (Table III), and results of the antibody tests were negative. Neither father has ever had any clinical evidence of adrenal deficiency. No member of the family is color blind, nor were other significant inheritable defects detected.

Table III Studies of Normal Sibling and Mother

Subject	Test Day	Creat. mg/24 hr	17-OHCS mg/24 hr	17-KS mg/24 hr	17-KGS mg/24 hr
Normal Sibling	Control	157	2.3	1.8	4.5
	Control	138	2.7	2.7	3.2
	ACTH (20 U b.i.d.)	173	6.1	1.7	11.6
Mother*	Control		10.3	7.1	
	ACTH (50 U x 3 day)		41.6	18.7	

*These data were kindly supplied by Herschel Sandberg, M.D., Sinai Hospital, Detroit, Michigan.

Discussion

The two boys described represent the only reported instance of Addison's disease in half-siblings. The disorder became evident in the first child at age three years four months, and in his younger half-brother at age two weeks. The infant was also afflicted by oral moniliasis, while the older boy had chronic eczema and recurrent episodes of asthma. In a recent review, 25 cases of congenital adrenal hypoplasia are described with death often occurring in the first few days of life.⁸ Signs and symptoms of this form of Addison's disease, which are often vague and nonspecific, include somnolence, weakness, refusal of feedings, vomiting, weight loss, dehydration, cyanosis, syncope, irritability, spasticity and sudden death.

As in congenital adrenal hyperplasia, congenital Addison's disease might reasonably represent an inheritable enzymatic deficit. However, the adrenal insufficiency which occurs in the adrenogenital syndromes is manifested as a salt-losing state rather than the chronic debilitating disorder with progressive pigmentation described in patient #1. Furthermore, the adrenal enzyme deficiency syndromes are characterized by excessive urinary 17-ketosteroids and virilism, except for very rare forms which impair the transformation of cholesterol or pregnenolone, and therefore also impair gonadal function and sexual differentiation. No excessive or abnormal adrenal steroid metabolites were detected in the urine of the children described here. Furthermore, glandular hypoplasia which has characterized the autopsied cases of congenital Addison's disease suggests a process of impaired cellular differentiation rather than a deficiency in hormonogenesis.

Another possible mechanism for the disorder, corticotropin deficiency, is an unlikely condition in the presence of skin pigmentation, which in patients with adrenal insufficiency is considered to be the result of excess ACTH.

The mode of inheritance of familial Addison's disease, like that of the adrenogenital syndrome, is thought to be due to a simple Mendelian recessive gene.^{2,3,9} In the family which we have reported, the two boys with Addison's disease had the same mother but different fathers, while a third male child, produced in the second marriage, was apparently normal. This finding suggests a sex-linked (X) recessive gene rather than an autosomal recessive trait because of the improbability of intermarriage involving three carriers of a rare disorder. A sex-linked (X) recessive gene could also be involved in five other reported families in which only male members are involved.^{9,10,11,12,13}

However, the large number of afflicted females with the disorder in other families militates against the concept of sex-linked recessive transmission in most cases. Accordingly, the occurrence of familial Addison's disease follows no uniform pattern of inheritance, the evidence suggesting the operation of a recessive autosomal gene

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in some families and a sex-linked recessive gene in others. The present cases may represent the latter mechanism.

Recent evidence incriminates an autoimmune state in the pathogenesis of "idiopathic" Addison's disease. Blizzard¹⁴ reported the presence of circulating antibodies to adrenal cortex in 51% of patients with atrophic adrenal glands. This mechanism has been involved in one instance of the familial disorder,³ but antibodies were not demonstrated in the sera of our patients or that of their mother.

The familial syndrome of Addison's disease, hypoparathyroidism and superficial moniliasis has not been specifically considered in this report although our youngest patient developed oral moniliasis while in the hospital. His serum calcium and phosphorous were normal. Familial Addison's disease has also been associated with spastic paraplegia,¹⁵ pernicious anemia,^{3,16} and cerebral sclerosis.¹⁷

Summary

Adrenal hormone and antibody studies of two half-siblings with adrenocortical insufficiency demonstrated deficiency of all urinary steroid metabolites and no evidence of an autoimmune process. One patient had transient oral moniliasis. The patients had the same mother and different fathers, and the younger child had one normal sibling. A sex-linked (X) recessive gene is suggested as a cause for the deficiency of adrenocortical function which was first diagnosed at age 3 years, 4 months in the older child but was present from birth in his half brother. In other familial cases Addison's disease is apparently inherited as a simple autosomal recessive trait.

Acknowledgement

We are indebted to Dr. Robert M. Blizzard of the Johns Hopkins Hospital for performing the antibody studies and to Dr. Gordon Manson of the Henry Ford Hospital for his suggestions in the preparation of this report.

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