CLINICAL CONFERENCE

Cushing's Syndrome and Suspected Mental Retardation in an 18-month-old Boy

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DR. BARNETT: The patient to be presented and discussed by Dr. Taft and by Dr. Sobel provided a series of perplexing problems relating to diagnosis, treatment and prognosis. Some of the questions raised have been answered but others relating particularly to prognosis and future treatment remain. To preserve the chronologic order of the problems as they were presented to us, the presentation will be introduced by Dr. Taft, to whom the patient was referred initially because it was believed that the primary difficulty was one of mental retardation.

DR. TAFT (Assistant Professor of Pediatrics): This infant, at the age of 18 months, was referred to the Developmental Evaluation Clinic by his private physician. The physician had requested an investigation to determine why the infant was slow in psychomotor development and why he was obese.

The relevant history revealed that this was the mother's first pregnancy which was uneventful. Except for vitamins no other medications were taken during the gestation. The delivery and the immediate post-natal course were unremarkable. The patient weighed 5 lb 4 oz at birth.

During the neonatal period the infant was extremely apathetic and listless. He sucked poorly. At 6 weeks of age he was hospitalized for bronchopneumonia.

From the history, his motor development was delayed. He gained head control at 6 months; rolled over at 8 months; and sat unsupported at 1 year of age. He followed objects at 4 months; spoke single words at 1 year; and had conditioned tricks at 13 months.

At approximately 8 months of age it was noticed by the parents that the patient was gaining weight rapidly and had a spurt in linear growth. At this time his appetite became ravenous.

The family history was essentially noncontributory. His mother was 24 years and his father was 30 years of age. There were no siblings. The parents were of normal stature and physique. There was no known family history of endocrine or neurologic diseases.

Dr. Sobel will describe the infant's habitus and the findings on physical examination. The neurologic examination was negative except for delayed maturation in the motor sphere. Head size, optic fundi, cranial nerves, muscle tone, reflexes and sensory findings were within normal limits.

The psychologist, using the Cattell Infant Intelligence Scale, obtained an over-all intelligence quotient of 78, which is borderline functioning. Review of the data revealed that the child was able to do some tasks at his chronologic age level. These were tasks requiring only minimal use of motor abilities to demonstrate intellectual functioning. Unfortunately, most infant intelligence scales place major stress on motor abilities, which if impaired may result in false estimates of intellectual capacity. In addition, children with motor handicaps are unable to explore their environment normally and consequently lack the usual experiences that stimulate intellectual growth.

At this point in the evaluation of this infant we considered the following factors in relation to the major causes of a delay primarily in the motor sphere:

1. Simple mental retardation: We did not believe that this had been demonstrated conclusively.

2. An abnormality of the motor pathways: There were no known etiologic factors in the past history. The neurologic examination was
negative except for delayed motor accomplishments. Fine dexterity appeared uninvolved, while gross motor tasks (crawling and walking) were at an immature level. This combination is unusual if a cerebral disorder is present (i.e., cerebral palsy) and was more suggestive of a peripheral abnormality. Muscle strength could not be accurately evaluated, but appeared diminished.

3. Obesity: This is often suggested by parents as a cause of their child’s delayed motor development, but we doubted if this degree of motor delay could result. In fact, in most instances in which obesity and delayed motor development coexist the obesity is secondary to the motor problem.

4. A primary metabolic disorder causing generalized weakness: As, by exclusion of the above factors, this remained a possibility, and especially because the child’s habitus was suspicious of a metabolic disorder, he was referred to the Pediatric Endocrine Clinic for further investigation.

Dr. Edna Sobel (Assistant Professor of Pediatrics): Dr. Taft has mentioned that a metabolic disorder might be a factor in the child’s apparent mental retardation. The most obvious problem was the differential diagnosis of obesity. We thought this was not simple exogenous obesity because most children with that type have, in addition to excessive adiposity, an unusually good muscle mass and are tall for their ages.

Hypothyroidism is also a possibility in an obese child who is growing slowly but whose appetite is not impaired. This child had been receiving thyroid therapy for several months before we first saw him. Nevertheless his stature, which had been at the 90th percentile, was now at the 75th percentile (at 10 months of age Fig. 1). His physical appearance offered no suggestion whatever of hypothyroidism.

At the age of 21 months, the patient’s length was within normal limits (86 cm, 75th percentile). He had a weight-age of 5 years (19.6 kg), which certainly would explain his trouble in getting around, although it did not tell us how he got that way. He had a very round face, appeared plethoric, had heavy eyebrows and facial acne. He had a cervico-dorsal fat pad (Fig. 2). His blood pressure was elevated (120 to 130/80). There was a trace of pubic hair and some rugation of the scrotum in which testes could not be felt.

The hemoglobin was 14 gm/100 ml, which was rather high for a child of his age; there were 5,200,000 erythrocytes/mm³. The electrolytes in the plasma were entirely normal. There was a trace of glycosuria on several occasions although the glucose tolerance test did not show any impairment of carbohydrate metabolism. The concentration of corticoids in the plasma was 32 μg/100 ml, which is beyond the average range (4-20 μg) and above the expected upper limit (28 μg). The concentration rose to 53 μg/100 ml in response to ACTH given intravenously; the magnitude of the response is normal, but the concentration reached was abnormally high.

The rates of excretion of 17-ketosteroids and of hydrocortioids in the urine were normal. There was an excessive excretion of aldosterone; this assay was not completed until after he had been operated upon.

Perhaps Doctor Elkin could show us the x-rays at this time.

Dr. Elkin (Professor of Radiology): We have nothing specific from the x-ray films to make a diagnosis of Cushing’s disease. The bones in general appear to be somewhat demineralized, which is not a specific thing. We cannot grade osteoporosis by any scale, but in relation to the density of the musculature and soft tissues the bones do appear less dense than we expect to see in a child of this size and age.

The muscle mass as seen in films of the extremities appears quite diminished in this baby as compared to a normal baby of this size (Fig. 3).

The urogram was not as successful as we would like, but the kidneys appear normal in position and outline; the calices appear normal. There is no evidence of an abnormal soft-tissue mass in either adrenal area. We do not have an air insufflation study. The bone age is within the normal range. Usually, in Cushing’s disease, in addition to demineralization, which I think this child has, we are apt to see some collapse of the vertebral bodies. This baby did not have any such abnormalities.

To summarize, from the radiologist’s viewpoint, there was nothing specific for a diagnosis of Cushing’s disease—just the nonspecific finding of some demineralization of bone and diminution of muscle mass in relation to the total soft tissues of the child.

Dr. Sobel: As you can see, the diagnosis of Cushing’s syndrome in this child was based on putting together many suggestive findings,
may respond to ACTH very much in this way, with a normal increase in plasma corticoids starting from an abnormally high concentration.

With an adrenal carcinoma as the cause of Cushing’s syndrome, one would expect a higher urinary excretion of 17-ketosteroids than he had, and less response to ACTH. However, in some patients with adrenal carcinoma there is a clear response to ACTH, and excretion of 17-ketosteroids in some instances is low. It depends a great deal on what hormones the tumor secretes, and whether or not it responds to ACTH.

In the presence of bilateral adrenal hyperplasia, which is extremely unusual in a child this age (only three cases have been reported), the increase of plasma corticoids in response to ACTH is usually much greater. This finding has reopened the whole question of the etiology of Cushing’s syndrome with adrenal hyperplasia, which may be the result of an excessive response of the adrenals to normal amounts of ACTH, rather than an excessive secretion of ACTH by the pituitary.

This child’s abdomen was explored by Dr. Keith Schneider using a transabdominal incision; the adrenals were equal in size, but we could not be sure whether or not they were enlarged. This is a very difficult interpretation to make in the operating room. We were sure that neither adrenal was small, which was a good indication that he did not have a tumor that had not been located.

Because of the child’s age, about five-sixths of the left adrenal gland was removed. There are so many hazards in childhood which may precipitate a crisis of adrenal insufficiency that total adrenalectomy was not considered appropriate therapy. Our plan was to remove all of the right adrenal gland at a latter date, if necessary, hoping that a chemical method of controlling Cushing’s syndrome might become available before another operation was indicated.

The patient had a very stormy post-operative course. At first he was given aqueous adrenal cortical extract intravenously and intramuscularly, and then cortisol acetate and ACTH intramuscularly. The plan was to discontinue the cortisol acetate gradually, and then decrease and discontinue the ACTH. He required a great deal more adrenal hormone than we had expected, partly because he had an epi-

rather than any one thing which would allow us to say that this was unquestionably Cushing’s syndrome.

Review of the many photographs which the parents had taken showed that there had been a very definite change in the child’s physical appearance between the ages of 6 and 8 months. At that time the eyebrows became heavy and the rounding of the face first appeared.

Because the etiology of Cushing’s syndrome in the pediatric age group is overwhelmingly in favor of tumor, we did not believe that we could wait to see whether or not more dramatic signs would become evident. The possibility of an adrenocortical adenoma was suggested by the response to ACTH. Adenomas
sode of atelectasis, possibly related to his obesity and the endotracheal tube which was necessary for his anesthesia. He then developed severe diarrhea, which made us fear that he might have an infection that was obscured by the large amount of hormone he needed to prevent episodes of adrenal insufficiency. He finally came through all these difficulties and is here to be shown. I think you might like to know that there has been moderate improvement in his physical appearance, but not nearly as much as that which occurs if the patient has a tumor which can be removed completely.  

The blood pressure is now normal. He is not gaining weight but he certainly is still chubby. He is able to stand by himself and gets around well in a walker. He is a very affable child.

He is receiving potassium chloride by mouth, with the thought that the muscle weakness may be related to potassium depletion, even though he does not have the extracellular electrolyte pattern characteristic of intracellular potassium depletion. As long as he continues this way and does not force our hand, especially by developing severe hypertension, the plan is just to wait and see what happens.

**Chairman Barnett:** Thank you, Dr. Sobel. Are there questions or comments about the patient?

**Question:** Where are the levels of corticosteroids in the blood and urine now?

**Dr. Sobel:** We are reluctant to withdraw blood from this child, as it can be obtained only from a femoral vein. He has had four “cutdowns,” with an episode of thrombosis at the site of one. He is not yet toilet trained so we are not collecting urine because we would prefer not to subject him to another hospitalization. The acne has disappeared completely, the cervico-dorsal fat pad is smaller, and there is less plethora. That is the basis for considering him to be improved.

**Question:** Would you explain the significance of two things—the cervical fat pad and also the smear of the buccal mucosa.

**Dr. Sobel:** The fat pad is something which has been observed in Cushing’s syndrome and, as you know, appears in patients receiving large doses of cortisone. I cannot explain it.

The smear of the buccal mucosa was done because we thought at first that the patient might have a congenital adrenal tumor, and that the cryptorchidism might indicate that “he” was a female pseudohermaphrodite who had been virilized in fetal life. His testes were found at operation; on biopsy one appeared perfectly normal. He will probably require surgical treatment for the undescended testes.

I do not think that the findings in a buccal smear can yet be regarded as a definite index of genetic sex.

**Question:** I have seen a case of adrenal tumor diagnosed pre-operatively with retro-grade aortogram. I was wondering if you had considered that in the diagnostic studies.

**Dr. Sobel:** I have been inclined to rely on the intravenous pyelogram. There is pretty good evidence that an adrenal tumor large enough to show up on air insufflation will displace the kidney, which allows one to avoid the use of a more hazardous procedure. I do not consider an aortogram as an innocuous procedure, partly because the course of the descending aorta is mid-line in children.

**Dr. Elklin:** I have seen several adrenal tumors diagnosed by aortogram. There may be vascular tumors. However, I also think that air studies will sometimes show tumors which you do not see by aortography.

**Dr. Sobel:** Dr. Elklin and I have discussed this problem. There have been some accidents with air insufflation and with aortography. As one cannot rely on negative studies to rule out a tumor, it is my opinion that it is best to avoid the added risk. If the surgeon plans to use a transabdominal incision, it may not be necessary for him to know the exact position of a tumor. Occasionally an adrenal cortical tumor is in an unusual location, such as in the liver.

**Dr. Elklin:** Well, I would favor pre-sacral air studies before surgical exploration if urographic studies are negative.

**Question:** Does any medical treatment have to be considered before operation?

**Dr. Sobel:** We could not be sure the patient did not have a tumor, and a malignant tumor which metastasizes leaves one with a completely uncontrollable situation. Because adrenal hyperplasia is so rare in young children, we did not believe it justified to postpone surgical exploration. We have not considered irradiation of the pituitary because the consequences of successful irradiation of the pituitary in such a young child are not known. Reduction of ACTH production might be accompanied by panhypopituitarism. The patient’s gland showed more hyperplasia of the glomerulosa than of the inner zones, which
suggests that excessive production of ACTH may not be the cause of his disease.

**QUESTION:** Would response to ACTH provide an answer to the question of whether or not there is a tumor?

**DR. SOBEL:** If you mean from the diagnostic point of view, some tumors do respond to ACTH. I have seen a 2-year-old boy whose excretion of 17-ketosteroids rose from 100 to 150 mg/day in response to ACTH. We were sure he had a tumor because of the very large amount of hormone he excreted; no tumor was demonstrated by intravenous pyelography. A small adrenal cortical tumor was removed the day after the test had been performed. Whether it was his non-tumorous adrenal tissue which was responding to the ACTH, or fluctuations in hormone production by the tumor, I do not know. In the present patient, the operation seemed a reasonable and conservative thing to do.

**REFERENCES**


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**THE NURSING OF MENTAL DEFECTIVES**

Charles H. Hallas, R.N.M.D. Bristol, England, John Wright & Sons Ltd., 1958, 182 pp., $5.00.

In England and Scotland, unlike the situation in this country, one of the nursing specialties is known as "mental deficiency nursing." The training for this is professionally supervised, and when completed, leads to official registration or certification, following a suitable examination. This book, written by a registered nurse, teaching the course in one of the official hospitals for mental defectives, is designed to serve as a textbook to fill a long-standing need, to assist these nursing students in their studies, and is also suggested as helpful reading for parents and others who may be caring for these children.

In this country, its major use would be by attendants, practical nurses, and possibly graduate nurses working in state or private training schools for the mentally retarded. An attempt is made to cover practically every aspect bearing on the problem, including legal considerations (unfortunately these vary considerably from American legal commitment procedures); medical aspects primarily related to classification; educational procedures; institutional and community management; psychologic and psychiatric implications; occupational and physiotherapy; and many others. In a book of about 170 pages, covering so wide a field, the result is a very superficial treatment which in many areas approaches a simple glossary of terms. Perhaps British student nurses need such a summary for purposes of review prior to taking examinations. Unfortunately, as a source book designed to help in the understanding of the over-all problem, and in developing effective techniques in management, it will be considerably less helpful than the many pamphlets, available at little or no cost, from the Children's Bureau, and many of the state agencies now interested in the field.

This book inadequately meets the need, which admittedly exists, for a textbook suitable for training nursing personnel in the field of the mentally retarded.

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