TWO CASES OF SARCOIDOSIS INVOLVING THE HYPOPHYSIS TREATED WITH CORTICOTROPHIN AND CORTISONE

By

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Bleisch & Robbins (1952) have reported 4 cases (collected from autopsy records) of cryptogenetic granulomatous involvement of the hypophysis, two of which were associated with hypophyseal deficiency syndromes. Of these cases, 3 were associated with a sarcoid-like systemic disease; one appeared to be confined to the hypophysis only.

In the literature they found a further 50 cases of giant-cell granuloma without any evident cause, involving the hypophysis. Of these 16 were associated with hypopituitarism and in 23 the condition had apparently caused diabetes insipidus. They stated that these 54 cases probably included some cases of noncaseating tuberculosis of a healed or chronic miliary type, some cases of sarcoidosis, and possibly a case of healed syphilis and one of reaction to trauma.

REPORT OF OWN CASES

Case 1. – A 52 year old man was hospitalized on October 23., 1952. He complained of rheumatic-like pains in the back and the right side of the chest, weakness and fatigue with an increased need of sleep (up to 16 hours a day), impotence and loss of libido. He always felt out of sorts and often depressed.

From 1928 to 1934 he suffered from repeated attacks of iritis.

In 1943 facial cutaneous manifestations and pulmonary involvement developed, and the Kveim test was positive.

In the period from 1939 to 1943 he had recurrent subacute attacks involving the
central nervous system (dizziness, vomiting, diplopia and nystagmus), and since then has continued having the above described symptoms.

Tuberculin reactions were doubtful. The test for syphilis was negative in the blood and the spinal fluid. The E. S. R. has varied (14–87 mm.).

The physical examination showed moderate obesity, with female distribution of fat, thin eyebrows, scanty pubic and absence of axillary hairs, no hair over the chest, arms and legs (formerly abundant hair over chest and extremities). The beard was sparse (shaved every second or third day).

The skin was sallow, thin and finely wrinkled. The nails had no semilunars except on the thumbs where they were small.

The nose was a diffuse blue-red, and was in many places covered with small yellow-brown papules.

Over the right eyebrow and on the right cheek were two pulsating arterial spiders, about 2–3 mm. in diameter.

The liver was palpable one inch below the costal margin. Testes were small and soft and the prostate could not be distinctly felt.
Laboratory data. – The volume of urine and fluid intake within normal limits. Blood sugar curve normal. Follicle stimulating hormone less than 40 M. U.

Biopsy from a papule on the upper lip showed the characteristic picture of sarcoidosis. X-ray of the sella turcica was normal. X-ray of the lungs showed extensive fibrotic changes with cavitations and pleural thickness.

Hgb. about 75–80 %. Serum cholesterol values before treatment 470 and 530 mg. %.

From 7/2 to 19/5-53 (3½ months) the patient was treated with cortisone (1.2 gm.), corticotrophin (685 I. U.) and protamine-zinc-corticotrophin (650 I. U.). He also received small doses of streptomycin (26.5 gm.) (prophylactic against possible tuberculous focus), and after one month's treatment small doses of thyroid extract (20.25 gm.) because of a falling B. M. R.

Unfortunately cholesterol-tests were not done during or immediately after treatment. 292 mg. % was obtained 15 months after treatment.

Blood pressure showed a transient rise from 110/65 to 125/65.

The patient gained 6 pounds. No signs of edema. Clinical and serological (13.6 mg. %) signs of hypopotassemia were noted during treatment, which rapidly returned to normal after KCl by mouth.

The tuberculin reactions were negative during treatment.

Electrophoretic determinations were (for technical reasons) first investigated after treatment. These showed an increase in serum gammaglobulin, lowest immediately after cessation of treatment, 20 %, and increasing up to 33.1 % (of total protein). Alfa 2 globulin was also slightly increased, maximum 11.3 %. The albumin-globulin ratio before treatment was 1.1–1.23, during treatment 1.36–1.63 and after treatment 1.01–1.17.

During treatment the rash showed marked decolouration and the papules on the nose
and the upper lip diminished in size and were much softer than before. A few months later, however, the exanthem returned completely.

The pulsating arterial spiders faded slowly during treatment, but later partly returned and in the one on the cheek, pulsation was observed.

The nails, the skin and the hair remained unchanged and there were no changes in the testes or the prostate.

X-ray of the lungs remained unchanged.

The liver diminished in size and became softer on palpation, and 3–4 months after treatment it was scarcely felt, but later returned to the same size and consistence as before.

The maximal breathing capacity increased from 58–62 litres/min. before treatment to 62–74 l/min. during treatment, but decreased later to 58–64 l/min. The vital capacity showed a transient rise from 2300–2500 ml, to 2500–2700 ml.

During treatment the patient spontaneously expressed a sense of well-being. One to two months after cessation of treatment he again felt depressed and complained of weakness, later, however, he felt very well and in August 1954 no subjective symptoms had returned. His drowsiness had mostly disappeared.

In 1955 subjective symptoms partly returned and substitution therapy was begun.

Case 2. – A 34 year old man was examined in September 1954.

In 1949 a routine X-ray examination showed a leftsided hilar glandular enlargement. Since 1950 he has had repeated attacks of eye inflammation. In 1951 there was a period of fatigue, and on examination a moderate, but generalized lymph gland enlargement was found, which has since remained unchanged.

Biopsy from a lymph gland showed chronic, specific inflammation; sarcoidosis ?, Tbc. ?.

Tuberculin reactions were negative. The E.S.R. was moderately elevated.

He complained of increasing impotence and loss of libido for the last 10 years. At the same time there was loss of hair over the chest and extremities, and he noted changes in his skin. He further complained of an increased need of sleep (12–14 hours a day).

On examination, the skin was sallow, thin and soft. The axillary and pubic hair were scanty. There was a moderate generalized lymph gland enlargement. No rash. The testes were markedly small and soft. The prostate was small, about the size of a pea, normal in shape and consistence. The liver was palpable ½ inch below the costal margin.

Laboratory data. – Volume of urine and fluid intake within normal limits, but the Robinson-Power-Kepler test was markedly positive. Blood sugars curve normal. Follicle stimulating hormone in urine less than 40 M.U.

X-ray of sella turcica normal. X-ray of the lungs showed a leftsided increased hilar shadow and small parenchymatous opacities in the upper hilar region. X-ray of hands and feet showed ostitis multiplex cystoides.

Hgb. about 80–90 %.

From 26/11-54 to 31/5-55 (6 months) the patient was treated with protamine-zinc-corticotrophin (515 I.U.). From 18/3 to 18/4 he also received small doses of vasoressin (60 I.U.).

During treatment X-ray of the lungs showed some regression in the hilar shadow, but after treatment there was no significant difference from the X-ray taken before treatment.
Cholesterol increased from about 150 mg. % at the beginning of treatment to 230 mg. % three months after treatment.

Full laboratory data during treatment can be found in Figs. 3 and 4.

In the period from 21/12-54 to 6/1-55 the corticotrophin dosage was 20 I. U. twice a week (100 I. U. in 15 days). This seems to have been an overdosage as indicated by the excretion of the 17-ketosteroids which fell to zero and the gammaglobulin which increased to 40 % of total protein. The E. S. R. increased somewhat and the B. M. R.
did not continue to fall. Only the eosinophils seemed unaffected and showed a further steady decrease.

During treatment, the patient felt well, and his drowsiness disappeared. The blood pressure was about 120/80 and showed no variations. There were no signs of edema. The electrolytes were within normal limits with no significant alterations. The vital capacity showed a transitory increase from 3600 to 4000 ml. and the expiration pressure increased by 20 °/o.

After cessation of treatment some of his subjective symptoms slowly returned, and as there only had been a very slight transitory increase in potence and libido, substitution therapy was started in September 1955.

**DISCUSSION**

In both cases the subjective and objective symptoms were suggestive of a lesion of the hypophysis. Excretion of F. S. H. less than 40 M. U. indicates that the atrophy of the testes is due to hypopituitarism, and the lowered B. M. R. suggests lack of thyrotrophic hormone.

During treatment there were transient changes in the serum proteins. Similar changes have been noted during corticotrophin or cortisone therapy in other diseases, and are assumed to be unspecific. As will be seen from Fig. 4 the serum gammaglobulin decreased during adequate corticotrophin therapy (when the 17-ketosteroids increased).

Robinson-Power-Kepler test was unfortunately not investigated in case number one, but there were no significant alterations of the output of urine during treatment. In case number two the amount increased steadily from 1375 ml. just before corticotrophin was administered November 1954 to 4000 ml. in Jan.-Feb. 1955, and then decreased slowly as the dosage of corticotrophin was lowered. When corticotrophin therapy ceased the volume was 2750 ml., three months later it was 1500 ml.

Vasopressin (betahypophamin) in doses of 10 I. U. was administered twice a week from 18/3 to 13/4-55 (60 I. U.). These small doses caused no significant decrease in the volume of urine (i. e. no more than could be expected after the simultaneously lowered corticotrophin dosage). The Robinson-Power-Kepler test was positive and almost unchanged by corticotrophin and vasopressin. The urinary volume in the four hours after the intake of 1400 ml. of water never exceeded the volume of the urinary output in the morning. Before treatment was started, the four hours total urinary volume was 175 ml. (24 hrs.: 1375 ml.). During treatment it was 450 ml. (24 hrs.: 4000 ml.) and 525 ml. (24 hrs.: 3500 ml.). During the simultaneous administration of vasopressin the urinary volume in four hours increased to 615 ml. (24 hrs.: 2400 ml.) and 1½ months after cessation of vasopressin (May - 55) it was 525 ml. (24 hrs.: 2750 ml.).

*Bean* (1945) refers to an increase of corticoids as a factor in the development of arterial spiders. *Solem* (1952) has demonstrated arterial spiders during
corticotrophin therapy and suggests that the increased value of 17-ketosteroids obtained indicates an etiological factor. It is strange that in our case number one, the arterial spiders slowly faded during treatment and later partly returned.

Robertson & Kirkpatrick (1951) investigated the effects of corticotrophin on a patient with Simmonds' disease. During treatment there was a marked general improvement in health, a rise in the blood pressure and a significant rise in the B.M.R. (believed to be a specific effect).

Variations of the B.M.R. in our cases are given in Figs. 2 and 3. The variations seem to correspond to hormone dosage (and the E.S.R.). The direct effect of corticotrophin has been a lowering of the B.M.R. Thyroid extract in daily doses of 0.15 gm. was insufficient to neutralize this lowering effect in case number one.

Favourable results of corticotrophin and cortisone treatment in sarcoidosis have been reported by Sitzbach & Posner (1951), Lovelock & Stone (1951), Small (1951) and Israel, Sones & Harrell (1954). Refvem (1952) reported good, but transient effects on the exanthem, but no objective improvement of the pulmonary fibrosis.

Our patients showed a higher vital capacity during treatment. It is reasonable to believe that the fibrosing parts in the lungs can be «softened» in the same manner as the papules on the skin, and that the effect is unspecific.

SUMMARY AND CONCLUSION

Two cases of sarcoidosis involving the hypophysis are reported.

Though it cannot be definitely proved at present, it seems justifiable to conclude that the involvement of the hypophysis is caused by sarcoidosis.

The patients have been treated with corticotrophin (case No. 1 also received small doses of cortisone, streptomycin and thyroid extract, case No. 2 small doses of vasopressin). In case No. 1 there was a temporary improvement in the exanthem and transient decrease in the size of the liver. There may have been some improvement of the liver function as shown by the lowered cholesterol value.

There was no objective improvement of the hypopituitarism in the two cases, but a marked subjective improvement during, and shortly after treatment.

No ill effects were observed.

Whittaker & Whitehead (1954) have reported on the effect of treatment with corticotrophin and cortisone combined with other hormones in 9 cases of hypopituitarism. In 5 cases a post-partum necrosis of the hypophysis probably caused the hypopituitarism, in 4 cases the etiology was uncertain.
In both our cases the symptoms of hypopituitarism appeared early in the course of the diseases.

When irreversible fibrosis has occurred in parenchymatous organs, involved by sarcoidosis, it cannot be expected that corticotrophin or cortisone will reverse the formation of granulomatous tissue, though some beneficial effect may still be obtained.

This emphasizes the importance of recognising sarcoidosis as a possible cause of pituitary dysfunction; it should also be recognised that the effect of treatment with corticotrophin or cortisone in pituitary dysfunction may be not only substitutional, but may affect the course of the disease.

REFERENCES