CAT-MONITORED SUPPRESSION OF ADRENAL HYPERFUNCTION IN COMBINATION TREATMENT OF CUSHING'S DISEASE

F. I. Todua, E. I. Marova,
G. G. Karmazanovskii, L. V. Bel'chenko,
and L. E. Kirpatovskaya

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The pathogenesis of Cushing's disease, a severe neuroendocrine disorder, is based on increased secretion of ACTH by the anterior lobe of the pituitary gland, with secondary adrenocortical hyperfunction. A symptom-complex of secondary hypercorticism is formed under these circumstances [1, 2]. Treatment of Cushing's disease (CD) aims to normalize pituitary and adrenal function. For this purpose a combination of therapeutic measures acting on the different stages of pathogenesis is used. Adrenalectomy is an operation of despair, purely life-saving and not removing the cause of the disease. The search continues world wide for methods of depressing adrenal function in CD as alternatives to adrenalectomy and chemotherapy. A nonsurgical method of adrenalectomy has been developed, in which immediately after diagnostic phlebography of the adrenals the central vein of the gland is occluded by a catheter, and the adrenal is then destroyed by injection of an excess of x-ray contrast medium into the vaccular system of the gland [4].

Invasive procedure under control of computer-assisted tomography (CAT) are quite widely used [3, 11]. Punch biopsy techniques in space-occupying lesions of the adrenals have been described and frequently used [5-10]. However, data on the use of adrenal puncture with the aim of injecting therapeutic preparations into the parenchyma of the gland for local action on hyperproduction of adrenal hormones could not be found in the accessible literature. Analysis of experience of the use of roentgenoendovascular destruction of the adrenals in patients with CD and of data on the efficacy of adrenal puncture indicated the positive aspects of these techniques and led us to propose a method of suppressing adrenal hyperfunction in CD under CAT control, and to test it in the investigation described below.

EXPERIMENTAL METHOD

As a result of the experimental part of the work, on mongrel male dogs weighing 4-12 kg, when various sclerosing agents were injected intraoperatively into the adrenals, we chose as the optimal sclerosing agent a mixture of 96% ethanol solution and 76% Verografin solution in the ratio of 3:1. Ethanol was used because of its well researched antiseptic and sclerosing properties, and also its lipolytic activity. The inclusion of 76% Verografin in the sclerosing mixture was necessary to enable visual monitoring of the spread of the sclerosing mixture by CAT. The volume of sclerosing mixture to be injected depends on the degree of hyperplasia and the volume of the gland, determined by CAT.

Combination therapy, including transcutaneous suppression of adrenal hyperfunction (TCSAH) under CAT control and irradiation of the pituitary gland, was given to 42 patients with CD. A mild form of CD was diagnosed in 21, moderately severe in 15, and a severe form in 6 patients. The diagnosis of CD was based on the results of a comprehensive investigation of the patients by biochemical, neuro-ophthalmologic, roentgenologic, and CAT methods. The indications for TCSAH in CD were a syndrome of hypercorticism with a cortisol level above 63.4 ± 18.4 μg%, hyperplasia of the single residual adrenal after contralateral adrenalectomy, inability to tolerate chemotherapy, and also an extremely severe form of CD accompanied by grave complications, when surfical adrenalectomy cannot be undertaken because of the severity

A. V. Vishnevskii Institute of Surgery, Academy of Medical Sciences of the USSR. All-Union Center for Surgery, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR V. D. Fedorov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 110, No. 11, pp. 554-557, November, 1990. Original article submitted April 18, 1990.

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TABLE 1. Assessment of Efficacy of Combination Therapy of Cushing's Disease, Including TCSAH

Degree of severity of hypercorticism	17-OHCS, μmoles/sec		Cortisol at 11 p.m., μg %	
	before TCSAH	after TCSAH	before TCASH	after TSCAH
Mild (n = 21)	22,7±4,6	10,7±3,9 <0,05	38,7±4,9	14,8±5,4 <0,05
Average (n = 15)	29,7±6,1	13,9±3,6 <0,05	43,8±7,7	16,3±3,8 <0,05
Severe (n = 6)	36,2±6,8	21,6±5,9 >0,5	82,6±	52,7±21,1 >0,5

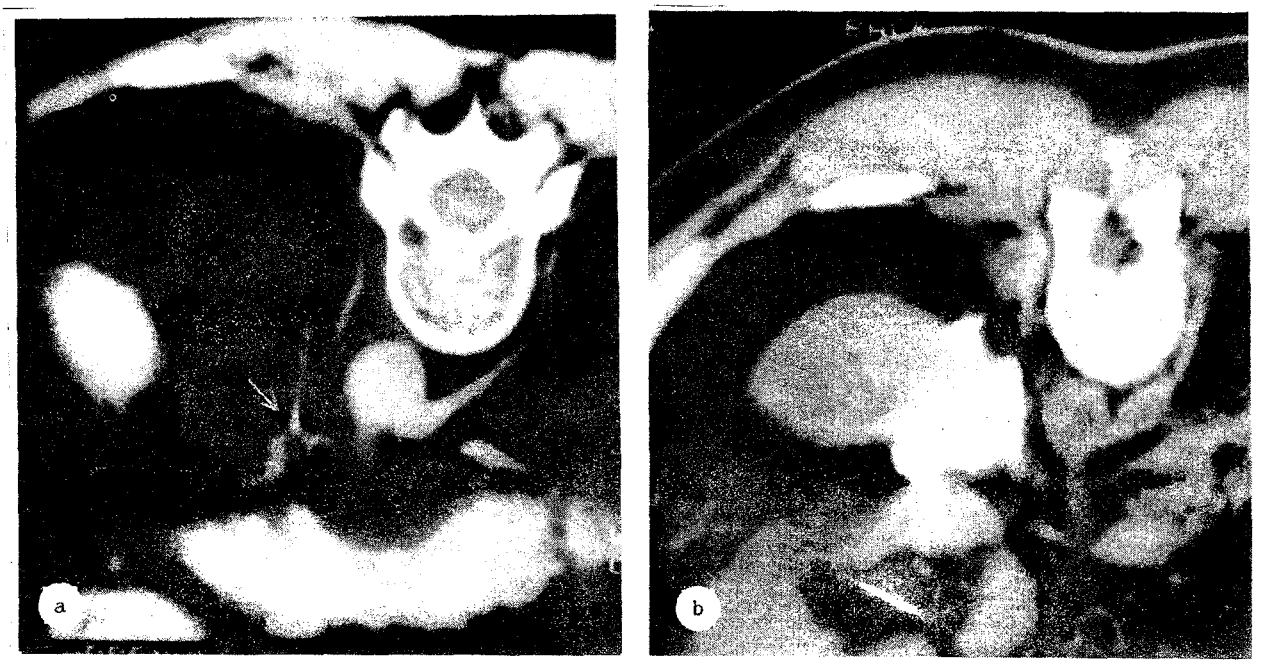

Fig. 1. Stages of transcutaneous suppression of adrenal hyperfunction in CD: a) puncture needle (arrow) in parenchyma of body of left adrenal; b) control tomogram shows good inhibition of adrenal and periadrenal cellular tissue (arrow).

of the patient's physical state. In all patients TCSAH was the first stage of treatment of CD and was followed by radiotherapy of the pituitary. In 38 patients the second stage of treatment was proton therapy of the pituitary by the method described in [1, 2]. Three patients received telegammatherapy to the diencephalo-hypophyseal region, but the disease recurred in 2 patients despite previous radiotherapy.

The technique of TCSAH was as follows: immediately after CAT of the adrenals, with the patient recumbent in the prone position, the level of puncture was marked out. A control scan was taken to determine the angle of slope of the needle during insertion from 45 to 90° and the distance from the point on the skin to the body of the adrenal. Keeping to these values, the needle was inserted into the parenchyma of the gland under local anesthesia with 0.5% procaine solution. The location of the needle was verified by a control tomogram. Next, the sclerosing agent, consisting of 96% ethanol solution and 76% Verografin solution in the ratio of 3:1, was injected into the adrenal in a volume of 8-15 ml. The quality of inhibition of the adrenal parenchyma and of the periadrenal cellular tissue was then verified in a series of tomograms. The manipulation ended with removal of the puncture needle and application of a sterile dressing to the puncture wound (Fig. 1a, b).

RESULTS

As Table 1 shows, in a series of 42 cases of combined treatment a positive effect was observed in 36 (85.7%). A clinical effect was not achieved in 4 patients with a severe form of CD. Repetition of CAT on these patients revealed partial sclerosis of the adrenal without the characteristic condensation and shrinking of the pedicles of the gland and absence of scar changes in the periadrenal cellular tissue. In 2 of the 6 patients with an extremely severe form of CD, hyperproduction of adrenocortical hormones was depressed after TCSAH on average for 12 months, enabling these patients to be prepared for surgical adrenalectomy.

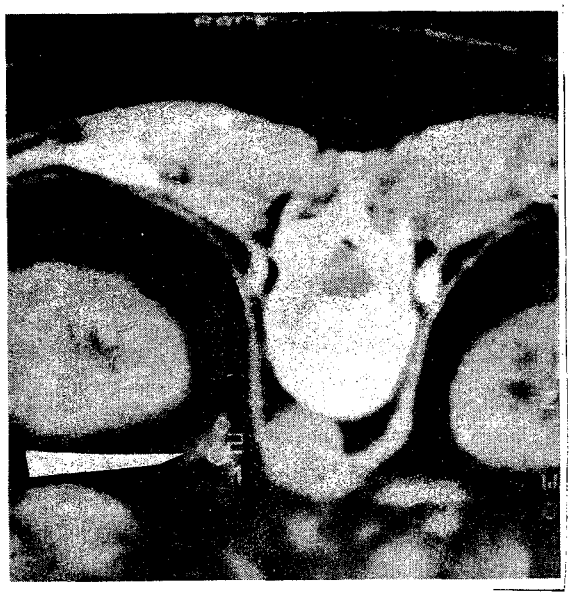

Fig. 2

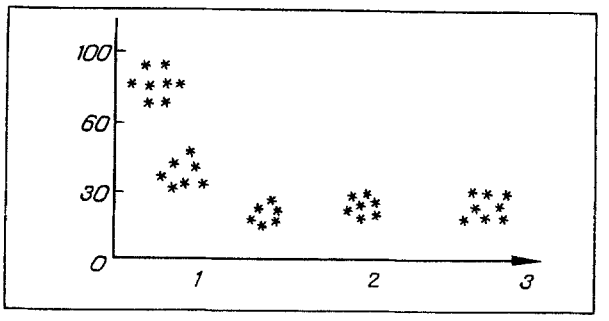

Fig. 3

Fig. 2. Adrenal gland 12 months after TCSAH (arrow).

Fig. 3. Dynamics of cortisol secretion (ordinate, μg%) 1 month (1), 12 months (2), and 3 years (3) after TCSAH.

In 12 patients with moderately severe CD, treated by irradiation of the pituitary 4 and 6 years before TCSAH, the technique proved insufficiently effective. These patients were additionally treated with inhibitors of adrenocortical hormone biosynthesis, and remission of the disease was achieved in one case after repeated pituitary irradiation and in another case after surgical adrenalectomy.

In 32 of 38 patients with a definite clinical improvement after TCSAH, control CAT of the adrenals was carried out after intervals of 1 month and 1 and 3 years. At the first scan (1 month after TCSAH) condensation of the parenchyma of the gland on average by 2-2.5 times and moderate deformation of the contours of the adrenal were found. Later the condensation of the gland remained and its deformation was increased; perifocal sclerosis of the periadrenal cellular tissue was observed with the formation of a residual cord (Fig. 2).

The dynamics of adrenocortical hormone secretion from 1 month to 3 years after TCSAH is illustrated in Fig. 3.

It must be particularly emphasized that TCSAH causes little trauma to the patient, in whom operative stress may induce additional activation of the pituitary. During the manipulation and for 24 h thereafter patients are aware of mild dragging pains in the lumbar region. Theoretically it should be possible to perform TCSAH on either the left or the right adrenal. However, infiltration of the periadrenal cellular tissue on the right side may involve the inferior vena cava in the process of aseptic inflammation, and for that reason careful consideration must be paid to the topographic relations of the integral organs in this region, and in some cases this may impose constraints on the performance of TCSAH on the right side.

Thus TCSAH, combined with irradiation of the pituitary, is shown to be the method of choice in the treatment of patients with mild and moderately severe forms of Cushing's disease," who are unable to tolerate chemotherapy and have physical contraindications to surgical adrenalectomy.

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