Case Report

THYROID EYE-SIGNS IN NEPHROTIC SYNDROME: A SIDE-EFFECT OF STEROID THERAPY?

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In spite of the considerable laboratory and clinical evidence attesting to the inhibitory effect of adrenocortical steroids on thyroid function,[5] a recent report raises the possibility that hyperthyroidism may be related to steroid therapy.[2] In the patient presented here, thyroid eye-signs and certain laboratory features of hyperthyroidism occurred during steroid therapy for the nephrotic syndrome and regressed upon steroid-withdrawal. It is therefore suggested that the thyroid signs could be related causally to the steroid therapy.

CASE REPORT

Sudden swelling of the abdomen and eyelids led to the admission to hospital of a Coloured boy, aged 7 years, in November 1960. The diagnosis of nephrotic syndrome was established by the finding of a solid proteinuria, a serum cholesterol of 500 mg./ml., and a plasma albumin of 0·70 G/100 ml. He was treated by 50 mg. of prednisone daily for 3 weeks with a good response, and discharged on a maintenance dose of 20 mg. daily.

His second admission on January 1961 followed a recurrence of symptoms. Two months of continuous or intermittent prednisone therapy at 25 - 60 mg. daily was not effective, but the oedema responded after 40 mg. of triamcinolone daily for 2 weeks. A moderate moon-face and slight hirsutes developed at this time. After discharge triamcinolone therapy was irregularly maintained until his third recurrence and hospital admission in May 1962. He was then treated with 40 mg. of methyl prednisolone daily.

About 12 days later he experienced a considerable diuresis following an intravenous infusion of plasma. Two days later prominent lid retraction, lid-lag and apparent proptosis were noted (Fig. 1). The following signs were all absent: ocular muscle palsies, goitre, frank tremor, and tachycardia. The serum protein-bound iodine was 1·2 μg./100 ml. Methyl prednisolone was maintained for 12 days, but because the eye-signs persisted it was then rapidly reduced to 20 mg. daily for 4 days per week, after which the eye-signs subsided within a few days.

During his fourth hospital admission in August 1962, methyl prednisolone was given as 24 mg. of methyl prednisolone capsules/day, but no eye-signs were noted. In October of the same year he was treated for about 6 weeks on 24 mg. of triamcinolone daily; the dosage was subsequently reduced to and maintained at 24 mg. 4 days/week, until his next hospital admission.

His sixth hospital admission was in May 1963; eye-signs were noted 1 week after commencement of 24 mg. of triamcinolone/day (Figs. 2, 3). The subsequent course and treatment are noted in Table I. From August 1963 to May 1964 he was maintained on intermittent steroid therapy, including 2 short courses, 11 and 7 days respectively, of triamcinolone and methyl prednisolone. At no stage was more than a slight lid-lag detectable.

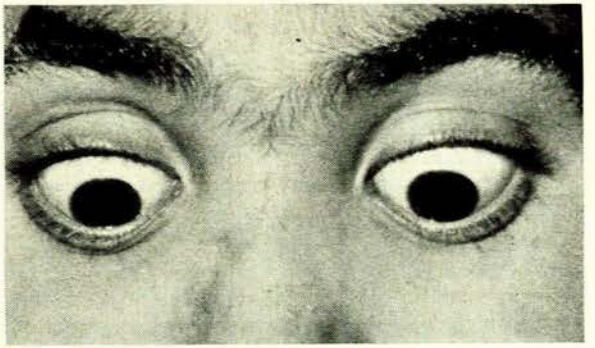

Fig. 1. Marked lid-lag after 10 days of treatment with 40 mg. of methyl prednisolone/day (May 1962).

In May 1964, he died unexpectedly while in hospital. Before this, lid-lag was the only detectable eye-sign. At necropsy the thyroid weighed 8 G (normal for his age) and histological examination demonstrated almost total absence of colloid, but autolysis of the follicular epithelium precluded any observations on the degree of epithelial cell activity. The kidneys were enlarged, the basement membranes thickened, and the tubular epithelium had undergone marked hydropic degeneration. The necropsy diagnosis was nephrosis with colloid depletion of the thyroid gland.

DISCUSSION

A boy suffering from a severe nephrotic syndrome twice developed prominent lid-lag, lid-retraction and apparent

TABLE I. THYROID FUNCTION TESTS IN RELATION TO EYE-SIGNS

Date	*Steroid therapy*	*Eyes*	*Radio-iodine*		*BMR*	*PBI*	*A/G*
			6 hrs. %	*24 hrs.* %		μg. %	*G/100ml.*
15.4.63–26.5.63	Triamcinolone: 24 mg./day for 35 days; 12 mg./day for 4 days; 6 mg./day for 2 days.	Lid-lag and retraction after about 1 week; lasted for more than one month.	(3.5.63) 41	52	+51	2·2	1·1/3·0 (25.4.63) 2·9/2·0 (7.5.63)
27.5.63–13.6.63	0	Eyes better 1-2 weeks after stopping triamcinolone.	(11.6.63) 36	54		2·5	3·0/2·2 (10.6.63)
14.6.63–2.8.63	Prednisone: 30 mg./day for 4 days; 60 mg./day for 15 days; then 30 mg./day.	Normal	(28.6.63) 20	28	—12	1·5	1·3/1·6 (26.6.63)
3.8.63 onwards	Prednisone: 30 mg./day	Minimal lidlag only.				1·0	1·7/2·2 (23.8.63)

Radio-iodine = thyroidal radio-iodine uptake. BMR = basal metabolic rate. PBI = protein-bound iodine A/G = albumin to globulin ratio.

proptosis during the course of corticosteroid therapy; on each occasion the eye-signs regressed after steroid-withdrawal (Figs. 1 - 3). The steroids concerned were methyl prednisolone and triamcinolone; during prednisone therapy there was only minimal lid-lag. Thyroid-function tests during the second episode of eye-signs included an elevated thyroidal radio-iodine uptake and a high basal metabolic rate; lower values were obtained after the triamcinolone was stopped. The low protein-bound iodine throughout the period of study was probably due to the abnormal plasma protein pattern of the nephrotic syndrome. For this reason the low protein-bound iodine does not necessarily negate the diagnosis of hyperthyroidism. Indeed an increased concentration of circulating free thyroxine could co-exist with a depressed total protein-bound iodine. Another difficulty of interpretation introduced by the presence of the nephrotic syndrome is that the thyroidal radio-iodine uptake may be increased, possibly in adaptation to the low plasma-bound iodine. Nevertheless, the association of the eye-signs with elevations in the basal metabolic rate and the radio-iodine uptake, and the concurrent regression of clinical and laboratory abnormalities upon steroid-withdrawal, are evidence for a genuine disturbance of the pituitary-thyroid axis with mild hyperthyroidism. This conclusion is to some extent supported by the colloid-depleted follicles found in the thyroid gland at necropsy.

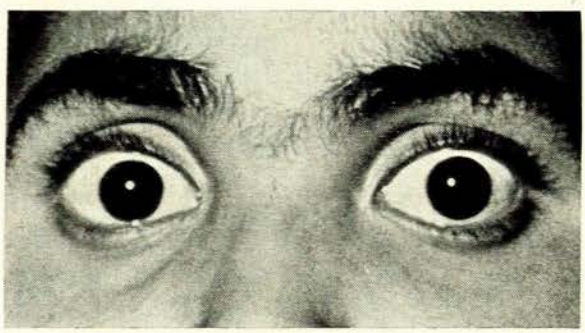

Fig. 2. Apparent proptosis after 9 days of therapy with 24 mg. of triamcinolone/day (April 1963).

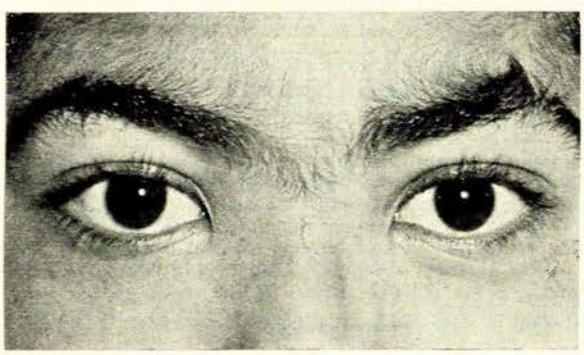

Fig. 3. Normal eyes after cessation of triamcinolone. Intercorneal distance comparable to that in Figs. 1 and 2

Prolonged high-dosage steroid therapy had given our patient features of a mild Cushing's syndrome, which is reported in association with exophthalmos.[4,6] Raised blood and pituitary gland exophthalmos-producing substance activity has in fact been found in patients with spontaneous Cushing's disease and exophthalmos,[6] presumably as part of an underlying pituitary overactivity. However, the administration of exogenous steroids would be expected to lead to regression rather than aggravation of this type of exophthalmos.

Our patient appears to be more closely related to the 2 cases reported by Brown and Lowman.[2] These patients developed frank thyrotoxicosis during prolonged steroid therapy. Our patient merely had features compatible with mild hyperthyroidism, but the expression of these features appeared to be related in some rough way to the steroid dosage.

Although the sum total of data from human and animal experiments suggests that thyroid function is depressed rather than stimulated by corticoid therapy,[5] cortisone administration to rats may promote thyrotrophin secretion[3] and result in exophthalmos.[1]

An association between hyperthyroidism and steroid administration therefore has both clinical and experimental support. The present case report sustains the possibility

that hyperthyroidism may be a rare side-effect of steroid therapy.

We are greatly indebted to our colleagues who advised us: Prof. Russell Fraser who saw and discussed this patient during his recent visit to South Africa; Dr. R. Hoffenberg, University of Cape Town, who saw the patient in consultation and criticized this manuscript: Dr. Michael Harrison, Western Infirmary, Glasgow, and Dr. Paul Walfish, Massachussetts General Hospital, Boston, who kindly commented on the data; and we wish to thank Dr. R. L. M. Kotzé, Medical Superintendent, Karl Bremer Hospital, for permission to publish.

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