Acute endocrine ophthalmopathy in a 12-year-old boy with long-acting thyroid stimulator

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The aetiology of ophthalmopathy associated with thyroid disease is unknown. Excessive secretion of pituitary thyrotropin (TSH) had been suggested as a cause of exophthalmos (thyrotropic) (Falconer and Alexander, 1951). However, assays for thyrotropic hormone in patients with endocrine ophthalmopathy failed to reveal an elevation of TSH in the blood either before or during the development of acute ophthalmopathy (Utiger, 1965; Odell, Wilber, and Paul, 1965; Kriss, Pleshakov, Rosenbloom, Holderness, Sharp, and Utiger, 1967). Adams and Purves (1956) described a new long-acting thyroid stimulator (LATS). Kriss and others (1967) found that endocrine ophthalmopathy and pretibial myxoedema correlated with the level of LATS. LATS differs from TSH in that its peak action of thyroid stimulation occurs 8 to 9 hours after its introduction into experimental animals, it has a longer biological half-life, and is not found in the pituitary gland. LATS is a γ S globulin, suggesting an antibody (Kriss, Pleshakov, and Chien, 1964; Sunshine, Kusumoto, Kriss, Pleshakov, and Chien, 1965; McKenzie, 1965; Kriss and others, 1967).

Acute endocrine ophthalmopathy is unusual in children. The case is reported of a 12-year-old Negro boy who developed acute ophthalmopathy accompanied by a high level of circulating LATS.

Case report

A 12-year-old Negro boy had developed severe acute bilateral swelling of the eyelids, proptosis, chemosis, and ophthalmoplegia 7 days before admission to Stanford Medical Center. He had been treated by his referring physician with oral tetracycline (250 mg. every 6 hours), diphenhydramine hydrochloride (40 mg. every 8 hours), and Cortisporin eye ointment without relief. There was no history of allergies, thyroid symptoms or disease, hay fever, headaches, sinusitis, or ingestion of under-cooked meat.

Examination He was acutely ill and apprehensive, and showed severe bilateral exophthalmos, periorbital oedema, almost complete external ophthalmoplegia, and chemosis (Fig. 1). There was no ocular discharge. Visual acuity was 20/20 in each eye (corrected). No palpable thyroid or pretibial myxoedema was present. The remainder of the examination showed nothing abnormal.

An assay for long-acting thyroid stimulator (LATS) revealed a strongly positive serum level (0.3 LATS units per mg. serum protein). Antithyroglobulin antibodies were not detectable. T₃, T₄, PBI, thyroxine iodine, and free thyroxine were all normal. Radioactive iodide uptake was 3 per cent. in 24 hours. The erythrocyte sedimentation rate was 56 mm. in the 1st hour. The white cell count (including eosinophils), haematocrit, urine analysis, skull, chest, orbit, and sinus x rays, and genetic studies for angioneurotic oedema were all negative.

Hospital course A lumbar puncture showed nothing abnormal. Cultures of cerebrospinal fluid, blood, eyes, and throat were negative.

Therapy Because atypical cavernous sinus thrombosis was suspected, the patient was treated with oral ampicillin (250 mg. every 6 hours), diphenhydramine hydrochloride (75 mg. every 6 hours), and chloramphenicol (250 mg. every 6 hours) for 5 days with no response. On the sixth day, an exposure keratitis developed in the left eye, and the lids were taped shut. On the seventh and eighth days the keratitis improved, the exophthalmos subsided slightly, and some horizontal movement of the left eye could be elicited. Oral prednisone (60 mg. per day) was begun and antibiotics were discontinued.

FIG. 1 Severe bilateral periorbital oedema, exophthalmos, ophthalmoplegia, and chemosis with long-acting thyroid stimulator (LATS)

Result After 36 hours there was marked improvement, with moderate horizontal eye movements, and decreased exophthalmos and lid oedema. One week later the eyes were normal (Fig. 2) except for a residual alternating exotropia. Steroids were discontinued after 3 weeks of treatment, and the residual exotropia was corrected surgically 7 months later.

FIG. 2 Marked improvement after one week of prednisone therapy

Repeat studies for LATS, antithyroglobulin antibody, PBI, free thyroxine, and erythrocyte sedimentation rate were normal one month and 6 months after treatment; 15 months later the 24-hour radioactive iodide uptake had increased to 15 per cent. and the patient remained asymptomatic.

Comment

The signs of endocrine ophthalmopathy include proptosis, ophthalmoplegia, and peri-orbital and conjunctival oedema. Thyroid stimulating hormone (TSH), which is pro-

duced in the pituitary gland, had long been suggested as the aetiology of thyrotropic exophthalmos. However, serum assays have revealed that there is usually no detectable TSH either before or during the development of acute endocrine ophthalmopathy (Kriss and others, 1967).

Adams and Purves (1956) discovered another thyroid stimulator known as long-acting thyroid stimulator (LATS). This is a γ ₂ globulin consistent with an antibody, the antigen for which may reside in thyroid cells (Kriss and others, 1967; Beall and Solomon, 1966). It has been detected in the thyroid cell cytoplasm using immunofluorescent techniques (Blum, Greenspan, Hargadine, and Lowenstein, 1967). It is not present in homogenates of the pituitary gland but is present in biopsy material from pretibial myxoedema.

LATS has been implicated in the development of endocrine ophthalmopathy (Kriss and others, 1967; McKenzie, 1965). Both the LATS level and the ophthalmopathy are independent of the thyroid status, appearing in euthyroid, hyperthyroid, and hypothyroid patients (McKenzie, 1961; Pimstone, Hoffenberg, and Black, 1964). Pretibial myxoedema frequently coincides with the ophthalmopathy. Kriss and others (1967) found that the severity of the ophthalmopathy as well as the pretibial myxoedema correlated with the level of circulating LATS. They also found, in a study of patients treated with I₁₃₁, that the onset of the ophthalmopathy coincided with the appearance of LATS and developed most rapidly during the peak level of LATS. Kriss detected LATS in ten (27 per cent.) of 38 hyperthyroid patients. Ophthalmopathy was present in seven of the ten patients whose sera were LATS-positive. However, ophthalmopathy was found in only two of the 28 patients whose sera were LATS-negative.

Lipman, Green, Snyder, Nelson, and Solomon (1967) found that LATS was closely associated with the number of manifestations of Graves's disease present (*i.e.* hyperthyroidism, ophthalmopathy, dermatopathy) rather than with any individual manifestation. The course of ophthalmopathy usually paralleled the course of LATS. Patients who had higher initial LATS levels or progressed to high levels had a poorer prognosis in regard to ophthalmopathy.

Orally-administered corticosteroids markedly depress the level of LATS and may decrease the ophthalmopathy and pretibial myxoedema (Hoffenberg and Jackson, 1958; Snyder, Green, and Solomon, 1964; Werner, 1966). However, exacerbations (including reappearance of LATS) may occur with steroid withdrawal.

LATS is strongly associated with endocrine ophthalmopathy but has not been proved to be the CAUSE of ophthalmopathy (Lipman and others, 1967; Werner, Feind, and Aida, 1967). It is also possible that a common aetiological factor causes both the presence of LATS and the ophthalmopathy.

The findings in our patient were consistent with endocrine ophthalmopathy. The LATS as well as the orbital signs disappeared with steroid treatment.

Summary

A long-acting thyroid stimulator (LATS) is related to endocrine ophthalmopathy. A 12-year-old Negro boy developed acute endocrine ophthalmopathy accompanied by a high serum titre of LATS which responded to corticosteroid therapy.

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