

Glucocorticoids and Secondary Stress as Combined Causes of Chronic Central Serous Chorioretinopathy

Dan Roberts, Director
Macular Degeneration Support, Inc.

Introduction

Central serous chorioretinopathy (CSC), also known as central serous retinopathy (CSR) is characterized by a serous detachment of the retina which often occurs in middle-aged, caucasian males who exhibit Type A behavior patterns. Chronic CSC may result from the biological effects of glucocorticoids working in opposition to the psychological demands of a Type A behavior pattern in people who are genetically-prone to retinal dysfunction. This theory is based on the following assumptions, which are supported by the literature:

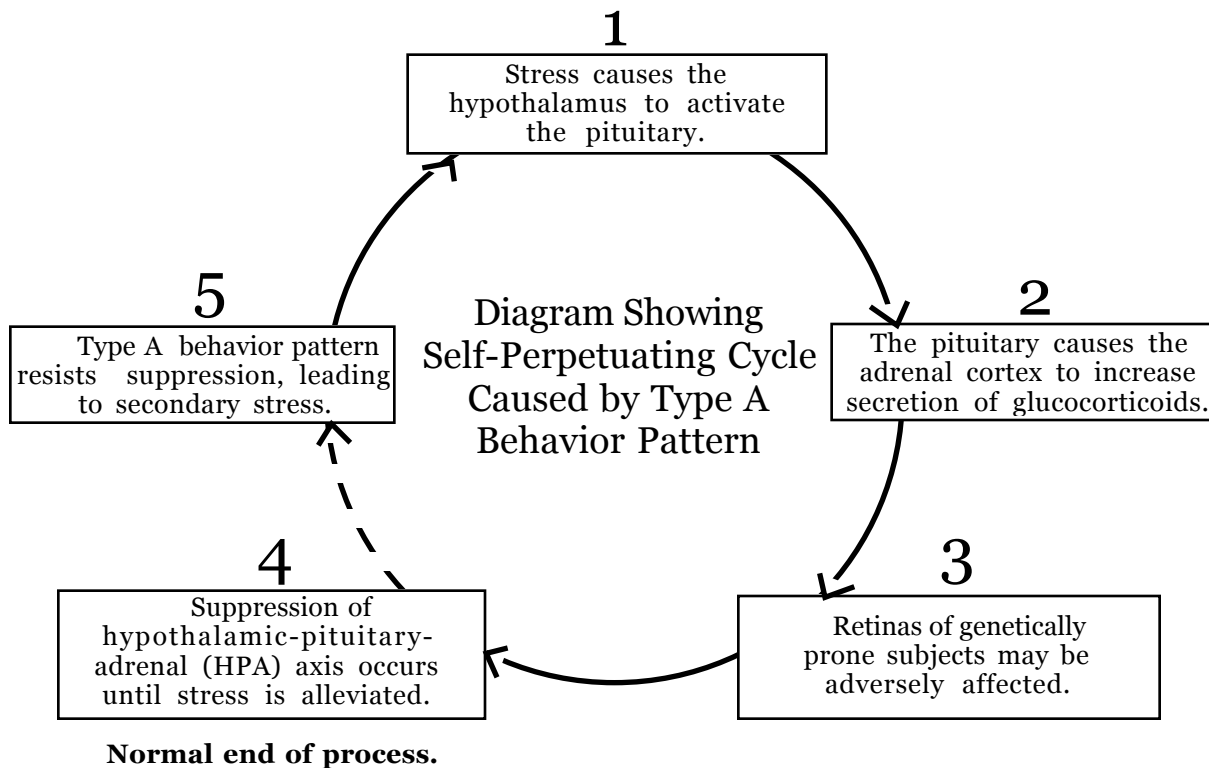
1. Sustained Type A behavior patterns can lead to hyperadrenal activity, which stimulates secretion of high levels of glucocorticoids into the blood.
2. High levels of glucocorticoids (corticosteroids) can cause CSC.
3. Retinal dysfunction can be a result of genetic makeup.

The following questions are addressed:

1. Are there unique psychic/physiologic mechanisms which cause genetically-prone Type A people to develop chronic CSC?
2. Is there a treatment for CSC other than psychic or pharmacologic alteration of behavior patterns?

The diagram below shows the progression from the initial incidence of stress through the expected hormonal changes. It then shows further progression through a unique function of the Type A behavior pattern, which is seen as a likely precipitator of a self-perpetuating cycle of hormonal imbalance leading to CSC. Each step in the diagram is discussed, along with clarifying descriptions and definitions.

Finally, the possibility of treatment with the antiglucocorticoid drug, mifepristone, is discussed, along with consideration of the accompanying danger of adrenal insufficiency.



Discussion

(With numbers corresponding to the diagram)

1

The **hypothalamus** has an important influence on many of the body's functions, including sexual behavior, emotions, hormone production, and the autonomic nervous system. It constitutes only about 1% of the brain volume, and it is found behind the eyes, directly below the brain's thalamus and above the pituitary gland. Stress, such as fear or excitement, causes the hypothalamus to release corticotropin-releasing hormones to the pituitary gland.

2

The **pituitary gland** is the master endocrine gland. In addition to promoting growth (somatotrophic hormones) and controlling water balance (antidiuretic hormones), it controls the functioning of almost all of the other endocrine glands in the body. It is located near the hypothalamus at the base of the brain. When stimulated by the hypothalamus, it releases adrenocorticotropic hormones (ACTH) into the adrenal cortex.

The **adrenal cortex** secretes glucocorticoids (corticosteroids) into the bloodstream, providing the necessary psychological and biological conditions for the body to deal with stress (the "fight or flight" response of the autonomic nervous system). These hormones regulate salt and water balance in the body, prepare the body for stress, regulate metabolism, interact with the immune system, and influence sexual function. The adrenal cortex is the outer section of the adrenal gland, one of which is located on the top of each kidney.

High levels of glucocorticoids could also occur without stimulation from the pituitary, which might result from:

- a. genetics (eg. inherited Type A behavior patterns),
- b. suppression of the immune system,
- c. systemic injection of synthetic cortisone,
- d. surgery,
- e. trauma (eg. stroke or damage from an accident),

- f. degeneration as a result of age or disease, or
- g. tumor.

3

Since the early 1970's, it has been known that overdoses of adreneline (i.e. epinephrine) can produce CSC,^{1, 2, 3} and research continues to link retinal problems with corticosteroids.^{4, 5, 6} A 1993 study by the National Eye Institute, for example, concluded that:

Central serous chorioretinopathy is an uncommon manifestation of endogenous Cushing's syndrome. Since central serous chorioretinopathy has been associated with other hypercortisolemic states, we suggest that glucocorticoids may play a role in the development of this disease.⁷

An explanation of how adrenelin negatively impacts the retina has been offered by Yannuzzi:

The most likely explanation for pathogenesis of the detachment [is] a biochemically mediated (adrenergic) alteration in the macula, resulting in damage and hypermeability to the choriocapillaris, degeneration of a few RPE cells, and consequent breakdown in the posterior blood-retinal barrier in a multifocal distribution.⁸

In subjects who are genetically-prone to retinal disorders, high levels of glucocorticoids may cause temporary problems, which can eventually disappear if the stress level is relieved or when hormonal balance returns. If the source of stress is not alleviated, however, there would be no period of recovery for the retina, and the problem would compound. Step 4 describes the natural resolution, and step 5 describes what might occur as a result of Type A behavior patterns.

4

Activity of the hypothalamic-pituitary-adrenal (HPA) axis diminishes proportionately to the amount of glucocorticoids secreted by the adrenal cortex. If the source of stress is alleviated, the HPA axis eventually regains equilibrium. This would then be the final step in the process for non-Type A people. (It should be noted that some people do not display detectable HPA axis suppression after introduction of high concentrations of glucocorticoids, and others may display suppression of only the hypothalamus and pituitary.)⁹

5

Type A behavior patterns include characteristics such as impatience, rushing through activities and conversation, competitiveness, conscientiousness, reliability, high energy, and obsession with achievement. Coronary heart disease studies have established that sustained Type A behavior can raise the body's adrenal state to levels which produce potentially-harmful amounts of cortisol. (One study reported Type A participants with forty times more cortisol than their Type B counterparts.¹⁰)

The Type A characteristic has been identified by Yanuzzi as a possible precursor of CSC, and treatment has been in the areas of both psychologic and pharmacologic. Patients have been encouraged to modify their behavior, or they have been treated with sedatives, barbituates, or tranquilizers. The use of beta-blockers has also been proposed.⁸ These efforts, however, may be compounding the problem, because a Type A person may actually become more stressed by inactivity and a sense of uselessness, initiating an even greater reaction from the hypothalamus and leading to higher levels of glucocorticoids. Even if no treatment is attempted, the natural reduction of activity in the HPA axis may have the same effect, in that the patient may resist the lower level of stimulus by actively searching out or creating additional stimuli. This "secondary stress" would, of course, result in further elevation of glucocorticoid levels, leading to sustained depression of the HPA axis, thus perpetuating a frustratingly self-defeating situation. Meanwhile, the retina continues to be barraged with high levels of glucocorticoids, and CSC becomes chronic and progressive.

If there is no intervention, this cycle may lead to prolonged suppression of the HPA axis, with the appearance of certain biological and psychological markers, including.

- a. shortness of stature,
- b. sexual abnormalities (eg. late-onset puberty),
- c. psychic disturbances (eg. emotional detachment),
- d. chemical imbalance leading to depression,
- e. eating disorders (eg. obesity or anorexia),
- f. temperature regulation disorders, and/or
- g. sleep disorders.

These markers, combined with family history studies and behavior pattern testing (eg. the Jenkins Activity Survey 8), could help to identify people who are prone to CSC.

Treatment

Based upon the process described here, the likeliest treatment for CSC might be systemic introduction of an antiglucocorticoid, in combination with psychological counseling to assist the patient in modifying behavior.

In 1980, Researchers at Roussel Uclaf, a French pharmaceutical company, synthesized an antiglucocorticoid drug which they labeled RU 486, and which was later named mifepristone. In 1982, the first study was published on the use of mifepristone for termination of early pregnancies. Since that time, it has been shown to be safe and effective in humans, not only for abortion (in combination with misoprostol, a prostaglandin), but as a treatment for conditions and diseases that are caused by elevated levels of cortisol.¹¹

Mifepristone binds to glucocorticoid receptors in the body, preventing cortisol from binding, and evidence suggests that this could also be an effective treatment for CSC. After a long legal and ethical battle, the drug was approved for use in the United States by the FDA in September 2000, and prior to that, it had been made available in this country under compassionate use protocols for a small number of people with Cushing's syndrome, meningioma, and breast cancer.¹²

There appear to be no dangerous side effects from mifepristone, but CSC patients should be monitored carefully for possible development of adrenal insufficiency.¹³ A dramatic reduction in glucocorticoid hormones after prolonged suprphysiologic levels could leave the suppressed adrenal glands unable to generate sufficient cortisol, and the patient could suffer from steroid withdrawal syndrome or adrenal crisis (hypotension). To avoid this, a program of gradually increasing dosage of the antiglucocorticoid should be custom-designed according to individual tolerance levels.

Summary

High levels of glucocorticoids appear to have a causal effect on CSC. In addition, studies have shown that the majority of people who contract CSC exhibit Type A behavior patterns, which may cause the subject to either actively or passively resist the diminished activity of the HPA axis during hypercortisolism. This "secondary stress" would lead to continual stimulation of the hypothalamus and could cause chronic CSC as a result of persistent high levels of glucocorticoids.

A possible way to break the self-perpetuating cycle might be the antiglucocorticoid drug, mifepristone, in combination with psychotherapy. The administering physician should be vigilant about possible hormonal difficulties, such as adrenal insufficiency, and be prepared to adjust dosages accordingly.

Conclusion

Mifepristone has proven safe and effective as an abortion drug in women and as a treatment for certain diseases. Perhaps it should now be seriously considered for clinical trials as a possible treatment for, and prevention of, CSC. The studies should also determine:

1. the effects of prolonged use of the drug,
2. correct dosages to maintain necessary glucocorticoid levels,
2. the effect of the drug on male physiology (preliminary studies have shown that RU 486 potentially can act as a contraceptive in males, as well as females), and
3. the dilemma which women with chronic CSC might face if desiring to conceive children.

Reasonable evidence exists of the possibility of treating CSC through hormone therapy, and the use of an existing, approved drug such as mifepristone for this secondary purpose should make its road into the ophthalmological market relatively smooth. Use of antiglucocorticoids, combined with a realization of the psychological effect of the Type A behavior patterns on the hormone system, could be an important step in the right direction.

For more information on mifepristone, see the following Internet sites:

RU-486 Abortion Pill (a.k.a. Mifepristone) at www.religioustolerance.org/aboru486.htm (An overview of mifepristone.)

Mifepristone Trial Sites in the U.S. at www.feminist.org/rrights/mifeptrials.html.

References:

- 1 Nagayoshi K. Experimental study of chorioretinopathy by intravenous injection of adreneline. *Acta Soc Ophthalmol Jpn*, 1971; 75:1720-1727.
- 2 Miki T, Sunada I, Higaki T. Studies on chorioretinitis induced in rabbits by stress (repeated administration of epinephrine). *Acta Soc Ophthalmol Jpn*, 1972; 76:1037-1045.
- 3 Yoshioka H, Sugita T, Nagayoshi K. Fluorescein angiographic findings in experimental retinopathy produced by intravenous adreneline injection. *Folia Ophthalmol Jpn*, 1970; 21:648-652.
- 4 Spraul CW, Lang, GE, Lang, GK. Retinal pigment epithelial changes associated with systemic corticosteroid treatment: report of cases and review of the literature *Ophthalmologica* 1998, 212:2:142-148.
- 5 Haimovici R, Gragoudas ES, Duker JS, Sjaarda RN, Elliott D. Central serous chorioretinopathy associated with inhaled or intranasal corticosteroids. *Ophthalmology*, 1997 Oct; 104:10, 1653-60.
- 6 Wakakura M, Ishikawa S. Central serous chorioretinopathy complicating systemic corticosteroid treatment. *Br J Ophthalmol*, 1984 May; 68:5, 329-31.
- 7 Bouzas EA, Scott MH, Mastorakos G, Chrousos GP, Kaiser-Kupfer MI. Central serous chorioretinopathy in endogenous hypercortisolism. *Arch Ophthalmol*, 1993 Sep; 111:9, 1229-33.
- 8 Yannuzzi LA. Type A behavior and central serous chorioretinopathy. *TR. AM. OPHTH. SOC.* Vol LXXXIV, 1986; 799-845.
- 9 Jasani MK, Boyle JA, Greig WR, et al. Corticosteroid-induced suppression of the hypothalamo-pituitary-adrenal axis: observation of patients given oral corticosteroids for rheumatoid arthritis. *QJM*, 1967; 36:261-276.
- 10 Williams RB, Lane JD, Kuhn CM, et al: Type A behavior and elevated physiological and neuroendocrine responses to cognitive tasks. *Science*, 1982; 218:483-485.
- 11 New international association provides evidence of cortisol's major role in AIDS and other diseases. *PR Newswire, Financial News*. June 21, 1996.
- 12 Nieman LK, et al. Successful treatment of Cushing's syndrome with the glucocorticoid antagonist RU 486. *Journal of Endocrinology and Metabolism*. Vol 61(3), 1985; 536-40.
- 13 Krasner AS. Glucocorticoid-induced adrenal insufficiency. *JAMA*. Vol 282, No. 7, 1999; 671-676.

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