Significance of Hypercortisolism in Anorexia Nervosa

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Abstract

1. A paper recently published in the medical press brings *substantial evidence that elevated (high) level of Cortisol is a cause or the cause of 'high cortisol' chronic diseases, and not the result of same.*

2. Cortisol level is elevated in anorexia nervosa and declines during recovery. Recent evidence suggests that sustained 'high Cortisol' as found in anorexia nervosa and other conditions (depression, alcoholism, Cushing's disease) induces ventricular swelling and subsequent brain atrophy that is reversible provided Cortisol levels are normalized, either by discontinuing corti-costeroid therapy if used, or by employing appropriate medication.

3. Pharmaceutical products that have Cortisol lowering/antagonist capabilities have been shown to induce beneficial, sometimes impressive results, when used in the treatment of chronic diseases, which are totally unrelated except they all have in common, hypercortisolism.

This manuscript submits the hypothesis that 'high Cortisol' is a cause, or the cause of anorexia nervosa; and if Cortisol antagonist pharmaceuticals are used to treat it, then demonstrable clinical improvements should be obtained.

The 'acid test' of this hypothesis namely its use in 42 patients with anorexia nervosa and results obtained so far ranging from very favorable to impressive in all patients treated, seems to provide a suggestive albeit preliminary indication that Cortisol antagonists, would find a place in the armamentarium of treating this disease.

Introduction

The high Cortisol origin, Cortisol antagonist therapy of anorexia nervosa was conceived as a result of a meeting in July 1983 between the two authors, James M. Parsons, M.D. (JMP), a psychiatrist in private practice in Melbourne, Florida and Alfred T. Sapse, M.D. (ATS), a research scientist in the field of stress, in Miami, Florida.

JMP has treated many anorexia nervosa patients with techniques which represented the current state of the art. The results

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obtained, very often disappointing, were comparable with those obtained by others. Since January, 1983, he included intravenous vitamin C and phenytoin in the treatment of anorectic patients. At that time, reports suggested that phenytoin could be of value in the treatment of anorexia nervosa and vitamin C in depression and depressive disorders. Surprisingly enough, the results, obtained since phenytoin and vitamin C were introduced in the therapy, became considerably better.

ATS had carried out research in the field of biochemistry of stress. As a research associate and following a lead from Dr. Hans Selye, he was looking for a biochemical vs. psychological common denominator of stress and 'stress' diseases. The result of his research actively carried out over a period of years was a manuscript entitled *Stress, Cortisol Interferon and Stress Diseases. I. Cortisol as the Cause of 'Stress' Diseases*, published recently (1984) in the medical press (1).

The highlights of this manuscript are:

1. Elevated level of Cortisol precede chronic diseases and do not follow them, when Cortisol is checked for this purpose in pre-disease conditions.

2. When elevation of Cortisol level was induced through long-term corticosteroid therapy, in patients suffering from diseases requiring this type of treatment, side effects would result. These side effects mimic various types of 'chronic diseases' ranging from depression, ulcers, hypertension, diabetes, dementias, and others.

These corticosteroid-induced 'chronic diseases' are practically indistinguishable from the endogenous 'high Cortisol' chronic diseases, as they are seen in the every day medical practice. The implication of these data, is that in both corticosteroid-induced chronic diseases and in chronic diseases associated with endogenous high Cortisol, the high Cortisol element is the cause and not the result of these diseases.

At this point it is of interest to mention, that some preliminary data generated by JMP's clinical studies on anorexia, strongly suggest that in some anorectic patients the onset of anorexia has coincided with institution of corticosteroid therapy of those patients for whatever reason used (2). These findings, rather unexpected, would have to be confirmed by others.

3. A number of pharmaceutical products have been shown to induce unexpected, beneficial and sometimes dramatic results when used in the treatment of various chronic diseases, which are totally unrelated, except they all have in common elevated levels of Cortisol. A check of references indicates that these pharmaceuticals have varying degrees of Cortisol antagonist capabilities. Among them:

a) Phenytoin (Dilantin, Diphenylhydantoin, DPH) a product approved by the FDA for the treatment of epilepsy.

A book authored by Jack Dreyfus called, *A Remarkable Medicine Has been Overlooked*, has presented abundant evidence that phenytoin induces beneficial results for a wide range of diseases including anorexia nervosa/bulimia, depression, dementias, hypertension, ulcers, migraine headaches, and many others. Literature research shows further that phenytoin has Cortisol antagonist capabilities when tested in tissue culture, in experimental animals, and in clinical use, including Cushing's syndrome.

b) Procaine is able to prevent experimental ulcers induced by stress in animals.

c) Vitamin C (Ascorbic Acid) has an inhibitory effect on Cortisol, following adrenal stimulation, and elevates blood concentration of salicylates.

d) Salicylates (Aspirin, etc.) have Cortisol lowering capabilities even when Cortisol levels are normal. Aspirin prevents release of prostaglandins from the spleen and platelets and prevents synthesis of prostaglandins from arachidonic acid. It is known that prostaglandin El and Fl increase the concentration of Cortisol by direct action on the adrenals. In this light, one may be tempted to associate the newly reported therapeutic effects of salicylic acid (Aspirin) in such 'high' Cortisol diseases as diabetic retinopathy and myocardial infarction, as being due to its potential Cortisol antagonist capability.

e) Lidocaine appears to be a powerful Cortisol antagonist. When used in surgery, when local anesthesia is indicated, lidocaine is the only anesthetic whose use would prevent elevation of Cortisol levels in blood/ urine, before, during and after surgery.

All other local anesthetics, commonly used in surgery, do not prevent elevation of Cortisol levels in plasma and/or urine, prior, during and after surgery. Recently, the use of lidocaine, administered intravenously, has been extended in clinical use to prevent myocardial infarction and in the treatment of arrhythmias.

Along with these 'old' Cortisol antagonists, new pharmaceuticals approved by the FDA for different claims are joining the ranks. Some are reputed to have some therapeutic capabilities that cannot be explained to date.

Among them are the histamine H2 receptor-inhibitor cimetidine (1), the serotonin and histamine antagonist cyproheptadine, and, especially, the dramatic Cortisol antagonist capabilities of clonidine hydrochloride (Catapres™) (3). In the case of clonidine hydrochloride, a review of the medical literature of recent years has shown that, not only can it dramatically lower the levels of Cortisol, but it is also able, in the hands of experimental researchers to induce surprisingly effective treatment effects in various conditions heretofore considered incurable and/or intractable (4).

Hypercortisolism and Anorexia Nervosa

Anorexia nervosa has been shown to be associated with elevated levels of Cortisol in blood and/or urine since 1957 (5). A plethora of articles dealing with this subject were published since (6).

In 1971, a new finding related to high Cortisol was reported, indicating that it can induce ventricular swelling followed by cerebral atrophy in Cushing's, alcoholism, and following corticosteroid therapy (7). In 1977, anorexia nervosa was singled out, and joined the spectrum of diseases associated with cortisol-induced ventricular swelling and next, brain atrophy (8).

However, the positive, encouraging element brought up by these new findings was that this cerebral atrophy in conditions including anorexia nervosa is reversible, provided that proper medication was used, or corticosteroid therapy, when used, was discontinued. This was a rather surprising development, since the old belief had been that a brain atrophy once in place is irreversible, i.e., permanent.

In 1983, Kellner and his associates at the NIMH reiterated,".. .that the increased Cortisol production in some (depressed and/or anorectic) patients might be capable of altering the gross structure of the brain and that such alterations might be reversible" (9).

Another very intriguing aspect of the high cortisol-anorexia nervosa saga is that the level of Cortisol previously elevated, declines during recovery from anorexia nervosa (10).

The Cortisol-Antagonist Therapy of Anorexia Nervosa

A meeting in July, 1983, between JMP and ATS, convinced the two that each had a piece of the puzzle, regarding a potential treatment of anorexia nervosa.

As a result of this meeting a high Cortisol origin-cortisol antagonist program was designed for the treatment of anorexia.

The following ingredients were used separately, or in a 'cocktail form', in intravenous (IV), intramuscular (IM) and in oral form, and within the ranges indicated below:

1. Phenytoin 100-1000 mg/day
2. Vitamin C 1000-5000 mg
3. Procaine HCL 100-400 mg
4. Lidocaine HCL 100400 mg Later on, when new Cortisol antagonists were identified they joined the 'old' ones. They were:
5. Cimetidine 300-1200 mg (Attention to drug interaction: Cimetidine/lidocaine; cimetidine/phenytoin.)
6. Cyproheptadine 4-20 mg
7. Clonidine Hydrochloride 0.1-0.5 mg

Regarding the amounts of each single ingredient used, or when used in 'cocktail' combinations, the clinical judgment of the treating physician would help establish the right combination for each patient. There are no standard combinations, since each patient has an individual profile and must be treated with special attention to the avoidance of known allergies, and drug intolerances.

Supplemental Therapies

The above described medical regimen was administered on an out-patient basis. Patients were domiciled at a health ranch and received supplemental therapies such as individual and group psychotherapy, family

therapy, behavior therapy, nutrients, vitamins, minerals, amino acids and the 'teaching kitchen.' This 'teaching kitchen' serves to prepare foods and also instruct the patients to select and prepare their own foods, tasty and nutritionally complete. In this way, the anorexic patient especially during the first 4-5 days of treatment, sees that there is no plot to fatten her (or him).

Diagnostic Procedures

The following criteria for the diagnosis of anorexia nervosa and bulimia were used: a) Feighner et al, 1972 (11), b) Diagnostic and Statistical Manual of American Psychiatric Association (DSM-III) 1980 (12).

Laboratory tests include SMA25 special attention paid to cholesterol levels. High cholesterol levels were reported in anorexia nervosa (13) and exogenous cholesterol is the raw material for 80% of the endogenously produced Cortisol (1). Also included are EKG, EEG and the Halstead-Reitan Neuro-psychological Battery (14). They proved to be very useful in the diagnosis and monitoring of an organic brain syndrome which we have discovered to be part of the disease known as anorexia nervosa. Among the special tests performed is the amino-acid assay in blood and/or urine.

Results

A number of 42 patients were treated so far. The average stay of the patient at the ranch varied between 2-3 weeks. Only very few patients stayed for four weeks. The cost of the treatment including room and board was a fraction of what is being paid for the average three months hospitalization. Upon departing the patient is given a three months supply of a cortisol-antagonist formula in liquid form. This is the only medical regimen the patient would follow at home.

While the detailed results of our therapy are to be reported in a manuscript being readied for the medical press, the following are the highlights:

1. Very impressive changes in the patients' attitude towards eating occur usually after 4-5 days. During the first 4-5 days most of the patients exhibit symptoms as seen in animal experimentations in which dogs, cats and monkeys were submitted to frontal lobe ablation, namely:

a) Abnormal preoccupation with food, b) hyperphagia (bulimia) and c) food rejection (15). This similarity of attitudes, together with disturbed EEG, and findings of frontal and frontotemporal damage on the Halstead-Reitan tests, provide a strong argument that the anorectic patient has a frontal/temporal lobe organic brain syndrome and is not suffering only from a strictly psychological disorder.

So far, we have not performed, neither have we asked the patients to submit to CT scanning. This situation might change shortly, since new information by Weinberger suggests that the CT scanning of anorexia nervosa patients should become a routine test (16).

The results show that after 4-5 days, all of the patients exhibit a marked attitudinal change toward food. They start eating, following normal patterns, and finding that the food is tasty and desirable. They look forward to resuming school or career. Attitude towards family, and treating physician changes. Most of our patients have gone through hospitalizations, forced feeding, and coercive behavior modification techniques. The former feeling of hostility and fear leaves and is replaced with a feeling of confidence and self assurance.

Weight gain occurs slowly, the average gain being between 5-10 lbs. the first 2-3 weeks. The most gratifying results are in the continuous weight gain that occurs after they leave the ranch. Patients followed at home for periods of up to one year, reported a speed-up weight gain averaging 8-10 lbs. a month. Most of them have returned to the ideal weight between the second and the fourth month. In terms of recurrences, only two short ones have been reported so far. Both were associated with family, or boyfriend traumas. They subsided quickly when the maintenance program was reinstated and there were no relapses, or serious recurrences to date.

Objective tests such as EEG, when abnormal, returned to normal within a three week period, except for one patient who was epileptic. The highly respected Halstead-Reitan test that showed frontal and/or frontotemporal brain impairment in almost all cases, at the beginning of the treatment, showed a definite tendency to returning to

normal after three weeks of treatment. No Halstead-Reitan further testing was done after the patients left the program, so we do not know the evolution of these tests. A randomized before and after sampling, utilizing the Halstead-Reitan, is planned for the future.

Laboratory tests have revealed some very intriguing and previously unknown facts. Among them, elevated levels of phenylalanine, and marked depression of other amino acids, especially glutamic acid and amino-butyric acid, before treatment which would rise at the end of treatment. This is a stimulating finding, in that gamma-aminobutyric acid (GABA) is a known key element in synthesis of the neurotransmitter acetylcholine.

When one knows that 'high Cortisol' diverts free glutamic acid into the Krebs cycle (effectively taking GABA for the needs of Cortisol metabolism in what may be described as a 'cortisol steal' effect), and when it is known that Cortisol antagonists can induce the normalization of those GABA levels (17) one must wonder about the real role if any of phenylalanine, GABA and Cortisol in anorexia nervosa.

A Note of Caution When Testing Blood and/or Urine for Cortisol

The high Cortisol level in plasma and/or urine of patients with anorexia nervosa is well documented, and confirmed by numerous studies. When proceeding with the collection of samples of blood and urine for Cortisol determination, we have asked commercial reference laboratories in our area to test these samples for Cortisol, namely for total Cortisol in plasma or for free Cortisol in 24 hours urine. Blood samples were collected at 0830 and 24 hours urine samples were collected daily. These samples were collected by couriers of reference labs. The results would be received at least 2 weeks later, and here is where the surprise starts.

While some of the results show as expected 'high Cortisol' before and 'normal' Cortisol after the treatment others are totally incomprehensible.

Some urine results show a level of 1 mcg. of total Cortisol before treatment (!). With this type of result, the patient should have arrived suffering from terminal Addisonism or been dead long before, of adrenal insufficiency. The same samples of plasma sent to two different reference laboratories showed a wide discrepancy in results reported. Sometimes the post treatment determination of Cortisol showed higher levels than before, in spite of impressive recovery of these patients. We aired our perplexity to various specialists in the field of Cortisol, only to learn that there is 'sheer chaos' in the testing of Cortisol outside research institutions, teaching hospitals, and universities.

Finally we came across a letter to the editor entitled *Technique and Accuracy of the Dexamethasone Suppression Test*, by Wood and his associates in Surrey, England (Arch. Gen. Psychiatry 40, 585, 1983) in which the values of different techniques of measurement of Cortisol were compared and statistically analyzed. The authors, after expressing their own frustrations as to the unpredictability of Cortisol testing, strongly recommend the use of a commercially available kit suitable for 50 Cortisol determinations by radio-immune assay. These tests can be performed 'in house.'

The corporation marketing these kits is located in England but has a Canadian subsidiary. We contacted this subsidiary and learned that these kits are available, economical, but that a proof of owning a license to handle radio-active materials would be required prior to shipping these kits.

We will order these kits shortly; also we might utilize the procedure of collecting the blood samples after a 10 minute stress test, a technique introduced by the Duke University group (18).

Conclusion

We believe, one year after starting the high Cortisol origin-cortisol antagonist approach to the therapy of anorexia nervosa, that this approach appears to work.

Coming down to the hard facts of life, we at the Alpha Anorexia/Bulimia Clinic, realize that even working non-stop with anorexia/ bulimia patients, we would be able, at best, to take care of a few hundred patients a year. When compared to the huge mass of at least two million patients desperately in need of help, that is not much.

Accordingly, we would like many of our

colleagues concerned with the present state of the art of anorexia/bulimia therapy, to visit with us and watch what we are doing. We would be happy if after they return to their place of work, they would use our method. We strongly believe that they would achieve the same impressive results that we have achieved.

While encouraged with the results obtained, we believe that this is only a beginning.

This Cortisol antagonist therapy as it is presently used has its shortcomings. It requires mixtures or cocktails of intravenous products, with the attendant necessity of computing osmotic factors with each patient's I.V. formula to ensure compatibility with human blood. Even when the results obtained are very impressive, we do not know which ingredient did the work or how it did it.

While continuing with what we are doing now, we are actively looking into developing our own single compounds or compound derivatives with Cortisol antagonist capability.

We believe also that pharmaceutical products presently on the market can be used in the treatment of high Cortisol diseases, some of them with no known cause or known therapy. One such pharmaceutical would be clonidine hydrochloride. We believe that this product has merits far beyond its present use.

Also, in collaboration with the Department of Immunology of a U.S. university, we are looking into potential advantages of building a Cortisol monoclonal antibody, to be tested in the future. If this can be done, it would look, at least to us, to be a magic bullet, a 'starwars medical weapon' that the future will hold forth to us, provided the Cortisol inhibition hypothesis continues to prove itself as a viable therapeutic concept.

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