Common Hormonal Problems in CFS - Adrenal

[UPDATED MAY 2023]

Underactive adrenal gland (DHEA and cortisol)

The adrenal gland is an essential part of energy delivery mechanisms. It represents the "gear box" of our car (which I am using as an analogy for human body). It allows us to match energy expenditure to energy demand so none is wasted. This is an essential evolutionary survival mechanism. In response to any stress (physical, psychological, mental or whatever) the gear box will pour out the required hormones to cope. For short term stress (seconds to minutes) the hormone is adrenalin, for medium term stress (minutes to hours) we need cortisol and for long term stress (hours to days) - DHEA.

To be effective the car (to continue with this car-body analogy) must have an engine, i.e. mitochondria, in a fit state to respond to the adrenal hormone kick.

In CFS/ME there is a general suppression of the hypothalamic/pituitary/adrenal (HPA) axis, often associated with adrenal fatigue. Indeed, as we age we all experience declining function in these departments!

If the pituitary gland is under-functioning then the adrenal gland will also under-function. However, the gland itself may fail as a result of chronic stress.

The Hungarian physiologist Hans Selye showed that if you stressed rats, their adrenal glands enlarged to produce more stress hormones (cortisol and DHEA) to allow them to cope with that stress. If the rat had a break and a rest, then the adrenal gland would return to its normal size and recover. However, if the rat was stressed without a break or a rest, he would be apparently all right for some time, but then suddenly collapsed and died. When Selye looked at the adrenal glands, they were shrivelled up. The glands had become exhausted.

The same thing happens in CFS. The Western way of life is for people to push themselves more and more. Many can cope with a great deal of stress, but everybody has their breaking point. The adrenal gland is responsible for the body's hormonal response to stress. It produces adrenaline, which stimulates the instant stress hormone response (fight or flight reaction). It also produces cortisol and DHEA, which create the short and long term stress hormone responses. When the gland becomes exhausted, CFS develops and tests classically show low levels of cortisol and DHEA.

The mother of adrenal hormones is cholesterol. That is converted to pregnenolone. This is the starting point for synthesis of progesterone, cortisol, DHEA, testosterone and oestrogen. All are essential in men and women.

Cholesterol

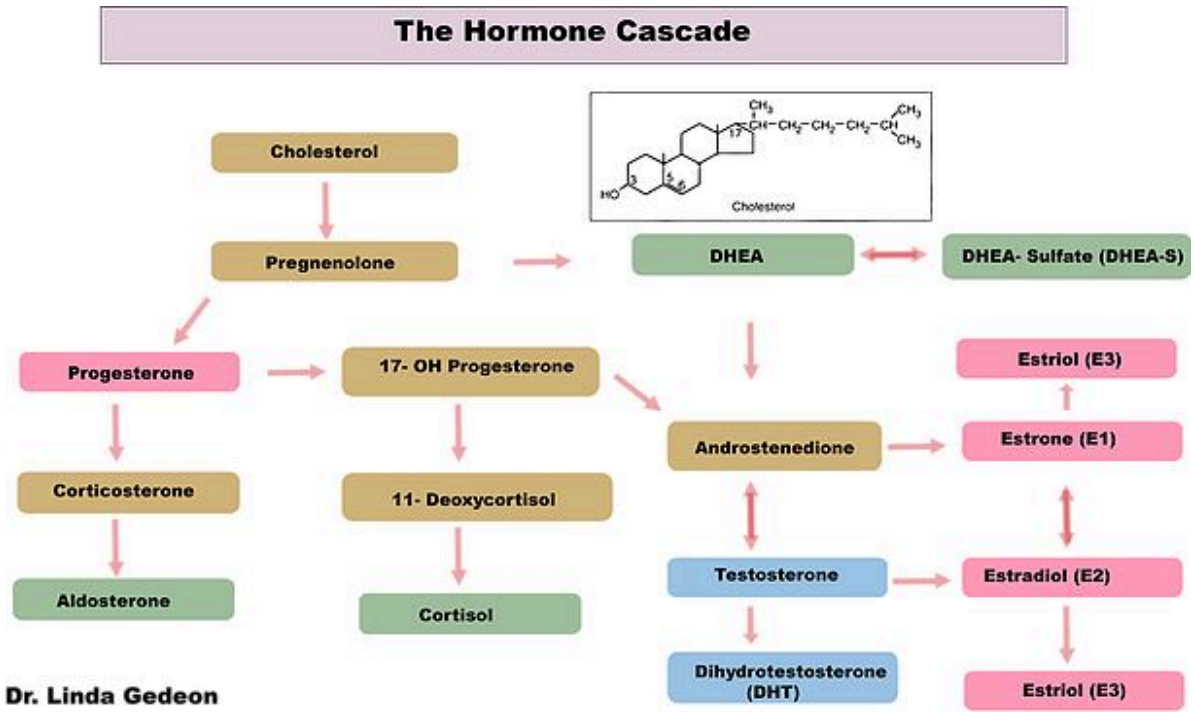
-> pregnenolone -> progesterone -> cortisol

> -> DHEA -> androstenedione -> testosterone

-> -> oestrone -> oestradiol

DHEA is an **anabolic** steroid (and precursor to others), that is to say it builds up tissues; in contrast to cortisol, which is **catabolic** and breaks down tissues. Both are essential for life in the right amounts: too little causes problems, as does too much. Research suggests it protects against the development of osteoporosis, which is a major consideration since all CFSs are at risk of this because of their inability to exercise.

A more complete picture of the hormone cascade can be seen below:



Courtesy of **Dr Linda Gedeon (http://www.drlindagedeon.com/hormone-cascade.html)**

Testing the adrenal gland for cortisol and DHEA levels

See **Adrenal stress profile - salivary**
In order to ensure the right amounts of both hormones, they must be measured. This can be done with the adrenal stress profile (ASP) test. By measuring and supplementing within the physiological range, with biologically identical hormones, there are no side effects.

The ASP test looks at cortisol and DHEA levels over 24 hours. This test is available through Genova Diagnostics Laboratory (you may order a kit using the link below - the test entails taking salivary samples through the day (yippee, no needles!)).

Indeed, salivary sampling is felt to be the most accurate way of assessing steroid hormone levels.

Interpretation of cortisol and DHEA level results of an adrenal stress profile test

DHEA is easy. Low levels mean a deficiency and supplementation with pregnenolone is indicated. See **Prescribing adrenal hormones for CFS (http://drmyhill.co.uk/wiki/Common_Hormonal_Problems_in_CFS_-_Adrenal#Prescribing_adrenal_hormones_for_CFS)** below. Sometimes I see a raised DHEA. This can occur in polycystic ovary disease in women and if there were symptoms suggestive of this (irregular periods, lower abdominal pain, infertility), then an ultrasound scan of the pelvis is indicated. High DHEA is a stress response and the causes of such needs looking for. I suspect the most common cause is metabolic syndrome and hypoglycaemia.

Cortisol is more awkward. Levels vary according to the short term level of stress and for how long that stress has been applied. Increasing cortisol production is the normal response to short term stress and is highly desirable, so long as the stress is removed and the adrenal glands can recover. On-going, unremitting stress means the adrenal glands, and the whole body, are in a constant state of alert, do not get time to recover and eventually pack up.

So, there are several stages of adrenal function gradually leading to failure:

1. **Normal levels of cortisol and DHEA**. Normal result. Normal adrenal gland function.
2. **Raised cortisol, normal DHEA**. This indicates a normal short term response to stress. So long as the stress is removed, the adrenal gland will recover completely. The adrenal gland is functioning normally but the patient is acutely stressed.
3. **High levels of cortisol, low levels of DHEA**. The body cannot make enough DHEA to balance cortisol. This is the first sign of adrenal exhaustion. This is a normal response to chronic stress. However, the patient needs a long break from whatever that chronic stress may be - insomnia, mental, physical or emotional overload, poor diet or whatever. Failure to correct leads to exhaustion. Pregnenolone supplementation can be used to make the patient feel better, but it must be part of a package of recovery without which worsening can be expected.
4. **Cortisol levels low, DHEA levels low**. The gland is so exhausted it can't make cortisol or DHEA. By this time patients are usually severely fatigued. Very low levels indicate Addison's disease - complete adrenal failure. Untreated Addison's disease inevitably results in death.
5. **Cortisol levels low, DHEA borderline or normal**. This probably represents the gland beginning to recover after a long rest. DHEA/pregnenolone may be used to help patients feel better whilst they continue their programme of rest and rehabilitation.

In practice, the interpretation is often not so straightforward because cortisol levels fluctuate through the day in response to the stresses of daily life, peaking in the morning and falling as the day progresses.

If there is a loss of circadian rhythm (i.e. flat levels of cortisol through day and/or morning DHEA low and evening DHEA low) then this may be symptomatic of hypothyroidism.

Where DHEA is low, I would expect melatonin to be low - a symptom of this could be poor sleep quality. In this event I would suggest melatonin 3-9mg at night. Sometimes the slow release melatonin gets better results clinically.

Prescribing adrenal hormones for CFS

I used to treat DHEA deficiency with DHEA. However, I believe pregnenolone is more physiological because it is upstream of all adrenal hormones including progesterone and cortisol.

Cholesterol is the raw material from which steroid hormones are made in the body. The next biochemical step is pregnenolone- this is the mother and grandmother of all steroid hormones. Starting off with pregnenolone means that all steroid hormones can be naturally synthesised in the correct physiological balance.

In theory this should greatly simplify the business of prescribing and monitoring hormones because the body can do its own natural balancing act. Please see **Wikipedia entry on Pregnenolone (http://en.wikipedia.org/wiki/Pregnenolone)**

A physiological dose of pregnenolone is 50mg. You can purchase pregnenolone from the Online Sales shop or other good supplement stores - see **My Online Sales Shop - Pregnenolone 50 mg - 60 capsules (https://www.salesatdrmyhill.co.uk/pregnenolone-by-swansons---50-mg---60-capsules-793-p.asp)** It is better absorbed under the tongue. This works because sublingual doses bypass the liver - the so-called "first pass effect".

This advice applies equally to men as it does to women. If you are taking DHEA now or if a future Adrenal Stress Profile (ASP) result shows low levels of DHEA, my advice is that you should consider taking/swapping to pregnenolone. If you do the ASP test through my practice, then I will recommend pregnenolone if indicated by the results. In addition to CFS sufferers, post menopausal women and those aged over 50 may also benefit from this therapy. For those 'transferring' from DHEA to pregnenolone, the conversion rate is approximately 1:2, so that if you are currently taking 5 mg daily of DHEA then you should transfer to 10 mg daily of pregnenolone.

In patients in which the Adrenal Stress Profile test shows a deficiency of cortisol it is worth trying hydrocortisone. This is the biologically identical hormone and if given in small doses (5-10mg in the morning) it has no side effects and induces no suppression of the adrenal gland. There are no long term side effects, there is no need to carry a steroid card, and no need to tail the dose off when stopping the course. Hydrocortisone should be seen as a crutch to the adrenal gland. The use of

hydrocortisone allows the adrenal gland to rest a little and, in time, resume normal production, at which point the hydrocortisone can be stopped. This removal of the hydrocortisone support should only happen once the patient feels considerably better, which may take several months or even years. There is no need to recheck levels of cortisol once on treatment.

It may be that pregnenolone will be more effective as cortisol replacement - time will tell - watch this space!

"Pregnenolone Steal"

I think pregnenolone may be particularly pertinent in the treatment of chronic fatigue syndrome, and indeed the ageing process, for two reasons.

As described above, pregnenolone is the most upstream of all adrenal hormones and immediately downstream from cholesterol. The conversion of cholesterol to pregnenolone takes place in the mitochondria and so one can easily see how poor mitochondrial function could result in poor output of pregnenolone and, therefore, adrenal hormones.

Pregnenolone steal – if the body becomes stressed, for whatever reason, then the production of adrenal hormones is moved away from the anabolic building, healing and repair hormones to the catabolic stress hormones such as cortisol. In essence, when sufficiently stressed, pregnenlone is diverted away from making anabolic hormones to making catabolic hormones, essentially cortisol. Consequently, less hormone is available for healing and repair. People with chronic fatigue syndrome are permanently stressed by many factors, not least of which is their inability to live up to their potential. Hence CFS sufferers will likely suffer from pregneolone steal. This is bad news not only because this will mean that there is less hormone available for healing and repair but also because pregnenolone steal worsens the problems of low pregnenolone production in CFS sufferers, as already described above, resulting from their poor mitochondrial function.

A hydrocortisone trial

A randomised, controlled, crossover trial of low-dose hydrocortisone treatment for CFS has been published. 32 participants, fulfilling both the Oxford and CDC 1994 criteria, completed this short-term trial. Participants received 5mg or 10mg of hydrocortisone for 28 days and placebo for 28 days.

The results revealed modest, statistically significant improvements in fatigue with this low-dose hydrocortisone treatment compared with placebo. The degree of disability was also reduced with hydrocortisone treatment but not with placebo. There was no significant difference in changes in fatigue score when 5mg and 10mg doses were compared. The authors suggest that, in view of the lack of dose response in this study, 5mg is a sufficient dose of hydrocortisone.

Participants who responded to this hydrocortisone treatment did not differ from 'non-responders' in terms of their pre-treatment cortisol levels. Although none of the participants in this study had a current psychiatric illness, those who responded to hydrocortisone treatment had fewer psychiatric symptoms prior to treatment.

Based on the results of the insulin stress test, this short-term, low dose hydrocortisone treatment was not found to cause significant suppression of adrenal gland function. None of the participants dropped out of the study and only minor side effects were reported.

The authors conclude that this low-dose hydrocortisone treatment resulted in "significant reduction in self-rated fatigue and disability in patients with chronic fatigue syndrome".

Reference - Low-dose hydrocortisone in chronic fatigue syndrome: a randomised crossover trial (https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(98)04074-4/fulltext)

Comment

This study sheds interesting light on the possible role of low cortisol levels in the disease processes involved in CFS. Caution is required, however, in interpreting the results. Participants' baseline cortisol levels could not predict their response to hydrocortisone treatment and participants appeared to have baseline cortisol levels within the normal reference range.

In another randomised controlled trial of hydrocortisone therapy, McKenzie at al., used a higher 'low-dose' hydrocortisone treatment of 25 - 35mg daily. They found that this dose was associated with some improvements in symptoms but caused significant adrenal suppression. Neither of these research teams currently recommended the use of hydrocortone as a treatment for CFS. The present study assessed the effects of hydrocortisone treatment in the short-term only. As the authors point out, further studies, involving longer durations of treatment and follow-up are required to assess the long-term effectiveness and safety of this treatment.

Reference - Low-Dose Hydrocortisone for Treatment of Chronic Fatigue Syndrome A Randomized Controlled Trial (https://jamanetwork.com/journals/jama/fullarticle/188004)

Related Tests

- **Adrenal stress profile - salivary**

External links and References

- **Wikipedia entry on Pregnenolone (http://en.wikipedia.org/wiki/Pregnenolone)**
- **My Online Sales Shop - Pregnenolone 50 mg - 60 capsules (https://www.salesatdrmyhill.co.uk/pregnenolone-by-swansons---50-mg---60-capsules-793-**

p.asp)

- For more useful information on pregnenolone please see here

Life Enhancement Pregnenolone (http://www.life-enhancement.com/magazine/article/348-pregnenolone-review)

- For those with secondary hypothyroidism (indicated by low or normal TSH but low T4 and T3) or suspected secondary hypoadrenalism due to poor pituitary functioning, low dose DHEA may prove helpful. A patient of mine has found that a really very low dose (3 - 5mg per day) can make an astonishing difference to quality of life. Other studies have found improvements at higher doses of between 20mg and 50mg - see
  - **Low dose dehydroepiandrosterone affects behavior in hypopituitary androgen-deficient women: a placebo-controlled trial (https://pubmed.ncbi.nlm.nih.gov/11994339/)** and
  - **Dehydroepiandrosterone improves psychological well-being in male and female hypopituitary patients on maintenance growth hormone replacement (https://pubmed.ncbi.nlm.nih.gov/16849414/)**
- A patient of mine brought to my attention a 1999 pilot study employing DHEA in the treatment of CFS, which was published in the Journal of Clinical Rheumatology. You will find further details here:

A pilot study employing Dehydroepiandrosterone (DHEA) in the treatment of chronic fatigue syndrome (http://www.ncbi.nlm.nih.gov/pubmed/19078357)

- For the hormone cascade and more, please see

Dr Linda Gedeon website (http://www.drlindagedeon.com/hormone-cascade.html)

- Links to studies on cortisol:

Low-dose hydrocortisone in chronic fatigue syndrome: a randomised crossover trial (https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(98)04074-4/fulltext)
Low-Dose Hydrocortisone for Treatment of Chronic Fatigue Syndrome A Randomized Controlled Trial (https://jamanetwork.com/journals/jama/fullarticle/188004)

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