Editorial: Non-Classic Adrenal Hyperplasia and Autoimmune Disease

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This issue's article by on Scleroderma with HAIR-AN syndrome brings to mind the underrecognized associations between non-classic adrenal hyperplasia (NCAH), insulin resistance (IR), and autoimmune disease.

We have previously reported that NCAH (adrenal hyperandrogenemia) is almost universally found in patients with a variety of autoimmune disorders, including Type 1 diabetes mellitus, Graves' (Basedow's) disease, Hashimoto's thyroiditis, vitiligo, psoriasis, and rheumatoid arthritis. In addition, it is universally encountered in patients with Type 2 diabetes mellitus (T2DM) (with the exception of those patients who developed this disorder after HCV infection and lack a family history for Type 2 diabetes) [1-11]. Recently, it has been reported that about 2/3 of patients with T2DM have evidence of autoimmunity, when highly sensitive tests for cellular autoimmunity are employed [12]. Only today, we diagnosed a patient with ulcerative colitis with both non-classic 21-hydroxylase deficiency and 11-hydroxylase deficiency.

In the HAIR-AN syndrome, as well as in many patients labeled as having polycystic ovarian syndrome (PCOS) in general, the diagnosis of NCAH is frequently missed because the treating physician fails to screen at all for it or screens for it only superficially. The gynecologic literature is rife with articles in which a single, normal baseline 17-OH-progesterone level is considered adequate to exclude a diagnosis of NCAH. No other metabolite is measured. It is only rarely that an author has had a cosyntropin stimulation test performed to see if a patient's 17-OH-progesterone or any other metabolite hyperresponds ($\geq$6x baseline). Many patients with HAIR-AN syndrome actually have a non-classic 3-β-ol dehydrogenase deficiency, which is virtually never accompanied by an exonic mutation. More likely it is due excessive methylation of the gene causing it to be partially silenced, promoter region polymorphisms, or downstream transcriptional/ translational issues.

While, there is a widespread appreciation of the role of insulin resistance (IR) in PCOS and in HAIR-AN syndrome, the constancy of IR as a feature of both NCAH and classic CAH is underappreciated [13-16]. The hyperinsulinemia accompanying IR leads to alterations in levels of the transcription factors SF-1 and nur77 resulting in reduced expression of the 21-hydroxylase gene and increased expression of the 17-hydroxylase gene, thereby shifting adrenal steroidogenesis away from cortisol and toward androgen synthesis [17]. Even less well appreciated is the concept that NCAH, classic CAH, and drug-induced adrenal hyperplasia may be treated with interventions that reduce IR [10,18-21].

There are a number of factors which may underly the confluence of CAH, IR, and autoimmune disease. One possibility is that the 21-hydroxylase gene as well as the genetic polymorphisms associated with autoimmune disorders are found in close proximity on chromosome 6. The former is closely linked to the HLA or histocompatibility locus, wherein the polymorphisms associated with autoimmune disorders are found [22]. 21-hydroxylase deficiency is the most common form of CAH; thus, mutations in the 21-hydroxylase gene could readily be associated with HLA locus polymorphisms. Also in close proximity to the 21-hydroxylase gene is the tenascin X gene. Polymorphisms in the latter have been reported in patients with variants of the Ehlers-Danlos syndrome and 21-hydroxylase deficiency, in some cases due to a contiguous deletion in the 21-hydroxylase gene extending into the tenascin X gene [23]. Tenascin X is a connective tissue extracellular matrix protein. Although not reported to date, it is possible that polymorphisms in the tenascin X gene could also result in scleroderma-like changes, as seen in the accompanying article, as well as other collagen-vascular disorders.

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E-ISSN: 2310-9874/15

IR is itself, a chronic, low-grade inflammatory state, characterized by elevated circulating as well as paracrine levels of reactive oxygen and nitrogen species and inflammatory chemokines and cytokines which may contribute to the development of autoimmunity. Conversely, elevated levels of certain inflammatory cytokines, eg TNF-α, can induce insulin resistance [24].

It is worth remembering that CAH is characterized by subnormal production of cortisol. If glucocorticoid supplementation usually ameliorates autoimmune disorders, it stands to reason that chronic glucocorticoid deficiency might predispose to autoimmunity.

Both CAH and many autoimmune disorders are associated with Vitamin D deficiency/insufficiency and treatment of the former with Vitamin D repletion has resulted in clinical/biochemical remission [25-28] possibly after binding to the adrenocortical Vitamin D receptor. Local applications of Vitamin D analogues as well as treatment with PUVA, which increases endogenous Vitamin D synthesis have been used in the treatment of autoimmune disorders such as psoriasis, vitiligo, and, as reported in the accompanying article, scleroderma [29-31].

Autoimmune adrenal disease need not produce global adrenal insufficiency; a forme fruste eg with an antibody vs 21-hydroxylase (as is frequently encountered in autoimmune polyglandular syndrome) could present much like CAH.

Finally, it has been recognized for decades that autoimmune disorders occur preponderantly in females and that high estradiol/progesterone ratios predispose to such disorders as autoimmune (Hashimoto's) thyroiditis [32]. In women who are anovulatory due to PCOS or CAH estradiol synthesis is increased as a result of increased testosterone production; testosterone is then aromatized to estradiol. Most of this aromatization takes place in the adipose tissue, of which most of these patients have an abundance. Since there is anovulation or sometimes inadequate luteal phase, progesterone levels are generally low.

In conclusion, patients with autoimmune disorders should routinely be screened for androgenic disorders such CAH, autoimmune (Hashimoto's) thyroiditis, and HAIR-AN syndrome-and vice versa and their Vitamin D status should always be assessed.

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Received on 23-04-2015 Accepted on 25-04-2015 Published on 29-04-2015

DOI: http://dx.doi.org/10.12970/2310-9874.2015.03.01.1