

Fungal exposure endocrinopathy in sinusitis with growth hormone deficiency: Dennis-Robertson syndrome

Toxicology and Industrial Health
25(9-10) 669–680
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DOI: 10.1177/0748233709348266
tih.sagepub.com



Donald Dennis¹, David Robertson², Luke Curtis³ and Judson Black⁴

Abstract

A retrospective study was carried out on 79 patients with a history of mold exposure, fatigue, and chronic rhinosinusitis (CRS) to determine whether there is a causal relationship between fungal exposure and chronic sinusitis, fatigue, and anterior hypopituitarism, especially growth hormone deficiency (GHD). Of the patients, 94% had a history of CRS, endoscopically and/or computed tomography (CT) confirmed; 100% had chronic fatigue and 100% had either significant history of indoor mold exposure and/or positive mold plate testing as measured by settle plates, with an average colony count of 21 (0-4 normal). A total of 62 had positive mold plate testing and 17 had positive history of mold exposure. Of 75, 73 (97.3%) had positive serum immunoglobulin G (IgG)-specific antibodies to fungal antigens. Out of 8, 7 were positive for urinary trichothecenes. Resting levels of insulin-like growth factor I (IGF-I) averaged 123 ng/mL (range 43-285, normal 88-249 ng/mL). Despite normal resting levels of IGF-I, significant deficiency of serum human growth hormone (GH) was confirmed by insulin tolerance test (ITT) in 40 of 50 tested. In all, 51% (40/79) were GH deficient. Primary or secondary hypothyroidism in T3 and/or T4 was seen in 81% (64/79) patients; 75% (59/79) had adrenocorticotrophic hormone (ACTH) deficiency. Fungal exposure endocrinopathy likely represents the major cause of GHD, affecting approximately 4.8 million people compared to approximately known 60,000 cases from all other causes. A literature review indicates a possible mechanism of GHD in fungal exposure is that the fungal glucan receptors in the lenticulostellate cells of the anterior pituitary bind to fungal cells wall glucans and activate the innate immune system, which activates macrophages that destroy the fungus and lenticulostellate tissue. Treatment of patients included normal saline nasal irrigations, antifungal and antibiotic nasal sprays, appropriate use of oral antibiotics and antifungals, facial steamer with CitriDrops. Thymate and/or Intramax vitamin supplements, hormone replacement, and reduction of indoor mold levels. Resolution of rhinosinusitis was seen in 93% (41 of 45) of the patients who achieved a mold count by settling plates of 0-4 colonies. Thirty patients were unable to lower their mold counts below four colonies and had various degrees of mucosal disease and fatigue remaining. Fatigue was improved in all 37 patients who received GH and cortisol and/or thyroid hormone, which were deficient. Fatigue was partially relieved in 7 of the 37 who did not achieve mold counts of fewer than four colonies.

Keywords

Fatigue, chronic rhinosinusitis (CRS), allergic fungal sinusitis (AFS), hypopituitarism

Introduction

In our private practice Otolaryngology Clinic, it was noted that approximately 17% of patients with chronic rhinosinusitis (CRS) and toxic mold exposure have significant fatigue that persists after control of sinusitis and environmental fungal loads. Routine endocrine, infectious disease and autoimmune work up were negative, or when any abnormality was found and corrected, the fatigue persisted. It was thought that the fatigue may be due to a fungal effect on the anterior

¹ Otolaryngologist and Facial Plastic Surgeon, Private Practice, Northside Hospital, Piedmont Hospital, USA

² Endocrinologist, Private Practice, Piedmont Hospital, USA

³ Occupational Physician and Industrial Hygienist, Illinois, USA

⁴ Endocrinologist, Private Practice, Northside Hospital, USA

Corresponding author:

Donald Dennis, 3193 Howell Mill Road, Suite 215, Atlanta, GA 30327, USA. Email: ddennis@mindspring.com

Table 1. Symptoms and signs of adult growth hormone deficiency

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- Fatigue
 - Exercise intolerance
 - Depressed mood
 - Increased anxiety
 - Social isolation
 - Lack of positive well-being
 - Increased body fat, especially central fat
 - Decreased muscle mass
 - Insulin resistance and increased prevalence of impaired glucose tolerance test
 - Increased LDL cholesterol and Apo B, decreased HDL cholesterol
 - Accelerated atherogenesis, hypertension
 - Decrease in cardiac muscle mass
 - Impaired cardiac function
 - Decreased total and extracellular fluid volume
 - Decreased total body sodium
 - Increased concentration of plasma fibrinogen and plasma activator inhibitor type I
 - Decreased bone density, associated with an increase risk of fracture
 - Monson (2008)
-

HDL, high-density lipoprotein; LDL, low-density lipoproteins.

pituitary causing growth hormone deficiency (GHD) and other endocrinopathies because many of these patients had low thyroid and cortisol levels and symptoms associated with GH deficiency: fatigue, exercise intolerance, slow healing, weight gain, poor concentration and insomnia. Because the increased recognition that hypopituitarism is associated with premature mortality and GH specifically is associated with multiple health risk (Monson, 2008; Table 1), it was thought important to determine whether these patients were GH deficient. Therefore, the insulin tolerance test (ITT) was done. The ITT showed 51% (40/79) of those with significant fatigue, environmental fungal exposure, and chronic sinusitis were GH deficient. And 80% (40/50) of those tested were positive for GHD even though their resting levels of insulin-like growth factor 1 (IGF-1) were normal (normal 88-249 ng/mL). Resting IGF-1 of GH deficient patients ranged from 43 to 285 ng/mL, with an average of 123 ng/mL.

A review of current literature was conducted to aid in the formulating of a hypothesis for the pathogenesis of anterior pituitary dysfunction in environmental fungal exposure with fatigue and/or CRS.

Prior to this study, adult-onset GHD incidence was estimated at 1 to 2 adults per 10,000 or 60,000 cases in US from all causes, finding 6000 new cases per year. (Mathioudakis and Salvatori, 2008). Our study suggests that fungal exposure may be the single most

important cause of GH deficiency affecting approximately 4.8 million people or 1 in 64 or 1.6% of the US population. In patients with CRS, significant fatigue, and a history of fungal exposure, the incidence of GHD is 51% in our study. Of the 79 patients in our study, only 13 had conditions that are associated with GHD. Four had head injuries, two empty sellas, and seven microadenomas. The other 82% (65/79) had no known condition associated with GHD.

There are many causes of adult-onset GHD, and GHD may exist with or without other pituitary hormone deficiencies (Mathioudakis and Salvatori, 2008). A Danish study reported on diagnoses that were determined to cause adult onset GHD in 1329 patients (Stochholm et al., 2006). The diagnoses included pituitary adenoma (53% of the 1329 cases), benign tumors in or near the pituitary (4%), cranio-pharyngioma (8%), malignant tumors (3%), cysts (2%), central nervous system infection (0.5%), granulomatous inflammation (0.6%), cranial irradiation (1.5%), postoperative hypopituitarism (2%), trauma (0.8%), Sheehan syndrome (2%), empty sella (1%), pituitary apoplexy (2%), pituitary hypoplasia (2%), aneurysm (0.4%), others (6%), and idiopathic (5%; Mathioudakis and Salvatori, 2008).

GHD can cause many health problems including chronic fatigue, n-terminal insomnia (awakens and cannot resume sleep), exercise intolerance, increased risk of arteriosclerosis and hypertension, increased insulin resistance, muscle weakness, increased central fat mass, reduced extracellular water with reduced total body sodium with reduced exercise tolerance, reduced left ventricular function, fractures, breathing problems, poor attention and concentration, depression, and neurological problems. (Monson, 2008; Mathioudakis and Salvatori, 2008; Table 1). A Danish study reported that 1329 patients with adult onset GHD had significantly higher rates of morbidity than 8014 controls including higher rates of infections, cancer, heart disease and trauma as well as significantly higher rates of problems with the blood, endocrine, nervous, digestive, and muscular skeletal systems (Stochholm et al., 2008). A related study reported that mortality was significantly higher in the adult onset GH deficient patients versus the controls for many different diseases including cardiovascular diseases, cerebrovascular diseases, cancer, infections, trauma, and endocrine/metabolic/nutritional diseases (Stochholm et al., 2007).

The relationship between exposure to molds and mycotoxins and damage to pituitary gland functions is poorly understood. Clinical infection of the pituitary glands by molds such as *Aspergillus* and *Mucor* have

been occasionally reported in the literature (Ponikau et al., 2004). Exposure to such mycotoxins as aflatoxins, zearalenone, and trichothecenes have been shown to cause abnormalities in the pituitary glands or pituitary cells from laboratory mammals (Abdel-Haq et al., 2000; Collins, 2006; Takahashi, 2008). Humans who have a genetic disorder known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) suffer from many mucocutaneous *Candida* infections from early childhood (O'Dwyer et al., 2007; Liiv, 2007). By age of 30 years, almost all patients with APECED produce pituitary autoantibodies and develop one or more major endocrine problems such as GHD, type 1 diabetes, hypothyroidism, hypoparathyroidism, adrenal failure, testicular failure, and ovarian failure (O'Dwyer et al., 2007; Liiv, 2007). Exposure to a variety of molds and mycotoxins in water-damaged buildings has also been linked to increased development of auto-antibodies and autoimmune disease (Gray et al., 2003). Breuel et al. report lenticulostellate cells of the anterior pituitary have fungal glucan cell wall receptors that stimulate toll-like receptors (TLR4) and *CD14* gene expression, which activate fungal antigen pattern recognition innate immunity, which in turn activates cytokines and macrophages destruction of the fungus and in doing so damages the pituitary folliculostellate (FS) cells (Breuel et al., 2004).

CRS is a very common disease that affects about 14% of the US population (Benninger et al., 2003). CRS is responsible for over 200,000 surgeries annually in the US (Dennis, 2003). Rhinosinusitis patients experience chronic nasal congestion and/or obstruction, thick nasal mucous, reduced sense of smell, facial pain and headaches, chronic fatigue, head fullness, and frequent bacterial infections (Benninger et al., 2006). A study of 297 consecutive medical outpatients reported that 65 patients (22%) had chronic fatigue without an obvious explanation (Chester, 2003). Signs of rhinosinusitis such as facial pressure, nasal obstruction, and frontal headaches and postnasal drip were significantly more common in the patients with unexplained chronic fatigue as compared to the patients without unexplained chronic fatigue ($p \leq 0.001$ for all comparisons; Chester, 2003). 'Severe' or 'Very Severe' fatigue was reported in a group of 322 rhinosinusitis patients (Bhattacharyya, 2003). Other studies reported high levels of chronic fatigue and chronic body pain in rhinosinusitis patients, which improved significantly, following sinus surgery (Chambers et al., 1997; Conte and Holtzberg, 1996; Hoffman et al., 1993; Winstead and Barnett, 1998).

A majority of rhinosinusitis cases are probably related to mold exposure. A study of 101 consecutive rhinosinusitis surgery patients reported that 94 (93%) had positive fungal cultures and positive histopathological findings consistent with mold related CRS (Ponikau et al., 1999). Dennis (2003) reported that the use of nasal irrigations, antibiotic/antifungal/steroid nasal sprays and environmental control to reduce mold exposure was successful in treating 94% of a group of 365 patients with CRS. Other studies have reported that treatment with intranasal antifungal drugs can cause complete or partial remission of symptoms in many rhinosinusitis patients (Ponikau et al., 2002; Ricchetti et al., 2002; Sherris et al., 2005). Fungal antigens activate helper T-lymphocytes in the blood of CRS patients, producing cytokines that recruit (interleukins 13 [IL-13]), (interferon γ [INF- γ]), and activate (IL-5) eosinophils. Lymphocytes from normal controls do not activate helper T-lymphocytes (Ponikau et al., 2004). Therefore, this is a systemic immune inflammatory reaction. Fungal-specific immunoglobulin G (IgG) antibodies are important indicators of fungal exposure in CRS patients because IL-5, IL-13, and INF- γ all contribute to the production of fungal-specific IgG antibodies. IL-5 activates B-cells for terminal differentiation into IgG-secreting cells. IL-13 causes IG Isotype switching to IgE and IgG1. INF- γ increases fungal antigen presentation to lymphocytes, thereby increasing fungal-specific IgG production (allergy glossary). Since lymphocytes of normal patients do not secrete IL-5, IL-13, and INF- γ in the presence of fungi, it is likely that these antibodies are higher in CRS patients with fungal exposure. Also due to a likely genetic defect on the T-cell receptor V β chain, CRS patients can respond to fungal antigens as a superantigen resulting in profound activation of up to 30% of the total body's T-cells, in contrast to <0.01% normal T-cell response (Krakauer, 1999; Schubert, 2001). Therefore, with a response 3000 times the normal T-cell response per fungal antigen and three inflammatory interleukins (IL-5, IL-13, INF- γ) per T cell responding to fungal antigen, there can be up to 9000 times (3000 T cells \times 3 interleukins per T cell) the systemic inflammation of a normal person. This is profound and may explain many of the systemic symptoms these fungal-exposed patients have.

Increasing epidemiological and clinical evidence has linked heavy indoor exposure to molds to other health problems such as asthma and wheezing (Fisk et al., 2007) and neurological and neuropsychiatric problems (Campbell et al., 2004). Molds such as *Aspergillus* and *Candida* frequently cause

life-threatening systemic infections in immunocompromised patients and also infect immunocompetent patients as well (Shao et al., 2007; Warnock, 2006).

In this paper, we report on 79 patients who experienced growth hormone (GH), thyroid, and/or cortisol deficiency and other health problems following heavy exposure to indoor molds. This paper will present endocrinological, immunological, anatomical, and environmental data from the patients. Most of the patients experienced considerable health improvement when their environmental mold exposure was reduced and they received antifungal nasal sprays, oral antifungals, and GH, thyroid, and/or cortisol replacement.

Methods and patients

Study subjects

Between May 2004 and September 2008, 79 patients aged 30-77 years (64 females and 15 males), who were diagnosed with CRS and failed traditional antibiotic and/or surgical therapy, who had persistent significant fatigue, and a history of environmental mold exposure were studied in our private practice Otolaryngology Clinic. Findings for inclusion in the study were (a) diagnosis of CRS on the basis of history, (b) abnormal endoscopic sinus exam, and (c) abnormal sinus computed tomography (CT) scan and/or history or evidence of environmental mold exposure, and significant fatigue. Sinus symptoms must have been present for at least 3 months and had to include 2 or more of the following: (a) facial pain or pressure, (b) facial congestion or fullness, (c) nasal obstruction or blockage, (d) nasal discharge/purulence/dyscoloration, (e) postnasal drainage, or (f) hyposmia/anosmia. Sinusitis must have been present for at least 3 months and been treated with antibiotics for 4-6 weeks (or more sinusitis episodes per year treated with antibiotics for 7-10 days each), with symptoms persisting or recurring after cessation of antibiotic treatment.

Treatment protocols

Both the patients themselves and the air in their home, office, or car environments (wherever the fungal load was found to be elevated) were treated to reduce the fungal load. Treatment of patients consisted of (a) normal saline nasal irrigations with 8 oz. Distilled water (not tap water, chlorine causes cilia destruction) twice daily to remove fungi mechanically and (b) two antimicrobial nose sprays containing an antifungal (Amphotericin-B, Voriconazole, or CitriSpray, and a

steroid), administered three sprays, 4 times daily after irrigation for 4-10 weeks, depending on time required to clear the sinus mucosa, as verified by endoscopic exam. Nasal spray protocol is summarized in Table 2. If infection was present, two structurally different antibiotics to which the bacteria were sensitive on routine culture and sensitivity were used. Nebulization was used if either fungal and/or bacterial infection presented as moderate pus on endoscopic sinus exam.

Environmental remediation consisted of reducing air fungal load by following an environmental treatment protocol that included finding and repairing moisture intrusion and implementing portable high efficiency particulate air (HEPA; Swiss-made IQAir is preferred since outflow particle count is zero at 0.3μ) and/or central HEPA air filtration in-line 94% efficient at 0.35μ central HVAC filter in combination with disbursement of botanical extract by evaporation. An odorless botanical extract was dispersed by the patient or environmental consultant by placing two to four foil-covered containers with wicks perforating the foil cover on top of a portable HEPA air filter, which exits clean air from the top of the machine. These were placed in each room used by the patient. With patient's permission, any source of moisture intrusion were identified and controlled. Cars were treated by spraying botanical extract into the HVAC system from the outside suction vent at the windshield on both sides and on the inside of the car. (Equipment sources: portable HEPA filters and botanical extract containers were supplied by Pavillion Pharmacy supplies extract, National Allergy Supply, Inc., and Mead Indoor Enviro Tech supplied HEPA filters, all located in Atlanta, GA, USA. Central in-line 94% efficient at 0.35μ filters and moisture intrusion correction was supplied by Mead Indoor Enviro-Tech, Inc., Atlanta, GA, USA) All environmental treatment devices were determined to be effective by an independent mycology laboratory prior to use in the study. Before each device was tested, a gravity-exposure Sabouraud dextrose agar (SDA) plate (Source: Immunolytics Lab, Albuquerque, NM, USA) was exposed for 1 hour inside a test room documented to contain fungal colonies too numerous to count (TNTC). All devices reduced the test room's fungal colony count from TNTC to 0-2 colonies by day 6.

Monitoring

Prior to treatment of the patient and environment, sinus endoscopic photography was performed, and nose and

Table 2. Sinus, endocrine and detox treatment protocol

1. Normal saline irrigation 4 oz. Each side 2 times per day
2. If visible pus on endoscopic or Sinus CT, begin with Clindamycin and Gentamycin sprays until culture results (sprays contain an antifungal, clotrimazole, or other) with steroids
 - Omit steroids if patient sensitive
 - If patient allergic to clindamycin, use cefazolin or trimethoprim/sulfamethoxazole
 - If allergic to Gentamycin use Ciprofloxacin
3. If fungus visible or history of significant fungal exposure, use Amphotericin-B or Voriconazole with above. Always use these at same time using antifungal first
4. Use sprays 2-10 weeks, or until mucosa is clear by endoscopic exam or CT sinus scan
5. Maintain with: CitriSpray (four citrus seed extracts, which are antifungal, antibacterial, and antiviral) mixed steroid, three sprays each nostril 2 times per day
6. Growth hormone replacement: Start 0.2 mg SQ in evening, women on oral estrogen need more start at 0.3 mg. In patients with poor medicine tolerance start at 0.1 mg. Evaluate every 2 months with IGF-1 level. Work towards an IGF-1 level of 240 ng/mL. If any negative symptom occurs, decrease dose. Most need daily dose. Titrate dose to clinical condition
7. Replace other hormones to physiologic level
8. Detoxification (e.g. drink distilled water, sauna, IV or oral antioxidants, IntraMax elemental carbon vitamins, 1 oz 1-2× day, or Thymate vitamins 1-4, 2× day)
9. Antigen Neutralization, and autogenous lymphocytic factor (ALF)
10. Acidophilus Trinev Trio

CT, computed tomography; IGF-1, insulin-like growth factor 1; SQ, subcutaneous.

Note: All sprays provided by Pavillion Compounding Pharmacy (Atlanta, GA).

air fungal cultures were taken. Bacterial cultures were taken when visible pus was present. A Calgi swab on SDA agar was used for the nose culture, a 1-hour gravity SDA plate exposure for environment. Plates containing nose swab samples were incubated in a dark area at room temperature for 3 days. If growth was observed, the plate was sent to the mycology laboratory (Quest Diagnostics Mycology Laboratory Atlanta, GA, USA) for counting and identification.

Air samples were taken by exposing open plates in areas where the patient spent most time, as well as areas of likely contamination (e.g. bedroom, kitchen, den, office, car, basement, crawlspace, attic) for 1 hour with the central HVAC fan in the “on” position. The plates were placed at least 0.91 m (3 ft) from any wall. After exposure, the plates were enclosed in foil and sent to a mycology laboratory (Immunolytics, Albuquerque, NM, USA) for evaluation.

After treatment of the patient and air to reduce fungal load (in accordance with the aforementioned protocols) 1 hour SDA plate exposures were repeated for the environmental air, and a second set of endoscopic sinus photographs were taken for each patient. Comparisons were then made between the environmental fungal counts and the endoscopic photographs. If nasal and environmental fungal cultures did not correspond, a different source of sinus infection was suspected.

The Rast IgG assay was used to detect serum IgG (delayed mold reaction) IgE fungus-specific antibody levels for 10 common fungal antigens: *Alternaria*

alternata/tenuis, *Aspergillus fumigatus*, *Candida albicans*, *Cephalosporium acre*, *Cladosporium herbarum*, *Helminthosporium halodes*, *Penicillium notatum/chrysogenu*, *Epicoccum purpurascens*, *Fusarium oxysporum*, and *Mucor racemosus*.

Fungal IgG antibodies

Antibodies were tested by Esoterix Laboratory Services, Inc. (Austin, TX, USA) with enzymatic immune assay.

Pituitary hormones and other blood chemistries assayed by Endocrinologists, Drs Judson Black and David Robertson, were freeT3, freeT4, thyroid-stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH), cortisol, luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (females), testosterone, IGF-1, GH, vitamin D, parathyroid hormone. These were carried out by commercial laboratories, as directed by the patient’s insurance coverage.

MRI scans of the pituitary were done on patients who had pituitary dysfunction.

Mycotoxin assay

First AM void Urine Trichothecenes were checked in eight patients; 10 trichothecenes are checked as a group without differentiation among the 10. Tricothecenes are evaluated by using enzyme-linked immunosorbant assay (ELISA). The test at RTL has been validated as a

qualitative test. Thus, RTL reports whether tricothecenes are PRESENT or NOT PRESENT. The sensitivity is 0.01 parts per billion (ppb) done by Real Time Laboratory in Dallas, Texas, USA, Dr Dennis Hooper.

Criteria for ITT were

1. Significant fatigue or any compelling symptoms,
2. discordinant hormones relationships:
 - a. Low freeT3 and/or low freeT4 with low TSH,
 - b. low DHEAS (primary adrenal hormone) below 10th percentile, suggesting under stimulation of the adrenal by pituitary, or low cortisol production with ACTH stimulation test.
 - c. Menopausal females without high LH and FSH. Low LH and FSH with premenopausal low estrogen or testosterone
 - d. Most patient with IGF-1 > 75th percentile are not GH deficient in this cohort.
 - e. IGF-1 below 50th percentile, most are GH deficient in this cohort.

Dosage of GH during replacement therapy:

1. Approximately 70% start at 0.2 mg subcutaneous in the evening,
2. women on oral estrogen start at higher dose of 0.3 mg subcutaneous (SQ) in evening,
3. patients with history of medication intolerance start at 0.1 mg SQ in evening.

Details of the ITT is beyond the scope of this paper and is published elsewhere.

ITT was positive for GHD if the GH response is <5 ng/mL. L-Arginine infusion was positive for GHD if the GH response was <4.0 ng/mL. Values between 3.0 and 7.9 ng/mL are borderline, and a second provocative test to assess GH deficiency is appropriate, such as L-Arginine infusion, or L-dopa ingestion.

ALCAT food allergy test was done on these patients on 150 foods in order to develop a non-allergic diet to reduce gut symptoms.

It measures leukocyte increase in mean cell volume in presence of the food antigen (white cell edema) to foods. The white cells begin to increase its cytoplasm volume in the presence of the food antigen when there is food intolerance. This occurs before food IgG antibodies are produced.

Foods are graded as severe, moderate, mild, or non reactive. A 4-day rotational diet is recommended.

Cell Science Systems Deerfield Beach, FL, USA 800-872-5228.

Results

Between May 2004 and September 2008, 79 patients aged 30-77, 64 females and 15 males, with significant environmental fungal exposure, fatigue, and/or CRS were evaluated for the cause of their persistent fatigue. In all, 94% (74/79) had chronic sinusitis; 100% had either a history of environmental mold exposure or positive environmental mold plates testing or both; 62 had positive mold plates testing and 21 had a positive history of mold exposure. Mold plate average colony count was 21 colonies (0-4 normal). Seven of eight urine tricothecenes (mycotoxins) were positive. Of 50 patients with ITT, 80% (40/50) had GHD. Of the 79 patients that presented with sinusitis, mold exposure, and fatigue, 52% (40/79) were GH deficient. Resting IGF-1 average was 123 ng/mL (normal 88-249 ng/mL), range was 43-285 ng/mL for those who were GH deficient on ITT; 75% (59/79) were ACTH deficient; 81% (64/79) were either primary or secondary hypothyroid; 44% (35/79) had GHD, ACTH deficiency (during ITT), and evidence of either primary or secondary thyroid hormone deficiency; and 13 had other possible reasons for GH deficiency: four had head injuries, two empty sellas, and seven microadenomas. Heart rate variability was tested on 13 patients averaged 9/5 with first number (9) being the function of the physiologic system (best 1 worst 13), and second number (5) is level of adaptive reserve (1 best 7 worst autonomic nervous system condition). Memory loss and/or cognitive dysfunction were present in 100% (by questionnaire). A total of 62% (49/79) were vitamin deficient; 73% had food allergies with 30% gluten intolerance; 73% had gastroesophageal reflux disease (GERD) with IgG *Candida* allergy and visible *Candida* on base of tongue (Table 3).

Literature review

The exact mechanism by which the indoor fungal exposure causes failure of the production GH and other hormones is not exactly known. It is postulated that heavy fungal exposure causes hypopituitarism for several reasons.

1. The incidence of GH deficiency in the population with CRS, fatigue, and significant mold exposure is 80 times higher than the population known to be GH deficient from all known causes: children with short stature, patients with head trauma, pituitary tumors or infiltrating disease (approximately 60 thousand vs 4.8 million).

Table 3. Growth hormone deficiency in fungal exposure data

- Total 79 patients, age 30-77, 64 female, 15 male
- 94% (74/79) had chronic sinusitis
- 100% had either a history of environmental mold exposure or positive environmental mold plate testing or both, 62 had positive mold plate testing, 17 had positive history of mold exposure
- Mold plate average colony count 21 colonies (normal 0-4)
- Trichothecenes mycotoxins: 7 of 8 tested were positive
- ITT positive GHD group, IGF-1 average 123, range 285-43 (normal 88-249 ng/mL)
- 51% GH deficient (40/79), 80% (40/50) ITT pts tested were GHD
- 75% ACTH deficient (59/79)
- 81% 1° or 2° hypothyroid (64/79)
- 44% had HGH, ACTH, and thyroid-stimulating hormone (TSH) deficiency (35/79)
- 100% fatigue, cognitive dysfunction, and significant mold exposure
- 49% vitamin D deficient
- 73% food allergies with 30% gluten intolerance
- 73% GERD with IgG *Candida* allergy and visible *Candida* on tongue base

ACTH, adrenocorticotrophic hormone; GERD, gastroesophageal reflux disease; GH, growth hormone; GHD, growth hormone deficiency; HGH, human growth hormone; ITT, insulin tolerance test; IGF-1, insulin-like growth factor 1; IgG, immunoglobulin G.

2. It is known that fungal cell wall glucans can bind to pituitary binding sites.
3. Mycotoxins are neurotoxic, especially aflatoxins and trichothecenes (Breuel et al., 2004).
4. Fungi produce a systemic immune reaction in approximately 16%-20% of the population. Mayo Clinic showed that the helper T-cells of CRS are sensitized by fungal antigen and release both TH1 cytokine, INF- γ and recruit and activate TH2 cytokines both eosinophils (IL-5) and B-cells (IL-13). Therefore, fungi can cause systemic hypersensitive disease. Mycotoxins cause a multitude of systemic toxic effects (Ponikau et al., 2004).
5. Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) is caused by changes in the autoimmune regulator (*AIRE*) gene on chromosome 21q22.3, characterized by two or more of the following: candidiasis, adrenal insufficiency, hypoparathyroidism, and autoimmune diseases. This genetic defect is likely responsible for the autoimmune component of the disease, while the fungus is likely causing the pituitary damage because 73% of our air-borne fungal-exposed patients with GHD, and other endocrinopathies, had GERD with endoscopic visible *Candida*. Breuel et al. used *Candida* as the

fungus in the experiment to show that *Candida* firmly binds to the glucan receptors in the FS cells of the anterior pituitary (Breuel et al., 2004).

The mechanism, which we feel is more likely, involves glucans produced by molds attaching to the fungal glucan site on the anterior pituitary gland (Breuel et al., 2004; Figure 1). This causes a stimulation of pituitary cell TLR4 and *CD14* gene expression followed by pattern recognition of innate immunity and production of cytokines and macrophages. The macrophages then rupture and destroy pituitary FS pituitary tissue (Breuel et al., 2004; Figure 1). Destruction of the FS cells disrupts autocrine and paracrine regulation of anterior pituitary cell function via cytokines and growth factors, intrapituitary communication between various cell types and modulation, and inflammatory responses (Rees, 2005). The pituitary FS cells are also believed to play a critical role of processing and activation of T4 (Fliers et al., 2006). Studies with human pituitaries have reported that certain proteins critical for thyroid metabolism are found only in the FS cells including the type II deiodinase enzyme (DR2) that converts T4 to T3 and the thyroid hormone transporter MCT8 (Alkemade et al., 2006).

Lieberman reported five cases of type I diabetes following heavy mold exposure in a water-damaged building (Lieberman, 2008, personal communication). Gray et al. report significantly higher levels of auto antibodies to immunoglobulins antinuclear autoantibodies, autoantibodies against smooth muscle, and central nervous system myelin (Gray et al., 2003). Therefore, heavy fungal exposure produces an environment that is a toxic soup of high levels of fungal spores, which can cause destructions of tissue via immune reactions, and multiple mycotoxins (over 400 mycotoxins exists), which can damage virtually every human tissue.

Removal of the fungal antigen from the patient and the environment is the single most important treatment item. Without this, all medical treatment will fail.

Medical treatment includes:

1. Saline nasal irrigations twice per day to remove fungal antigen and toxins;
2. antifungal nasal sprays Amphotericin-B or Voriconazole;
3. oral antifungals: if candidiasis, which occurs with most cases, Diflucan 100 mg per day for 14-30 days. Nystatin 1, 2 times per day. If other fungus, Sporonox 200 mg 2 times per day for 30-60 days. Or if CNS fungus Voriconazole

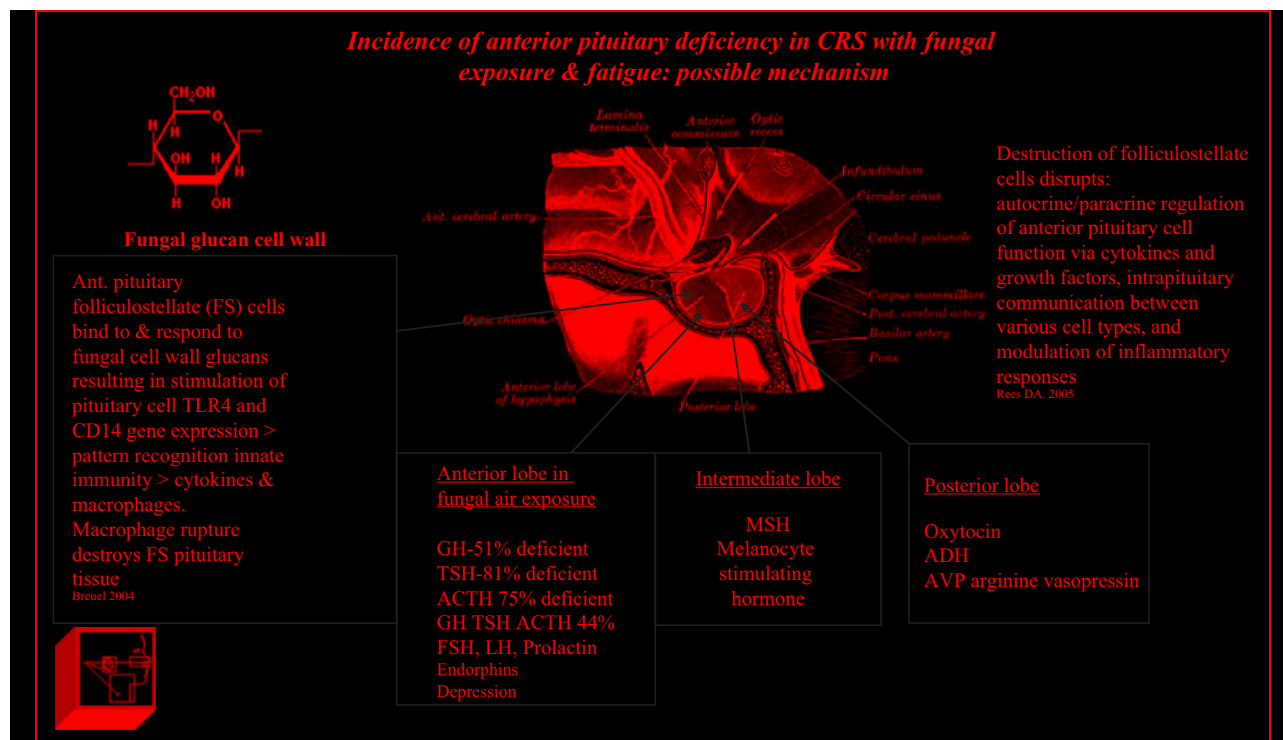


Figure 1. Incidence of anterior pituitary deficiency in CRS with fungal exposure and fatigue: possible mechanism. Pituitary fungal glucan receptors bind to fungal cell wall, activate the innate immune system, and destroy surrounding folliculostellate (FS) cells, which disrupt intrapituitary communication between cells and inflammatory responses causing hypopituitarism and systemic health risk (Breuel et al., 2004; Rees, 2005). ACTH, adrenocorticotropic hormone; CRS, chronic rhinosinusitis; GH, growth hormone; TSH, thyroid-stimulating hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

- 200 mg, 2 times per day for 30-60 days. Maintenance with GSE (grapefruit seed extract) 75 mg 2, 2 times per day until symptoms subside;
4. low carbohydrate anti-yeast diet with attention to avoid food allergies, identified in the ALCAT food test, to stop gut inflammation;
5. EICO-RX (fish oil concentrate, EPA, DHA, GLA, tocopherols), 2 caps 2 times per day. Lauric, myristic, and palmitic acids and their monoglycerides have antifungal activity;
6. acidophyllus bulgaricum and Trinev Trio 3 acidophilus bacteria to compete with gut fungus and restore gut ecology;
7. vitamins: Intramax liquid multi-vitamin with elemental carbon to detoxify the system. Thymate to increase thymic protein A production to increase T-cells;
8. detoxify with sauna, IV antioxidants, vitamin C, taurine, glutathione, B complex, trace minerals, and oxygen if indicated;
9. replacement of all hormones to physiologic levels;
10. remove any sinus fungus.

Patient presentation

A 26-year-old female with toxic mold exposure from a leaking house trailer presented with left leg and arm paralysis, left eye blindness, partial blindness in right eye, catheter in paralyzed neurogenic bladder, and unable to walk or stand without assistance.

Treatment.

She did not reenter her home or remove anything from the home. She washes the clothes she was wearing in antifungal detergent. She began on Sporonox 200 mg 2 times per day, saline nose washes, Amphotericin nose spray, 3 sprays 4 times per day, and Intramax vitamins with carbon. After 5 weeks, her arm, leg, and bladder paralysis resolved and her vision improved in the right eye with light perception in the left eye. The key was fungal antigen removal from the patient and removal of the patient from the moldy environment. For very sick patients, this is the only effective way to ensure a safe environment.

Dosage of GH

1. Approximately 70% start at 0.2 mg SQ in evening.
2. Women on oral estrogen start at higher dose of 0.3 mg SQ in evening.
3. Patients with history of medication intolerance start at 0.1 mg SQ in evening.

Estrogen, testosterone, thyroid, cortisol, and vitamin D as needed to physiologic levels.

Discussion

On the basis of these 79 patients and 5 years clinical experience of being involved with treatment of both the CRS and the hypopituitarism of mold-exposed patient and 21 years of treating thousands of CRS in mold-exposed patients, it can be stated that as long as fungi remain, so will the inflammation, sinusitis, fatigue, and systemic symptoms. Growth on a 1-hour gravity SDA plate exposure, although not perfect, is simple, reliable, and predictable method of assessing environmental fungal levels to determine human health risk.

The author has shown when fungi were successfully removed from the nose and air, 94% of patients showed endoscopic sinus mucosal improvement to normal appearance (i.e. no mucosal edema, polyps, or purulence; Dennis, 2003). Endoscopic view of the sinus mucosa, especially in operated patients, is representative of systemic inflammatory status. Although normal sinus mucosa does not mean there is no systemic inflammation, presence of chronic mucosal inflammation with high IgG fungal-specific antibodies does correlate with systemic inflammation in most cases (Figures 2 and 3).

Hormone replacement with environmental fungal load reduction (0-2 colonies in significant fatigue patients) dramatically improves the fatigue to normal levels in over 90% of patients. Without lowering fungal air loads, fatigue improves to some extent (typically 2 points on a 10 point scale) but does not return to normal levels. So hormone replacement improves fatigue in all patients, but in the presence of significant fungal air loads (gravity plates ≥ 5 colonies per 1 hour exposure) both systemic inflammation and significant fatigue remain.

GHD is a serious health risk and slows or prohibits the recovery from toxic mold exposure and detoxification process by slowing cell replacement and immune resistance (Table 1). Therefore, it is extremely important to diagnose and treat GHD and other hormone deficiencies that accompany it.

Decreased psychological well-being and quality of life are recognized as particularly important, and from a patient's perspective has become arguably the major indication for GH replacement therapy. A questionnaire has been developed, which focuses on symptoms that are most frequently positive in hypopituitary adults. The Quality of Life Assessment in Growth Hormone Deficient Adults (QoL-AGHDA) is a test of 25 yes/no questions with a summation score. High score denotes poorer quality of life (Monson, 2008). In practice, a simple questionnaire that has fatigue graded 0-10, CRS questions, and environmental mold questions is helpful in identifying those that need testing. Persistent fatigue scores ≥ 5 after treatment should be considered for endocrine testing.

Fungal antigen stimulation of T-cell IL-5, IL-13, and INF- γ production, enhancing fungal-specific IgG levels in CRS patients is not a part of the pathology that causes GHD in fungal-exposed patients because 6% of them did not have CRS. So the real incidence of GHD in the population of fungal exposure is higher than the 1.6% or 4.8 million people this study predicts.

Significant food allergies (30% were gluten intolerant) with GERD and endoscopic visible *Candida* were present in 73% of our fungal-exposed patients. In clinical practice, it is rare to see the triad of GERD, significant food allergies, endoscopically visible base of tongue *Candida*, and elevated IgG-specific *Candida* without significant environmental fungal exposure. It is unclear whether this relationship is due to *Candida* proliferation due to fungal load immune suppression or a cross reactivity between the air fungus cell wall glucan and the gut *Candida* glucan cell wall common to all fungi. The *Candida* IgG in almost all of these patients is high and is the likely cause of the gut inflammation causing the food allergies, because 8 weeks after the gut yeast and environmental fungal load is reduced, most of the mild food allergies resolve.

In treating GHD patients, it is important to follow their IGF-1 levels of GH dose adjustment. Although treatment was generally targeted at achieving approximately 75th percentile levels, symptom improvement determined the optimal dosing in each patient. Five patients increased their IGF-1 levels to higher than normal within 9-24 months after starting GH, the main indication of which was anxiety and feeling nervous. The GH was discontinued, the thyroid hormone and/or hydrocortisone treatments were generally reduced if the fatigue returned. If the IGF-1 once again became decreased to low levels, then the GH was restarted at 0.1 mg SQ each evening.

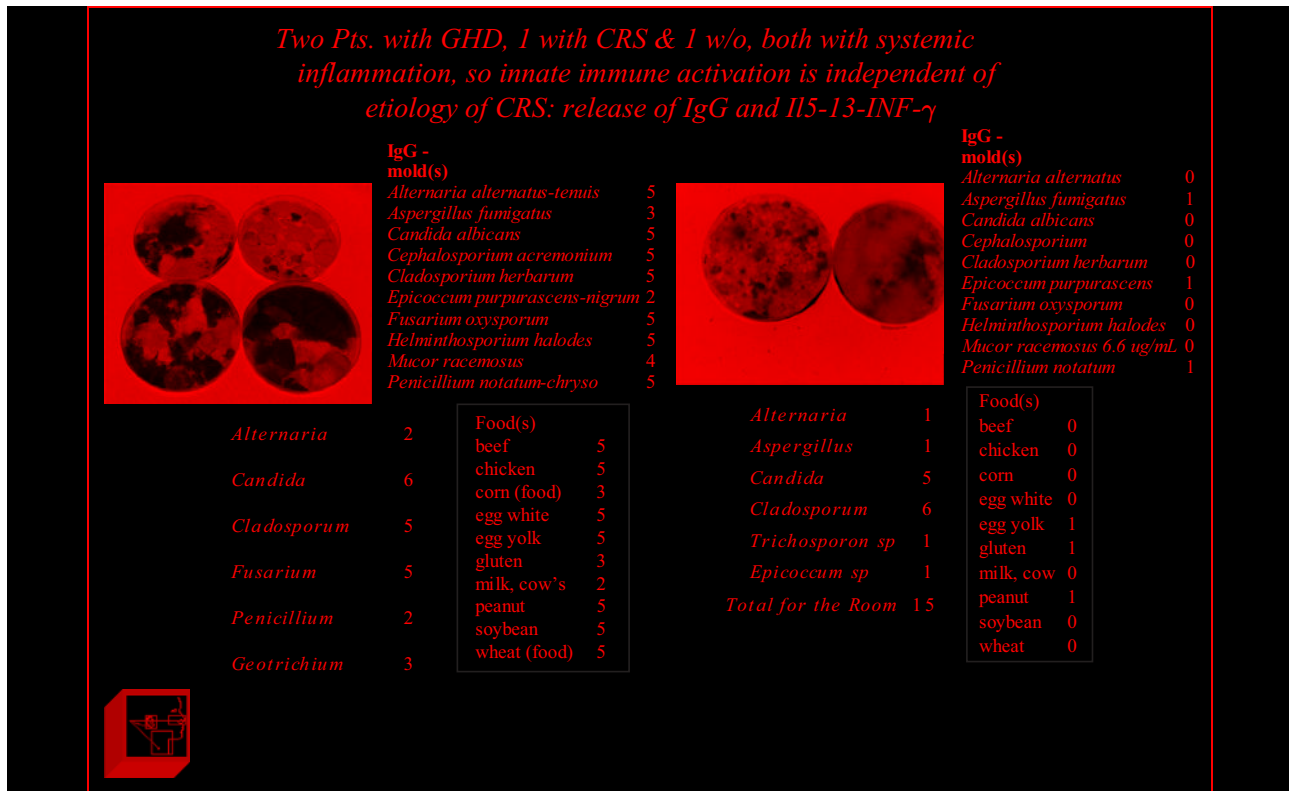


Figure 2. Two patients with GHD, one with CRS and one without, both with systemic inflammation, so innate immune activation is independent of etiology of CRS: release of IgG and IL5-13-INF- γ . Two patients' high fungal air loads and GH deficiency: left patient with chronic sinusitis and high fungus-specific antibodies indicating T-cell release of IL-5, IL-13, INF- γ and gut inflammation with high food allergies. Right shows little IgG fungal antibody activity, no CRS and no significant food allergies. Therefore, the mechanism for pituitary endocrinopathy is not the mechanism for CRS. CRS, chronic rhinosinusitis; GHD, growth hormone deficiency; GH, growth hormone; IL-5, interleukin 5; IL-13, interleukin 13; INF- γ , interferon gamma; IgG, immunoglobulin G.

Conclusions

In patients with fatigue, and fungal exposure with or without CRS, endocrinopathies, including GH deficiency, are likely due to an immune response to fungal antigen.

When the fungal antigen is removed from the patient and the environmental air, the immune reaction stops; the sinus mucosa improves or resolves; the systemic symptoms improve or resolve. When the deficient hormones are replaced, the fatigue improves or resolves. Fungus colonization of sinuses is likely responsible for most CRS, GHD and related endocrinopathy, and for a complex of systemic symptoms, especially fatigue, as a result of activation of the innate immune system via the fungal cell wall glucan receptors in the FS cells in the anterior pituitary. Exceptions to this are underlying disease, failure to find the source to the mold exposure, and permanent systemic immune damage resulting from lengthy fungal exposure. CRS and endocrinopathy patients who have recurring exposure to environmental air

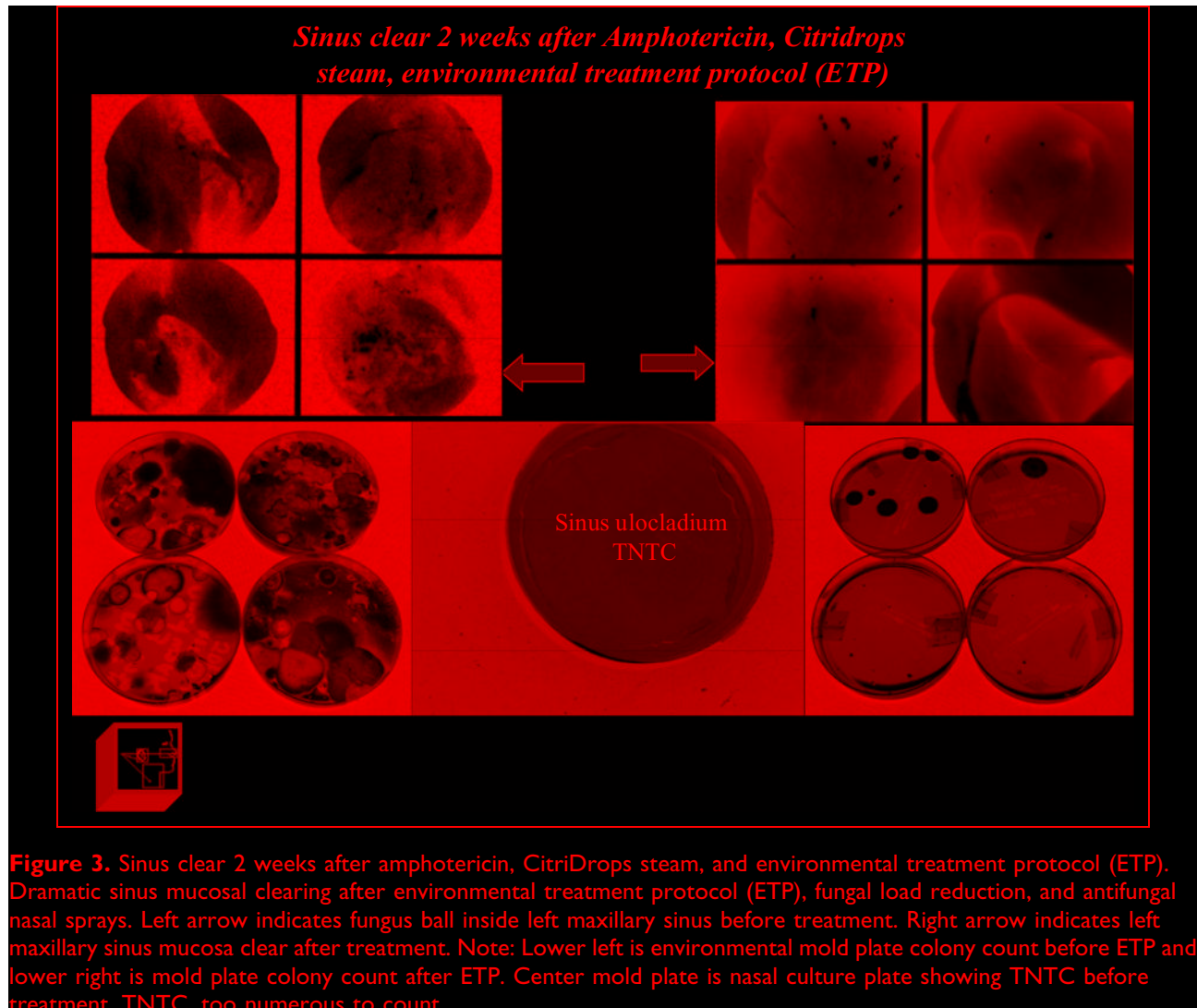
containing fungal concentrations in excess of four colonies per 1-hour agar plate exposure appear to have an increased risk of persistent CRS and/or endocrinopathy and other systemic symptoms, regardless of the medical treatment provided.

Declaration of Conflicting Interests

The authors declared no conflicts of interest with respect to the authorship and/or the publication of this article.

Acknowledgements

The authors thank Vicki DesRochers for tirelessly compiling the data and numerous references, taking care of these sick patients and for constant encouragement in completing this important work; the staff for supporting this work and for the help in assembling the data; Malcolm Wilkinson, RPh, for compounding all of the antimicrobial preparations for all these patients and for his patient education and support; and Stacey Gilmore, Meredith Thompson, PA-C, and Staci Kies, PA-C, for caring for these patients and helping in assembling the data.



References

- Abdel-Haq H, Giacomelli S, Palmery M, Leone MG, Saso L, and Silvestrini B (2000) Aflatoxins inhibit prolactin secretion in culture. *Drug and Chemical Toxicology* 23: 381–386.
- Alkemade A, Friesma EC, Kuiper GG, et al. (2006) Novel neuroanatomical pathways for thyroid hormone action in the human anterior pituitary. *European Journal of Endocrinology* 154: 491–500.
- Benninger MS, Desrosiers M, and Klossek JM (2006) Management of acute bacterial rhinosinusitis: current issues and future perspectives. *International Journal of Clinical Practice* 60: 190–200.
- Benninger MS, Ferguson BJ, Hadley JA, et al. (2003) Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology, and pathophysiology. *Otolaryngology and Head and Neck Surgery* 129: S1–S32.
- Bhattacharyya N (2003) The economic burden and symptom manifestation of chronic rhinosinusitis. *American Journal of Rhinology* 7: 27–32.
- Breuel KF, Kougiyas P, Rice P, et al. (2004) Anterior pituitary cells express pattern recognition receptors for fungal glucans: implications for Neuroendocrine immune involvement in response to fungal infections. *Neuroimmunomodulation* 11: 1–9.
- Campbell A, Thrasher J, Gray M, and Vojdani A (2004) Molds and mycotoxins: effects on the neurological and immunological systems in humans. *Advances in Applied Microbiology* 55: 375–406.
- Chambers DW, Davis WE, Cook PR, Nishioka GJ, and Rudman DT (1997) Long-term outcome-analysis of functional endoscopic sinus surgery: correlation of symptoms with endoscopic examination findings and potential prognostic variables. *The Laryngoscope* 107: 504–510.

- Chester AC (2003) Symptoms of rhinosinusitis in patients with unexplained chronic fatigue or body pain. *Archives of Internal Medicine* 63: 1832–1836.
- Collins TF, Sprando RL, Black TN, Olejnik N, Eppley RM, Alam HZ, Rorie J, Ruggles DI (2006) Effects of zearaleonone on in utero development in rats. *Food and Chemical Toxicology* 44: 1455–1465.
- Conte LJ, Holtzberg N (1996) Functional endoscopic sinus surgery, symptomatic relief: a patient perspective. *American Journal of Rhinology* 10: 135–140.
- Dennis D (2003) Chronic sinusitis: defective T-cells responding to superantigens, treated by reduction of fungi in the nose and air. *Archives of Environmental Health* 58: 433–441.
- Fliers E, Unmehopa UA, and Alkemade A (2006) Functional neuroanatomy of thyroid hormone feedback in the human hypothalamus and pituitary gland. *Molecular and Cellular Endocrinology* 251: 1–8.
- Fisk WL, Lei-Gomez Q, and Mendell MJ (2007). Meta-analyses of the associations of the respiratory health effects of dampness and mold in homes. *Indoor Air* 17: 284–296.
- Gray MR, Thrasher JD, and Crago R (2003) Mixed mold mycotoxicosis: immunological changes in humans following exposure in water-damaged buildings. *Archives of Environmental Health* 58: 410–420.
- Health on the Net Foundation. (1995) *Allergy Glossary*. Available at: <http://www.hon.ch/Library/Theme/Allergy/Glossary/allergy.html>
- Hoffman SR, Mahoney MC, Chmiel JF, Stinziano GD, and Hoffman KN (1993) Symptom relief after endoscopic sinus surgery: an outcomes-based study. *Ear, Nose, & Throat Journal* 72: 413–420.
- Krakauer T (1999) Immune response to staphylococcal superantigens. *Immunologic Research* 20: 163–173.
- Liiv I, Teesalu K, Peterson P, Perheentupa J, Uibo R (2007) Identification of the 49-kDa Autoantigen Associated with Lymphocytic Hypophysitis as α -Enolase. *The Journal of Clinical Endocrinology & Metabolism* 87: 752–757.
- Mathioudakis N, Salvatori R (2008) Adult-onset growth hormone deficiency: causes, complications and treatment options. *Current Opinion in Endocrinology, Diabetes, and Obesity* 2008: 352–358.
- Monson JP (2008) Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society Clinical practice Guideline. *Clinics in Endocrinology and Metabolism* 91: 1621–1634.
- O'Dwyer DT, McElduff P, Peterson P, Perheentupa J, and Crock PA (2007) Pituitary autoantibodies in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED). *Acta Biomedica* 78: 248–254.
- Ponikau JU, Sherris DA, Kern EB, et al. (1999) The diagnosis and incidence of allergic fungal sinusitis. *Mayo Clinic Proceedings* 74: 877–884.
- Ponikau JU, Sherris DA, Kita H, and Kern EB (2002). Intranasal antifungal treatment in 51 patients with chronic rhinosinusitis. *Journal of Allergy and Clinical Immunology* 110: 862–866.
- Ponikau JU, Shin SH, Sherris DA, et al. (2004) Chronic rhinosinusitis: an enhanced immune response to ubiquitous airborne fungi. *Journal of Allergy and Clinical Immunology* 114: 1369–1375.
- Rees DA (2005) Folliculostellate cells: what are they? *Endocrine Abstracts* 10: S31.
- Ricchetti A, Landis BN, Maffioli A, Giger R, Zeng C, and Lacroix JS (2002) Effect of anti-fungal nasal lavage with amphotericin B on nasal polyposis. *The Journal of Laryngology and Otology* 116: 261–263.
- Schubert MS (2001). A superantigen hypothesis for the pathogenesis of chronic hypertrophic rhinosinusitis, allergic fungal sinusitis, and related disorders. *Annals of Allergy, Asthma & Immunology* 4: 181–187.
- Shao PL, Haung LM, and Hsueh PR (2007) Recent advances and challenges in the treatment of invasive fungal infections. *International Journal of Antimicrobial Agents* 30: 487–495.
- Sherris DA, Ponikau JU, Weaver A, Frigas E, and Kita H (2005). Treatment of chronic rhinosinusitis with intranasal amphotericin B: A prospective, randomized, placebo-controlled trial. *Journal of Allergy and Clinical Immunology* 115: 125–131.
- Stochholm K, Gravholt CH, Laursen T, et al. (2006) Incidence of GH deficiency – a nationwide survey. *European Journal of Endocrinology* 155: 61–71.
- Stochholm K, Gravholt CH, Laursen T, et al. (2007) Mortality and GH deficiency: a nationwide survey. *European Journal of Endocrinology* 157: 9–18.
- Stochholm K, Laursen T, Green A, et al. (2008). Morbidity and GH deficiency: a nationwide study. *European Journal of Endocrinology* 158: 447–457.
- Takahashi M, Shibutani M, Sugita-Konishi Y, Inoue K, Woo GH, Fujimoto H, Hirose M (2007) A 90-day sub-chronic toxicity study of nivalenol, a tricothecene mycotoxin, in F344 rats. *Food and Chemical Toxicology* 46: 125–135.
- Warnock D (2006) Correlation of MIC with Outcome for Candida Species Tested against Voriconazole: Analysis and Proposal for Interpretive Breakpoints. *Journal of Clinical Microbiology* 44: 819–826.
- Winstead W, Barnett SN (1998) Impact of endoscopic sinus surgery on global health outcomes: a perception study. *Otolaryngology and Head and Neck Surgery* 119: 486–491.