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Exposure to Interior Environments of Water-Damaged Buildings Causes a CFS-like Illness in Pediatric Patients: a Case/Control Study

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ABSTRACT

The case definition for pediatric chronic fatigue syndrome (CFS) is symptom based, with a defined set of exclusions for confounding illnesses. These exclusions form a differential diagnosis of chronic fatiguing illnesses; the list of exclusions will grow as potential confounders are newly confirmed. Patients sickened by exposure to water-damaged buildings (WDB) have a multi-system, multisymptom illness, but only recently has fatigue become commonly accepted in WDB literature as a common symptom. Published data on symptoms in patients with WDB illness show fatigue is present in over 90% of adult patients. Physiologic disturbances in these patients are densely present and contribute to form a case definition for WDB illness in adults that demonstrates that each patient has a chronic, systemic inflammatory response syndrome (CIRS), with abnormalities in regulatory neuropeptides; markers of pro-inflammatory cytokine response; genetic association shown by HLA DR; TGF beta-1; autoimmunity; and split products of complement activation. We reviewed our pediatric cases of WDB illness comparing cases to a roster of controls, a group of well patients seen in the practice for well-child or well-adolescent care. Each case, but no controls, met the current pediatric case definition of CFS; each case, but no controls, had CIRS. We propose that (1) the pediatric case definition of CFS be modified to

specifically exclude patients with exposure to WDB that lasts more than 30 days (2) environmental exposure to WDB be included in a pediatric CFS history (3) laboratory testing in all potential pediatric CFS patients include assessment of CIRS (4) pediatric patients currently diagnosed with CFS be reviewed to exclude WDB illness as shown by exposure and CIRS markers.

BACKGROUND

The current published pediatric case definition of CFS, a product of the IACFS Pediatric Case Definition Working Group, is symptom-based, requiring at least 3 months of persistent chronic fatigue with post exertional malaise, un-refreshing sleep, wide-spread pain, neurocognitive manifestations and either autonomic, neuroendocrine or immune manifestations (1). The case definition includes no biochemical parameters and no biomarkers for pediatric CFS are identified. The definition requires that all other known medical conditions be excluded; this absence of other plausible explanations for the illness symptoms relies on a thorough differential diagnosis of illnesses that can cause a multisystem, multisymptom illness. The differential diagnosis of CFS in turn must accommodate advances in medical knowledge.

Written in 2006, the pediatric CFS case definition does not include a specific exclusion for patients with exposure to the interior environment of water-damaged buildings (WDB), including homes, schools and workplaces. We define WDB illness as a chronic illness with multiple health symptoms from multiple health systems acquired following exposure of at least 30 days to the interior environment of a building with a history of water intrusion followed by amplification of growth of resident toxigenic microbes, including but not limited to fungi, bacteria, actinomycetes and mycobacteria; as well as inflammagens, including but not limited to hemolysins, spirocyclic drimanes, proteinases, beta glucans, mannans and volatile organic compounds. The evidence for amplification can be an environmental report showing speciation of individual organisms; presence of visible mold growth or simply, musty smells (5). The definition does not include a factor for an initial duration of exposure or ongoing exposure, as the illness can be acquired acutely and then persist despite removal from exposure. As a rule, however, the illness onset is gradual with duration of exposure exceeding 30 days.

This absence of exclusion of WDB illness in the CFS pediatric case definition reflects the absence of general acceptance of fatigue as a typical WDB illness symptom in the pre-2006 WDB

literature. A comprehensive review of studies on WDB illness performed in 2003 by the Institute of Medicine at the request of the Centers for Disease Control and Prevention in 2002 did not identify enough papers published before 2003 that provided adequate support for consideration of causation of fatigue by exposure to the interior environment of WDB (2). Beginning in 2004 (3), however, recognition of fatigue as part of the roster of symptoms seen in affected patients became more commonly seen. By mid-2006, (4) fatigue was well represented as part of the symptom complex in pediatric patients as well as in adult patients (5, 6, 7, 8, 9, 10). By the fall of 2008, fatigue was well-established as part of the WDB illness syndrome (11).

Ongoing work by our group (12) has shown that adults have a multisymptom illness with multiple body systems represented. Affected patients invariably have HLA DR haplotypes found in approximately 24% of the well population (5). They have distinctive laboratory evidence of abnormalities in innate immune response. Loss of neuropeptide regulatory control of inflammatory responses is shown to absent of markedly low levels of alpha melanocyte stimulating hormone (MSH) and vasoactive intestinal polypeptide (VIP). Presence of a downstream dysregulated inflammatory responses is shown by elevated levels of matrix metalloproteinase-9 (MMP9); a split product of complement activation, C4a; and evidence of abnormalities in Th-17 immunity as shown by elevated levels of transforming growth factor beta-1 (TGF beta-1). We also have shown excessive presence of auto-antibodies in adults, with antibodies to gliadin, actin and cardiolipin commonly found. Correction of these inflammatory abnormalities provides clinical benefit with reduction of symptoms in patients previously chronically ill, without salutary response to any medical intervention, matching improvement in laboratory abnormalities.

Our primary hypotheses were (1) the symptoms of WDB-illness pediatric patients were not different from those identified by the pediatric case definition for CFS but were markedly different from controls; (2) laboratory abnormalities would be present in pediatric patients that paralleled those found in adults (3) the laboratory findings in pediatric age patients would be markedly different from controls. If we found that our hypotheses 1, 2, 3 were confirmed then we would want to strengthen the case definition of pediatric CFS by specifically excluding those pediatric patients who acquired their CFS-like syndrome after exposure to a WDB, understanding that the WDB illness patients would otherwise be incorrectly labeled as having CFS. By specifically identifying WDB-illness as a cause of a CFS-like syndrome, the occurrence of a potentially treatable illness could be separated out from true CFS by history and use of laboratory testing, possibly enabling health providers to provide effective therapies to an unknown number of CFS patients.

METHODS

In order to understand the efficacy of the pediatric CFS case definition as a tool for classification of cases of WDB illness as something other than CFS we performed a retrospective chart review to identify pediatric WDB illness patients seen at one site since 2005. We identified 163 cases, comparing their data to 55 controls seen during the same time. Each of the cases was confirmed by (i) evidence of illness acquired only after exposure to the interior environment of a water-damaged building; (ii) presence of a multisymptom, multi-system illness; and (iii) absence of confounders as shown by differential diagnosis (iv) response to therapy using an orally administered, non-absorbable, anion binding resin cholestyramine (CSM) as evidenced by reduction of symptoms and improvement in laboratory abnormalities.

Internal review board (IRB) approval for retrospective analysis was obtained from the Copernicus Group IRB, Cary, NC. Patients were identified by age < 18, presence of all elements of a pediatric case definition for WDB illness (4), successful reduction in symptoms and improvement of clinical course associated with use of an orally administered, non-absorbable anion binding resin, cholestyramine (CSM) prescribed according to a published protocol (5, 6). Differential diagnosis techniques were used to determine whether or not a cause of illness other than WDB illness could be identified. Patients were not remunerated for study participation. Control patients were identified as individuals coming for wellness evaluation, with no acute or chronic illness identified before or during the evaluation.

Chart review was performed to document that all elements of the 2006 pediatric case definition were assessed and present, though such assessment was recorded as part of a medical history performed by one physician (RS) and not by use of a questionnaire. Symptoms were orally assessed by the examining physician during the interview.

Medical records from other providers who had seen the patients prior to the clinic intake visit were also reviewed but no diagnoses made previously were used in this chart review.

Laboratory studies were performed by CLIA licensed, high complexity facilities, LabCorp, Quest Diagnostics, National Jewish Center and Cambridge Biomedical. Testing included HLA DR by PCR using SSOP; melanocyte stimulating hormone (MSH); MMP9; C4a; TGF beta-1; AGA, ACLA; CBC, CMP, CRP and von Willebrand's profile. Additional testing for patients older than 12

(N=88) included ESR, testosterone, cortisol, lipid profile, C3, C4, IgE and immunoglobulin panel (total IgG, total IgA, total IgM).

The prevalence of each symptom was investigated overall as well as within the illness and control groups. Significant differences were tested using the two sample t-test and considered statistically significant if the p-value was less than 0.001.

RESULTS

Our three primary hypotheses were confirmed. (1) Symptoms of WDB-illness pediatric patients met all criteria for diagnosis of pediatric CFS; and they were markedly different from controls. (2) Laboratory findings in pediatric age WDB-illness patients were similar to adult WDB-illness patients and those findings were (3) significantly different from controls.

The symptoms of cases included those found in the pediatric CFS case definition. Each of these cases met all elements of the CFS pediatric case definition, yet each was actually a WDB illness case and not a CFS case.

Cases and controls were similar in age, gender and ethnicity, though the smaller number of controls prevented exact matching to cases (Table 1). All cases had been sick for more than 6 months. All cases and no controls had presence of a multisymptom illness from at least four organ systems without confounders acquired following residential or educational exposure lasting more than 30 days to the interior environment of a WDB. Cases demonstrated presence at baseline of a multisymptom, multisystem inflammatory illness, with multiple metabolic parameters identified that were significantly different from controls (Tables 2, 3), particularly including deficiency of alpha melanocyte stimulating hormone (MSH); elevated levels of transforming growth factor beta-1 (TGF beta-1); elevated levels of the split product of activation of the fourth component of complement (C4a); together with increased incidence of antigliadin antibodies and anticardiolipin antibodies; and von Willebrand's profile. We stratified additional symptoms by incidence at baseline (Table 4). A group of three separate HLA DR haplotypes, analyzed by PCR, were present at a ratio of incidence in cases compared to incidence in controls that exceeded 2.0. This increased ratio identifies relative risk for HLA haplotypes 4-3-53; 11/12-3-52B and 14-5-52B (Table 5). Even though the numbers of cases is small, of note is that in the 11 subsets of HLA DRB1, only three (0401, 0402 and 0404) met the 2.0 relative risk criterion.

MMP9 showed a difference between cases and controls ($p < 0.005$) that did not meet our strict requirement for p values to be < 0.001 , though it is much different from labs shown in Table 6. MMP9 shows better utility as a parameter that reflects change in inflammatory cytokine release during treatment than as a diagnostic element. Each case but no controls also had at least three of six objective parameters from a list of six tests including HLA DR, MSH, TGF beta-1, C4a, AGA and ACLA. No differences were seen between cases and controls for all other parameters (Table 6). Of note on table 6 is that no significant differences between elements of complete blood cell count (CBC), metabolic profile (CMP) and level of hs-CRP were found.

DISCUSSION

These results for pediatric WDB illness patients' symptoms and laboratory findings are similar to those reported in 2005 (4). Each patient has an illness that is best described as a chronic, systemic inflammatory response syndrome. The molecular mechanisms underlying increased susceptibility for WDB illness in patients with particular HLA DR haplotypes are still undefined. However, genetic association of illness with increased relative risk noted for particular haplotypes of HLA DR suggests a linkage to defective antigen presentation. This result is consistent with a finding of HLA association in patients with persistent illness from Lyme disease following antibiotic therapy (15) and reported previously in WDB cases (5) as well as in autoimmune hepatitis (16). Associations of HLA DQ3, as in this WDB illness cohort, with persistent inflammatory problems are seen in WDB illness (17, 18, 19, 20).

Deficiency of the regulatory neuropeptide MSH, found in $> 95\%$ of cases but in $< 10\%$ in controls, suggests that the observed dysregulation of innate immune responses (21, 22) in this cohort is no different than other cohorts of cases of WDB illness (5, 6, 7, 12). Absence of regulation of innate immune inflammatory responses has not been evaluated systematically in CFS, but given the importance of neuropeptide regulation (21, 22), levels of MSH, and possibly vasoactive intestinal polypeptide (VIP) as well may be important in revealing the mechanism of diversity of symptom development after similar illness, thereby answering some of the criticisms of others, including Pariente (14).

Elevated levels of TGF-1 also suggest involvement of Th-17 immunity, supporting the concept that WDB illness involves more than Th-1 and Th-2 responses. Because of adverse effects of

TGF beta-1 on T regulatory cells, the significant presence of auto-immune findings in this cohort would not be unexpected (23, 24). Further, the role of TGF beta-1 as a stimulant to pro-fibrotic effects in lung parenchyma may support an explanation of the preponderance of pulmonary symptoms seen in cases compared to controls (25, 26).

Results of von Willebrand's profile shows that the acute phase reactant Factor VIII remains abnormal in WDB illness, as does ristocetin associated cofactor and von Willebrand's antigen itself. Though unexplained bleeding isn't uncommon in WDB illness (data not published), it is rarely seen in CFS. Disturbances of coagulation, a marker of a chronic inflammatory response syndrome, are clearly seen in WDB illness patients (12) and in the pediatric group reported herein but no comment can be made about incidence of coagulopathy in general or specific abnormalities in von Willebrand's profile in CFS patients.

Complement activation through the mannose binding lectin system will generate increased levels of split products of C4 activation (27). Elevated levels of C4a, seen in other systemic inflammatory response syndromes (28, 29, 30, 31) reflect ongoing auto-activation of MASP2 (27).

In this WDB-illness cohort, the combination of HLA-based genetic susceptibility to WDB-illness leading to neuropeptide deficiency after illness onset, with activation of TGF beta-1 and complement split products, as well as increased autoimmunity and dysregulated coagulation parameters all support presence of a CIRS (28).

The specific innate immune abnormalities seen in this cohort have not been reported in CFS earlier, though discussion of innate immune responses is recently reviewed by Raison and Reeves elsewhere (13). Of interest however, is the finding that this cohort is at variance with the Raison study that associated elevated hs-CRP (high sensitivity C-reactive protein) and white blood cell count with fatiguing illness. These lab parameters are themselves non-specific: they do not provide a reliable biomarker for CFS as discussed by Pariante (14) in a review of the Raison paper.

The findings in this WDB cohort provide an opportunity to strengthen the application of pediatric CFS case definition in clinical medicine by ensuring that CFS-like syndromes, especially WDB-illness, are not called CFS. With explicit recognition of the WDB-illness syndrome, including specific laboratory findings, clinicians will be better able to distinguish CFS from CFS-like illnesses by answering important concerns that effect patient care. (1) Have some pediatric age patients with WDB illness been diagnosed with CFS when they actually had WDB

illness? Clearly, these 163 patients would have been called CFS if the history of exposure to WDB were not included in the evaluation. If the patient with a tentative diagnosis of CFS is shown through history to have exposure to a WDB, then the consequences of that diagnosis for therapy will be very different if the illness is WDB illness and not CFS. WDB-illness pediatric patients look at first glance a lot like CFS patients, but therapeutic interventions that help WDB-illness patients are of no benefit in CFS patients. If the CFS case definition were modified to exclude the “new” confounder of exposure to WDB, clinicians will likely take the short time needed in history to ask about WDB.

(2) How can a treating physician for a CFS patient actually know if the patient has exposure to WDB? An environmental exposure history is the first step to answer this question. Looking for historical evidence of water intrusion and microbial growth takes little interview time. Presence of (i) visible mold or (ii) musty smells or (iii) microbial amplification as confirmed by environmental testing in an environment shared by a putative pediatric CFS case creates a ready confounder for the diagnosis of CFS. Of note in this regard is the now-widespread availability of the Environmental Relative Mold Index (32, 33), a rapid, inexpensive and reliable method for DNA testing for fungal species. Finding disproportionate presence of fungi found in WDB compared to those found in non-WDB provide a mechanism to proceed with further investigation into presence of WDB-illness (34, 35).

(3) Since the symptoms of pediatric CFS and pediatric WDB-illness are essentially identical and labs of the WDB patients are routinely noted to be markedly different from controls, what can we say about labs reported to be useful in CFS? We did not see much difference between cases and controls for CBC and CRP, as opposed to the findings of Raison. The various tests of innate immune responses discussed herein show a ready path for approaching a putative CFS diagnosis. If a CIRS is identified in lab testing, then additional inquiry into WDB exposure is indicated.

(4) Given the increasing awareness of the prevalence of WDB-illness, physicians may also revisit patients felt to have CFS, especially those who have no significant clinical response to therapies known to benefit CFS patients. Do they truly have CFS? The inflammatory cascades of innate immune responses of such patients will not spontaneously abate, even with removal from exposure to a WDB. Simply sending saved samples of blood from initial time of diagnosis could assist with this new approach to a CFS patient. Even if no patient blood samples were saved from earlier diagnostic work-ups, our experience is that the laboratory abnormalities of WDB illness are durable over time (data not shown). No known therapies for CFS that don't include bile-

sequestering agents such as CSM will correct the illness of putative WDB-illness patients. Revisiting the CFS diagnoses will add a measure of thoroughness to the previously completed differential diagnosis process used to arrive at the original CFS diagnosis.

The implications for CFS from this group of WDB-illness patients are clear: the diagnosis of CFS is enhanced by the specific addition of WDB-illness to the list of exclusionary medical diagnoses. Including an environmental exposure history, particularly to WDB, expands the rigorous differential diagnosis process used to diagnose CFS. CFS remains an important illness in the pediatric population. WDB-illness may provide “addition to CFS by subtraction” of what looks like CFS but isn’t.

Future directions in laboratory testing now underway in our WDB-illness populations and our CFS populations include genomics testing using mRNA from thousands of genes obtained from peripheral blood cells. Reliance on specific elements of innate immune responses to characterize WDB-illness, such as MSH, TGF beta-1 and C4a, for example, will likely evolve as identification of activation or suppression of specific genes in relation to proteomics becomes available. Such genomic testing may reveal unknown elements important in defining causation in CFS as well. For now, we can add to the specificity of the case definition for CFS by including specific recognition of WDB-illness and performing a short list of tests of innate immunity.

Disclaimers

Author RCS takes responsibility for accuracy of all data reported. No other persons other than the cited authors contributed to this study. This study is supported by private contributions to a non-profit, 501-c-3 corporation, The Center for Research on Biotxin Associated Illnesses, Pocomoke City, Maryland. RCS reports receiving fees for testimony time in cases involving exposure to WDB. MSM reports no conflicts of interest.

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