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SUCCESSFUL COMPLETION OF THE QUESTIONS AT THE END OF THIS PAPER HAS BEEN APPROVED FOR CONTINUING EDUCATION BY THE BDDT-N; 1 CREDIT PHARMACOLOGY, 1 CREDIT NUTRITIONAL MEDICINE

Diet-Based Management of Inflammatory Bowel Disease: The Role of Food Intolerance

Hypoallergenic diets have been used successfully by complementary healthcare providers as a management strategy for inflammatory bowel disease, and other automimmune disorders, for several decades. Clinical evidence in the area demonstrates significant variability in the type of dietary restriction imposed, but a selection of "usual suspects" emerges as common sources of dietary sensitivity. Nightshade vegetables, citrus fruit, several animal products, and berries have all been implicated as sources of dietary aggravation in specific cases. The focus of the following review will be to highlight evidence as it exists in relation to two key dietary sources of autoimmune disease aggravation; casein and gluten.

The strongest evidence of immunological aggravation from cow's milk comes from studies of allergic disease in newborn infants

Early exposure to food allergens has been well established as a major contributing factor to development of allergic illness in infancy, and as such allergen avoidance has become entrenched as primary care standard for reduction in risk of allergic disease in high- risk individuals. The American Academy of Pediatrics (American Academy of Pediatrics 2000) as well as the European Society for Pediatrics, Allergology and Clinical Immunology (ESPACI) and the European Society for Pediatric Gastroeneterology, Hepatology and Nutrition (ESPGHAN) (Host 1999) outline the importance of hypoallergenic infant formula for the prevention of allergic diseases in infancy. These organizations recommend exclusive breast- feeding for four to six months. When not possible, or when supplemental feeding is required, hypoallergenic formula (hydrolyzed cow's milk formula) is recommended for all high- risk infants (first degree relative with a history of allergic disease).

Cochrane performed a meta analytic review of evidence in the area in 2002. The analysis concluded hydrolyzed milk formula (formula which has undergone enzymatic treatment to break down casein and other intact proteins present in cow's milk) achieves reductions in risk of asthma or wheeze of 60% relative to standard cow's milk formula, during the first year of life (Ram 2002).

A recent study not included in the above- mentioned review administered one of four formulas (cow's milk formula, extensively hydrolyzed casein formula, partially hydrolyzed whey formula, or extensively hydrolyzed whey formula) to 2252 newborn infants at high risk of atopy. Infants were followed for three years. Hydrolyzed casein and whey formulas achieved significant reductions in risk of atopic dermatitis, but significant impact on risk of asthma was not achieved (von Berg 2007). Duration of eczema was reduced 48%, while the likelihood of ever developing eczema was reduced 33% (von Berg 2007).

Chronic constipation is accompanied by objective evidence of inflammatory bowel disease; cow's milk elimination effectively treats the constipation and resolves the objective findings consistent with inflammatory bowel disease.

Dr's Carroccio and Iacono, pediatric gastroenterologists at the Palermo University Hospital in Italy, noticed tremendous success of hypoallergenic diets in the management of pediatric constipation. The team became interested specifically in the role of dairy elimination as treatment, and published a paper serving as a review of the area as well as case data from their hospital in 2006 (Carroccio 2006).

The team reviewed 15 human studies which examined the topic at hand. All but one (14 of 15 studies) confirmed strong links between milk elimination and successful treatment of constipation. Specifically, Carroccio and Iacono reported that elimination of dairy achieves a 50%- 70% success rate in treating constipation in children (Carroccio 2006).

In one trial sighted by the team, 65 children with chronic constipation were randomly assigned to cow's milk or soy milk for a two week period, followed by a one week washout, then crossover to the opposite treatment. 44 of 65 children (68%) experienced a complete resolution of constipation while receiving soy milk, including resolution of anal fissures and pain on defecation. Not a single child experienced a resolution of constipation while receiving cow's milk (Iacono 1998).

Two important correlations emerge from the evidence reviewed above. A) Clinical responsiveness to a dairy- free diet is not associated with elevated total or dairy- specific IgE levels in serum. B) In patients with chronic constipation, eosinophilic infiltration of rectal mucosa is a characteristic finding based on histological analysis. This infiltration is reversed upon implementation of a dairy- free diet (Carroccio 2006).

In a similar trial, fifty- two children with chronic constipation non- responsive to laxatives were assigned to a dairy- free diet. Within two weeks after implementing the dairy free diet, bowel function normalized in 24 of the 52 subjects. The remaining 28 patients were placed on a more restrictive, oligoantigenic diet. An additional six patients achieved normalization of bowel function (30 of 52 patients experienced resolution of symptoms through implementation of a hypoallergenic diet). Re-challenge with eliminated allergens resulted in recurrence of symptoms in all 30 patients. Onset of constipation ranged from four- fourteen days. Again, eiosinophilic infiltration of the mucosa was present (Carroccio 2006).

While the focus of the research team is management of pediatric gastrointestinal ailments, a brief report on four cases of adult constipation managed by the team is presented. In this brief recount of four cases, all four adults experienced a normalization of bowel function following an oligoantigenic diet. All four subjects experienced a return of constipation within 4-14 days of reintroduction of either dairy or wheat. Again, objective demonstration of lymphocytic and eiosinophilic infiltration of rectal mucosa was reported (Carroccio 2006).

Does gluten impact the course of inflammatory bowel disease?

Celiac disease is an immune- mediated disorder that affects primarily the gastrointestinal tract, caused by a dietary intolerance to gluten. Gastrointestinal manifestations include; diarrhea and/ or constipation, weight loss, failure to grow, vomiting, abdominal pain, bloating and distension, and anorexia. Extraintestinal manifestations include; anemia, dermatitis herpetiformis, short stature, delayed puberty, recurrent fetal loss, osteoporosis, vitamin deficiencies, fatigue, protein calorie malnutrition, recurrent amphthous stomatitis, elevated transaminases, dental enamel hypoplasia, and thyroiditis. Neuropsychiatric manifestations include; depression, anxiety, peripheral neuropathy, ataxia, epilepsy, and migraine headache (Cook 2000, NIH 2004).

Estimates suggest that approximately 0.5- 1.2% of Americans are afflicted with celiac disease, and that the vast majority of these individuals go undiagnosed (Cook 2000, NIH 2004). In one study assessing prevalence in a US sample of subjects, 1.2% of subjects were found to be positive for celiac disease (serology followed by small intestine biopsy), whereas only 0.3% of the sample (23% of celiac patients) had received the diagnosis prior to enrollment in the present trial of prevalence (Cook 2000).

The discussion to follow will review:

- Preclinical (in vitro and animal) evidence outlining impact of gluten exposure on several parameters related to gastrointestinal health.
- Observational evidence demonstrating an impossibly large (>30%) proportion of individuals suffering from various ailments to possess objective markers of celiac disease/ gluten sensitivity.
- Human intervention trials demonstrating profound clinical improvement upon elimination of gluten for a wide array of common, debilitating disorders routinely observed in outpatient primary care settings.
- Human intervention trials examining the impact of comprehensive hypoallergenic diet approaches (multiple food eliminations) for management of a broad array of common health concerns, most specifically in the realm of autoimmune disease.

Preclinical evidence of gluten intolerance; implications for gastrointestinal health, diabetes, and neurological dysfunction.

Bernardo et al conducted a landmark preclinical study to determine the impact of gluten on cells of the small intestine. Small intestine biopsies of individuals with celiac disease, and healthy control subjects were conducted. Subsequently, gluten was applied to the cell cultures of both groups. The cells from individuals with celiac disease responded in a predicable manner. First the production of IL-15 lead to an innate immune response and ended with adaptation of small intestine immune cells into Natural Killer- like cells, poised to attach to villi within the small intestine (Bernardo 2007).

A surprising response was observed in the cells from healthy subjects to gluten treatment. Cells from the small intestine of healthy subjects also exhibited an autoimmune response to gluten. The cells reacted to gluten by producing IL-15, as did the cells of the individuals suffering from celiac disease. Correspondingly, the cells from the healthy subjects also initiated an innate immune response, just as the cells from individuals suffering from celiac disease. The only difference being, cells from healthy subjects did not display the adaptation of immune cells into Natural Killer- like cells. This portion of the process was only seen in patients suffering from celiac disease (Bernardo 2007).

The implications of this study are highly significant. The authors used their findings to question the safety of gluten even among non- celiac patients. The immune reaction observed to gluten among healthy subjects may not lead to destruction of villi within the small intestine, but it certainly may lead to other manifestations experienced by celiac patients. Such an immune response is likely to result in "leaky gut", the same phenomena found in full- blown celiac disease. Molecules which are not meant to cross the intestine "leak" through gaps in cells created by an inappropriate immune response. The result is absorption and circulation throughout the body of partially digested molecules, capable of having impact in every major organ system.

Several investigators have demonstrated similar deleterious gastrointestinal effects from gluten administration in animal models. Pusztai et al demonstrated growth retardation, inhibition of dietary protein digestion and absorption, hypertrophic growth of the small bowel, hypertrophic growth of the pancreas, atrophy of the thymus, and entry of gliadin metabolites into systemic circulation upon gliadin feeding in healthy, "non- celiac" rats (Pusztai 1993). Sjolander et al subjected isolated rat small intestine (healthy rats) to varying dosages of gluten. Morphological changes induced included disarrangement of the cytoskeleton, increased endocytosis, and shortening of the microvilli; changes consistent with early stages of celiac disease (Sjolander 1986). Lorenzsonn and Olsen examined the effects of acute intraluminal administration of gluten in healthy rats. Observed outcomes included increased shedding of the brush border membrane, reduction in intestinal surface area, acceleration of cell loss, and shortening of the villi (Lorenzsonn 1982).

The impact of gluten is far more reaching than direct effects on the gastrointestinal tract. Significant preclinical evidence has emerged suggesting gluten feeding has a direct and powerful role in the development of diabetes.

MacFarlane et al utilized IgG isolated from blood of rats with a form of diabetes similar to human type I diabetes.

The authors sight several observational papers in which humans with type I diabetes are found to suffer from very high rates of gluten enteropathy, high concentrations of anti gliadin antibodies in their blood, and a heightened T-cell response to wheat proteins. A cDNA library of wheat was probed with IgG antibodies from the rats. Several cross-reactions were observed, and the authors noted that the protein most powerfully bound by the rat IgG (G1b1) correlates strongly with pancreatic islet inflammation and damage. Furthermore, the authors demonstrated that antibodies to the wheat protein G1b1 are readily found in a significant subset of human type I diabetic patients, but not in age and sex matched non diabetic control subjects (MacFarlane 2003).

Partial digestion products of gluten and gliadin were administered to rats, for the purpose of determining their impact on postprandial insulin levels. The intervention significantly and markedly increased the postprandial insulin response of the animals. The researchers note that this is not a gastrointestinal effect of gluten, but could only be reproduced among rats which are gluten intolerant. It is the result of systemically circulating partial digestion products of gluten and gliadin (Fukudome 1995).

Preclinical evidence has also begun to provide a mechanistic basis for observed neurological manifestations of gluten sensitivity. Alaedini et al isolated anti gliadin antibodies from animals and humans, and sought to determine their reactivity with various neural proteins. Antigliadin antibodies from both animals and humans demonstrated strong binding affinity for a neural protein termed synapsin I (Alaedini 2007).

Hadjivassiliou et al have characterized a subset of patients with ataxia who respond to gluten elimination with a near- complete reversal of symptoms, human data from this lab to be reviewed shortly. In an effort to mechanistically explain the observed phenomena, the investigators report on jejunal biopsy samples from nine human patients with "gluten ataxia" and seven patients with ataxia from other causes. Autopsy brain tissue was also available from one "gluten ataxia" patient and one patient with ataxia from other causes. The team demonstrated that anti- tissue transglutaminase IgA is present in both the jejunum and the brain of patients previously identified as having gluten ataxia, but that its presence was not detected in a single sample of jejunum or brain of patients with ataxia from other causes (Hadjivassiliou 2006a).

Objective determination of gluten sensitivity in humans with various ailments demonstrates an "impossibly large" proportion of individuals suffer from gluten intolerance.

Regardless of the pathology in question, in theory, no more than 1% of individuals should be found to be gluten

intolerant. In brief, objective determination of gluten intolerance/ sensitivity in patients with autoimmune disease has revealed the following;

A) The prevalence of celiac disease (assessed using antiendomysium antibodies and antireticulin antibodies) is dramatically elevated relative to healthy control subjects.

B) The presence of IgA and/ or IgG antigliadin antibodies are not diagnostic of celiac disease, but suggest gluten sensitivity. Both in control subjects and patients with autoimmune disease, the titers of IgA and IgG antigliadin antibodies are more commonly elevated relative to the diagnostic markers of celiac disease. In patients with autoimmune disease, elevated IgA and/ or IgG antigliadin titers are far more common relative to elevations of these markers in healthy control subjects.

Therefore, gluten intolerance appears to be an important and often overlooked phenomena among individuals suffering with autoimmune disease. A significant subset of patients, upon assessment, will be found to have celiac disease. A dramatically larger subset than this will be found to be gluten sensitive (elevated IgA and/ or IgG antigliadin antibodies) without having celiac disease.

Fifty patients with ulcerative colitis (UC) were assessed for the presence of antigliadin antibodies (AGA). Sixteen patients with IBS and 37 healthy individuals served as controls. Seventeen of 50 (34%) patients with UC tested positive for IgA and/ or IgG antigliadin antibodies. None of the subjects in the "healthy" control group, and two of 16 (12.5%) IBS patients tested positive (Kull 1999). No subject in any group tested positive for antireticulin antibodies or antiendomysium antibodies. Therefore, although a formal diagnosis of celiac disease was not applied to any subject in the study, a very large subset of subjects with UC tested positive for markers suggestive of clinical improvement upon gluten withdrawal.

One hundred and seventy two patients with autoimmune thyroiditis, 396 patients with nongastroenterologic malignancies, and 4000 blood donors were screened for IgA class antiendomysium antibodies. 3.4% of patients with autoimmune thyroiditis, 0.75% of patients with nongastroenterologic malignancies, and 0.25% of blood donors were found to be positive (Berti 2000). This represents a 450% increase in prevalence relative to nongastroenterologic malignancy and a 13600% increase in prevalence relative to a large sample of blood donors. Recall that Kull (1999) demonstrated 34% of UC subjects to be positive for IgA and/ or IgG antigliadin antibodies, without a single subject testing positive for antiendomysium antibodies. Berti (2000) has demonstrated a very elevated rate of celiac disease, but failed to report on the prevalence of the more common phenomena of gluten sensitivity (assessed using IgA and IgG antigliadin antibodies).

Seventy eight patients with rheumatoid arthritis and 25 age and sex- matched controls underwent assessment for IgA and IgG antigliadin antibodies as well as assessment for antireticulin antibodies. Elevated IgA and/ or IgG antigliadin antibodies was observed in 37% of patients with rheumatoid arthritis and 12% of control subjects. Antireticulin antibodies were present in 4% of patients with rheumatoid arthritis and none of the control subjects (Paimela 1995). The present investigation reaffirms trends appearing thus far; A large subset of patients with autoimmune disease (1/3 or more) test positive for antigliadin antibodies (marker of gluten sensitivity), a much smaller subset of patients tests positive for antireticulin antibodies or antiendomysium antibodies (diagnostic markers of celiac disease).

One hundred and eight patients with IBS and 43 healthy control subjects were subjected to plasma determination of IgG4 and IgE titers to 16 common foods. Skin prick testing was also performed for the same battery of test foods. Plasma titers of IgE and skin prick testing demonstrated no significant differences between IBS patients and controls. IgG4 plasma titers were significantly elevated among IBS patients to four of the tested foods; wheat, beef, lamb, and pork (Zar 2005).

Controlled human intervention trials have demonstrated significant efficacy from dietary elimination of gluten and other common food allergens in several autoimmune disorders.

145 patients with diarrhea-dominant IBS, 30 patients with untreated celiac disease, 44 patients with treated celiac disease, and 57 patients with active IBD were recruited to determine associations between markers of gluten sensitivity and treatment response. IgA and IgG antibody concentrations against gliadin and tissue transglutaminases were determined, followed by a six month period of gluten elimination. All patients also underwent upper and lower gastrointestinal endoscopy, as well as abdominal ultrasound (Wahnschaffe 2007).

Plasma markers of gluten sensitivity were present in nearly all cases of untreated celiac disease. IgA antibodies were present in a very small subset of treated celiac disease patients (7%), whereas IgG antibodies were present in over half (55%) of treated celiac disease patients. This suggests IgA antibodies are a marker of active disease, whereas IgG serves as a marker of gluten sensitivity (Wahnschaffe 2007).

37% of IBS subjects tested positive for IgG antibodies, while 18% of patients with IBD tested positive. Among the subset of subjects with IBD, an equal proportion of ulcerative colitis and Crohn's disease patients tested positive (Wahnschaffe 2007).

Subjects in the IBS subgroup were invited to participate in a six month trial of gluten elimination. Antigliadin IgG decreased 34% and anti transglutaminase IgG decreased 20% following six months of a gluten free diet (Wahnschaffe 2007).

Recall that subjects were suffering from diarrhea- dominant IBS. Overall, 50% of subjects following a gluten free diet achieved normalization of the gastrointestinal symptom score, and 37% achieved formed stools at normal frequency. 30% of subjects experienced both a normalization of gastrointestinal symptom score and formed stools at normal frequency following six months of a gluten free diet (Wahnschaffe 2007).

IgG antigliadin and anti transglutaminase were powerful predictors of a positive response to a gluten free diet, although positive treatment outcomes of a gluten free diet were still demonstrated even among subjects testing negative for the immunological measures of gluten sensitivity. Among subjects who tested positive for IgG antibodies, 70% achieved normalization of gastrointestinal symptom score, 50% achieved formed stools at normal frequency, and 45% achieved both outcomes. Among subjects who tested negative for IgG antibodies, 29% achieved normalization of gastrointestinal symptom score, 29% achieved formed stools at normal frequency, and 14% achieved both (Wahnschaffe 2007).

Studies of comprehensive hypoallergenic diet interventions demonstrate significant heterogeneity in terms of the types of dietary restrictions imposed. None- the- less, a review of intervention trials in the area reveals a handful of "usual suspects", foods found in many different settings to be common sources of symptom aggravation; a short list of such foods include gluten containing grains, dairy products, alcohol, and caffeine.

In a thorough review paper of the area over 35 controlled human intervention trials of hypoallergenic diets for an array of common, predominantly autoimmune disorders are presented (Gaby 1998). Several intervention trials in each of the following areas are discussed; migraine, arthritis, irritable bowel syndrome, inflammatory bowel disease, asthma, aphthous ulcers, recurrent otitis media, gallbladder disease, nephritic syndrome, and ADHD. Of the more than 35 clinical trials reviewed, only one failed to demonstrate significant clinical impact from the intervention. Of greater relevance, the magnitude of impact achieved in most of the trials reviewed is immense.

Hill et al recruited 107 exclusively breastfed infants experiencing significant symptoms of colic to determine if hypersensitivity to food proteins among mothers contributes to colic in breast fed infants. The mean cry/ fuss duration per 48 hour period at baseline of the children was over 650 minutes. A 25% or greater reduction in cry/ fuss duration was considered to be a significant response to the intervention (Hill 2005). Mothers were randomly assigned to a control group (maintain current diet) or hypoallergenic diet group (eliminate wheat, cow's milk, eggs, peanuts, tree nuts, soy, and fish). The intervention spanned seven days.

74% of infants whose mothers followed the hypoallergenic diet experienced a 25% or greater reduction in 48 hour cry/ fuss duration versus 37% of children whose mothers were in the control group. The mean reduction in cry/ fuss duration among children whose mothers followed a hypoallergenic diet was 38% (Hill 2005). It is important to note that these outcomes likely underestimate the impact of a hypoallergenic diet on colic symptoms of breastfed infants. The very short treatment duration (seven days) and the very large placebo effect (37% of control subjects experiencing a 25% or greater improvement) understate the true impact of the hypoallergenic diet intervention.

Hafstrom et al randomized 66 patients with rheumatoid arthritis to a control diet or a gluten- free vegan diet for one year. Subjects were assessed at baseline, and every three months thereafter. The American College of Rheumatology 20 (ACR20) improvement criteria served as the main endpoint measure (Hafstrom 2001). After one year, 40.5% of subjects following the gluten free diet versus 4% of subjects following the control diet met ACR20 improvement criteria.

Gluten elimination provides a very large magnitude of benefit for a subset of patients with schizophrenia, ataxia, and other neurological/ behavioural disorders.

A team of researchers from John Hopkins School of Medicine compiled a very thorough review of evidence relating to gluten sensitivity as a causal factor in schizophrenia. Although the percentage of schizophrenic patients proposed to respond to gluten elimination is small (10% or less), the magnitude of benefit delivered in this subset of schizophrenic patients is immense, often capable of completely reversing the diagnosis (Kalaydjian 2006).

The team reviews a sequence of findings which, in combination, powerfully support the need to objectively

assess for gluten sensitivity among schizophrenic patients. Observational evidence in and around World War II demonstrates that in nations suffering from shortages of wheat and cereal grains, hospital admissions for schizophrenia decreased. During the same time period in the USA, wheat and cereal grain consumption increased. In line with the hypothesis of a causal role for gluten in schizophrenia, hospitalizations for schizophrenia increased in the USA during this time period (Kalaydjian 2006). Additional supportive observational evidence comes from prevalence rates of celiac disease among schizophrenic individuals. In the general population, the prevalence of celiac disease is considered to be 0.5- 1.2%. Among schizophrenic individuals, the prevalence of celiac disease has been reported as 4.2%.

A series of controlled human intervention trials are also reported within the review. While most schizophrenic individuals are not expected to obtain significant impact from a gluten- free diet, several studies of gluten elimination have produced profound impact among a significant subset of schizophrenic patients (Kalaydjian 2006).

A team of neurologists from England published a large body of literature examining the role of gluten as a causal factor in ataxia (gross incoordination of muscle movements, typically due to dysfunction of the cerebellum). The team has since coined the term "gluten ataxia" to describe a subset of patients with ataxia who achieve complete or near- complete resolution of ataxia upon gluten withdrawal. Again, the team proposes up to 10% of patients with ataxia respond to gluten elimination in such a manner (Hadjivassiliou 2006b, Hadjivassiliou 2006c, Sanders 2003, Wilkinson 2005).

Two hundred and fifteen patients with axonal neuropathy were screened for objective parameters of gluten sensitivity and for presence of celiac disease. 34% were found be positive for IgG and/ or IgA antigliadin antibodies. 29% of gluten sensitive patients were demonstrated to have celiac disease (Hadjivassiliou 2006c).

In one of several published intervention trials performed by the team, 35 patients with ataxia (all of whom were positive for IgG and/ or IgA antigliadin antibodies) were assigned to a gluten free diet (n=25) or control (n=10) for one year. The predefined main outcome measure was change in sural sensory action potentials. Consistent improvement in the treatment group was observed, while control subjects exhibited consistent deterioration. Subjective symptom scores from patients also demonstrated powerful treatment effects, with subjects following a gluten- free diet reporting consistent improvement, while control subjects experienced consistent deterioration (Hadjivassiliou 2006b). A second trial with 43 participants, also of 12 months duration, produced similar outcomes (Hadjivassiliou 2003). Gluten elimination was helpful in all patients positive for IgG and/ or IgA antibodies to gluten, irrespective of whether or not celiac disease was present.

Fifteen patients with gluten ataxia (diagnosis of ataxia plus positive for IgG and/ or IgA antigliadin antibodies) and 10 control subjects underwent proton magnetic resonance spectroscopy imaging of the brain. Patients demonstrated significant differences in cerebellar levels of N-acetyl aspartate and ratios of N-acetyl aspartate: choline relative to control subjects. These trial outcomes confirmed alteration in cerebellar neuronal physiology between patients with gluten ataxia relative to control subjects (Wilkinson 2005).

A selection of clinical intervention trials has surfaced regarding the role of hypoallergenic diets in several other areas, notably a Cochrane review of such strategies in autism (Millward 2008) as well as a review of several reports of their use in systemic lupus erythematosus (Brown 2000).

Conclusion

Hypoallergenic diets are able to achieve a highly significant magnitude of clinical benefit for a wide array of concerns related to autoimmune disease. Objective assessment of food allergy/ sensitivity through determination of plasma IgE and IgG antibodies to food allergens provides a valuable tool through which to select patients likely to achieve a positive response to dietary intervention.

The strongest evidence of a causal role for food sensitivity in autoimmune disease relates to gluten and dairy. In both cases, objective determination of sensitivity increases the likelihood of a positive treatment response upon their removal from the diet. However, in both cases, a failure to objectively identify immunological reactivity does not exclude symptom resolution upon elimination of these two common aggravating foods. The vast majority of individuals who test positive for plasma markers of immunological reactivity achieve significant clinical benefit from dietary elimination of gluten and/ or dairy; a relatively smaller, yet surprisingly significant subset of subjects who do not test positive for markers of immunological reactivity still achieve highly significant benefit from dietary elimination of gluten and/ or dairy.

Complementary healthcare providers have long maintained that similar approaches offer an equivocally impressive

magnitude of efficacy for management of a wide array of neurological disorders, including the autistic spectrum of disorders (autism, ADD/ ADHD, Asperger's syndrome, Tourette's syndrome, etc…), depression, anxiety, schizophrenia, neurodegenerative diseases, and others. Published evidence in these areas is weak relative to evidence in the realm of autoimmune disease, yet intervention trials are now beginning to surface.

First-line management of any autoimmune presentation must include objective evaluation of allergy/ sensitivity to gluten. The prevalence of IgA and/ or IgG antigliadin antibodies among individuals afflicted with a wide array of autoimmune disorders is extremely large, comprising one- third or more of all such patients. Among this subset of patients, gluten elimination should be considered the first- line treatment option of choice. Gluten elimination is anticipated to achieve complete or near- complete resolution of illness in the vast majority of this subset of patients.

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Questions

1. Prevalence of celiac disease among adults in estimated to be?
   A)1%
   B)5%
   C)10%
   D)15%

2. Testing positive for the following plasma marker(s) is considered diagnostic of celiac disease.
   A)IgA and/ or IgG antigliadin antibodies.
   B)IgM antigliadin antibodies.
   C)Antiendomysium and/ or antireticulin antibodies.
   D)None of the above is predictive of celiac disease.

3. Although not diagnostic for celiac disease, testing positive for the following marker(s) is suggestive of gluten intolerance. In such individuals, gluten elimination is expected to achieve significant clinical benefit for a wide array of autoimmune (and possibly neurological/ psychiatric) disorders.
   A)IgA and/ or IgG antigliadin antibodies.
   B)IgM antigliadin antibodies.
   C)Antiendomysium and/ or antireticulin antibodies.
   D)Recovery of lactulose in the urine following oral challenge.

4. Evidence from well- controlled, human clinical intervention trials has demonstrated efficacy from dairy elimination for which of the following disorders in children?
   A)Upper respiratory tract infection.
   B)Pediatric cancers (neuroblastoma, leukemia).
   C)Conduct disorder.
   D)Eczema, asthma, and constipation.

5. Approximately "X" percentage of subjects with autoimmune disease are anticipated to test positive for objective markers of gluten sensitivity. Approximately "Y" percentage of subjects with autoimmune disease are anticipated to test positive for celiac disease.
   A)15%, 10%.
   B)35%, 4%.
   C)50%, 10%.
   D)50%, 4%.

6. Elimination of dairy in children with chronic constipation has been shown to reverse objective signs of inflammatory bowel disease.
   A)True
   B)False

7. Preclinical evidence has demonstrated that gluten may be a causal factor associated with diabetes.
   A)True
   B)False

8. Preclinical evidence has demonstrated that milk induces immune complex deposition in the cerebellum, suggesting a causal role of milk in ataxia.
   A)True
   B)False

9. Observational evidence demonstrates a dramatically elevated prevalence (400%+) of celiac disease among individuals with schizophrenia.
   A)True
   B)False

10. Hypoallergenic diets have failed to benefit colic in infants when imposed on breastfeeding mothers.
    A)True
    B)False

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