

Celiac Disease and Neurological Symptoms

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Abstract

New research has revealed that Celiac disease, an autoimmune illness affecting the small intestine, has more ties with neurological side effects than once was thought. The classic and most well known presentation of Celiac disease is gastrointestinal, including symptoms such as abdominal pains, nausea, diarrhea, and flatulence. Researchers have more recently found a correlation between Celiac disease and neurological illnesses such as epilepsy, depression, dementia, and ADHD. Physician awareness of the disease and the neurological side of the illness should be heightened in order for patients to receive earlier diagnosis and a better quality of life. Because of the difficulty to diagnose this disease when the presentation is neurological, there is indication for mass screening programs to be implemented.

There is a growing awareness of gluten-intolerances and an increased number of people switching to a gluten-free diet and life-style. Package Facts reported a 30% rise in gluten-free products bought in the US between 2006 and 2010 (Case, 2012).

Consumers have found that grocery stores and restaurants are starting to stock gluten-free options. Many of those who are making this switch are doing so because of a disorder called celiac disease (CD) (Case, 2012).

However, because of varying symptoms of the disease and the lack of knowledge by physicians, CD is still under-diagnosed. Dr. Peter H.R. Green stated at the 2008 meeting of The American Academy of Allergy, Asthma, and Immunology that it is estimated that 1% of the population of the US have CD, but only 3% of those with the disease have been diagnosed (Brunk, 2008). Large proportions of those who have the disease are not diagnosed until adulthood (Rubio-Tapia & Murray, 2010). One of the reasons so many are not being diagnosed early is because the disease is being masked by symptoms that seem to be unrelated to a gastrointestinal disease. Many of those with CD have neurological symptoms that look strikingly like other disorders or diseases. It has been estimated that between 6-10% of those with CD present with neurological symptoms (Alehan, Ozçay, Eroı, Canan, Cemil, 2008).

Sadly, many physicians and patients are unaware of the variety of presentations of CD presents, which results in misdiagnosis (Zelnik, Pacht, Obeid, Lerner, 2004). Some patients struggle for years with symptoms that respond poorly to an unrelated treatment plan. Mass screenings could be a way that the United States can rectify the estimated 97% of those who go undiagnosed. These screenings are cost effective and can help lower mortality rates (Brunk, 2008).

Pathophysiology

CD is an autoimmune disease that could potentially affect every system of the body. Those with CD have leaky intercellular tight junctions in the small intestine, which cause gluten, rye, and barley proteins to leak into the lamina propria (Zawahir, Safta, Fasano, 2009). This stimulates an inflammatory response caused by the innate immune system response creating proinflammatory cytokines. Because of the inflammation there is cell damage and these lysed cells produce transglutaminase 2 (TG2). TG2 is a protein that assists with angiogenesis, the process of formation of blood vessels from preexisting blood vessels (Gilbert, 2000). Immunoglobulin-A (IgA) that is specific to the patient is produced in response to the abnormal levels of TG2 (Zawahir & et. al, 2009). The antibody IgA then attacks TG2 (Myrsky, Kaukinen, Syrjänen, Korponay-Szabó, Mäki, & Lindfors, 2008). When angiogenesis is inhibited by the antibody formation, there is no sprouting of new endothelial cells, migration of mesenchymal cells from connective tissue, or maturation of the new blood vessels (Gilbert, 2000). This decrease in blood flow to the tissues causes the mucosa on the small intestine to become severely damaged due to the missing capillary beds (Myrsky & et al., 2008).

When seen in an endoscopy, the microvilli and folds in the intestine appear flattened, atrophied, scalloped, lesioned, and/or fissured (Zawahi & et al., 2009). Because the microvilli are responsible for the absorption of nutrients, those with untreated CD lack the ability to absorb many of the nutrients needed for daily life, causing multiple systems in the body to be affected (Ryan & Grossman, 2010). Because CD can cause damage throughout the body, there are not only gastrointestinal symptoms, such as diarrhea, abdominal pain, and weight loss, but also problems in the

musculoskeletal system, neurological system, and integumentary system (Ryan & et al., 2010).

The lack of nutrients is not the only cause of multiple systems being affected by gluten. Researchers in Finland have found that there are antibody deposits in hepatic blood vessels, which can cause mild liver abnormalities (Myrsky & et al., 2008). Those with neurological symptoms have also been found to have antibodies in the brain vessels. This causes neuroblast apoptosis, gluten ataxia, and other neurological disorders (Myrsky & et al., 2008).

Genetics and Possible Causes

There is a heavy link between CD and genetics. CD is linked to the alleles HLA (Human Leukocyte Antigen)-DQ2 or HLA-DQ8 (Ryan & et al., 2011). Those with CD have more than a 90% chance of having a genetic expression of HLA-DQ2. Monozygotic twin studies have shown that there is a 83-86% likelihood that if one twin has the disease, the other will as well (Wolters & Wijmenga, 2008). A person with the disease has a 5-15% likelihood that another family member will also have CD. There is also higher prevalence of CD in different ethnicities and geographical locations. For example, there are a high number of people in northern Europe with CD (King & Ciclitira, 2000); many in the Middle East, India, and North Africa have also been diagnosed at higher rates than the rest of the world (Zawahir & et al., 2009). The reason for this has been highly studied; and most likely it is because of genetic variances and tendencies in ethnic groups and families (Zawahir & et al., 2009).

A Swedish study investigated the potential for cultural causes. In the mid-1980s, there was a 300% increase in children less than two-years-old being diagnosed with CD

(Wolters & et al., 2008). This was related to changing the recommendations for when gluten was introduced to the infant. It was previously four months, but they changed the recommendation to six months. This caused infants to be exposed to gluten without breastfeeding simultaneously. The government changed the recommendation back to four months for gluten introduction, while also breastfeeding. As a result, CD diagnosis of children dropped. There was also a thought in Sweden that because children born in the summer had a higher likelihood of being diagnosed with CD, infections in the winter when gluten was introduced could be the cause. This has not been proven, but merely speculated. In addition, there have been correlations between human intestinal adenovirus and rotavirus infections and higher CD diagnosis. However, the propositions that cold winters with higher infection rates or cultural introduction to gluten at a later age is the cause of higher CD diagnoses is doubtful, especially because there is also a high incidence in the disease in many different cultures and climates (Wolters & et al., 2008).

Diagnosis

There are many markers in the body that lead health care providers to a diagnosis of CD and some markers are more diagnostic than others. The various pathologies of the disease are the cause of these markers (Ryan & et al., 2011). The inflammatory response in the intestine causes the microvilli to flatten and atrophy. Antibodies are made against the gluten proteins. Many with CD also have a genetic factor predisposing them to the disease. Because of these processes, there are various tests that can be done to diagnosis a person with the disease (Ryan & et al., 2011).

It was once thought that a biopsy of the small intestine was the gold standard for testing CD (Hill & et al., 2008). A biopsy is usually encouraged or scheduled after a positive serum test. However, research has shown that serum tests (used to test various antibodies in the blood) are just as effective and demonstrative as biopsies and therefore many can be spared the discomfort biopsies bring. The antibodies created by those with CD, exposed to gluten are IGA and IgG antigliadin-antibodies (AGA-IgA), TGA, and antiendomysium antibodies (EMA), and HLA-DQ typing (Hadithi & et al., 2007). Recent studies have shown that tTGA levels in the blood is the most accurate at diagnosing CD (Hill & et al., 2008). First-generation assays to test for tTGA were not as accurate as other tests, but second-generation assays have started using human purified or human recombinant tissue transglutaminase-2 and have become much more sensitive and accurate (Hill & et al., 2008).

The biopsy can be tested for specific antigens on the intestine using immunohistochemistry (Ramos-Vara, 2005). Biopsies have been considered beneficial because of the visibility of damage to the intestines. However, there are problems with them. First, biopsies can show the atrophy and lesions in the intestines, but CD is not the only disease process that causes lesions and atrophy (Ramos-Vara, 2005). Second, even though this antigen testing can be accurate, many laboratories in the U.S. do not have this kind of technology (Hill & Holmes, 2008). Another issue with biopsies is that of compliance. After a positive serum test, patients usually are prescribed a gluten-free diet. The study Hill and Holmes conducted also discovered that it takes from 6-319 days for a biopsy to be performed due to physicians and patients schedules. This means, many have been on a gluten-free diet for a length of time. The diet change almost always causes the

negative symptoms to resolve in the patients. However, in order for the biopsy to confirm a patient positive with CD, the patient will have to maintain a gluten diet in order for the gluten to have a diagnostic effect. This causes many to be hesitant about having the biopsy performed, due the return of their negative symptoms from CD or the worry of added damage to the intestines because of the ingestion of gluten (Hill, et al., 2008).

Because the disease is linked to specific alleles, genetic testing results in almost a 100% accurate diagnosis (Rashtak & Murray, 2007). This test also has benefits for those who wish to be tested for CD but are already on a gluten-free diet and do not wish to resume a gluten diet in order to receive an accurate biopsy or antibody test. The genetic allele is always present in CD patients, whatever diet they are on. However, there are drawbacks to the genetic testing. Genetic testing, no matter what is being tested, should be regarded with delicacy due to the familial issues it can bring up and the sensitivity it has. Genetic counselors should be available if the patient requests (Rashtak & et al., 2007).

Clinical Manifestations

Many believe that because CD is a gastrointestinal disease, the only symptoms associated with this disease are gastrointestinal; this belief is false. The symptoms are wide spread and multisystem (Thom, Longo, Running, & Ashley, 2009). Because of this, CD is often attributed to other disease processes, such as liver disease, epilepsy, eczema, anemia, fatigue, and osteoporosis. Since these symptoms are often isolated disease processes in some cases, CD is many times attributed to these solitary disorders and CD sometimes overlooked as the culprit for the problems the patient is experiencing (Thom

& et al., 2009). It has been estimated that 7% of the time, the extragastric disorders, such as epilepsy, ataxia, and depression are diagnosed before CD (Gobbi, 2005).

Many who are diagnosed with CD have side effects that are neurological instead of, or alongside of, gastrointestinal symptoms. A study done by a group of doctors in Israel researched the association of neurological disorders with CD (Zelnik & et al., 2004). It was found that those with CD had neurological disorders such as hypertonia, migraines, and headaches, 51% of the time and those without CD had a 19.9% chance of having a neurological disorder. Many of these neurological disorders were mitigated by a gluten-free diet (Zelnik & et al., 2004). Other studies have researched the prevalence of CD in those with neurological disorders and have had similar results (Salur & et al., 2000).

Ataxia

The inflammatory response in the intestines that occurs with gluten ingestion in a person with CD triggers the release of AGA as well as anti-TGase2 (Boscolo & et al., 2007). Those who suffer from idiopathic ataxia and have AGA antibodies in their system are diagnosed with “gluten ataxia” (GA) as opposed to the idiopathic familial ataxia unrelated to gluten and AGA (Boscolo & et al., 2007).

The manifestation of GA in CD patients is fairly common. Results vary on the percentage of those with ataxia who have AGA. A study performed on 224 patients with idiopathic ataxia discovered that 41% of the population had AGA, while only 13% had familial ataxia (Hadjivassiliou & et al., 2003). Another study found 10.6% of those in the idiopathic ataxia population with GA, while another study presented with 17.7% of the population (Boscolo & et al., 2007). However, one study has shown there to be no

GA patients in the population of idiopathic ataxia of 32. Because of studies like these, there is a controversy on whether or not AGA is indeed a cause of ataxia. This controversy is common in most studies seeking to relate CD with other neurological disorders (Boscolo & et al., 2007).

An interesting study in Italy researched the affects of the AGA and anti-TGase2 antibodies on mice (Boscolo & et al., 2007). Researchers injected the antibodies into the central nervous systems of the mice. The injection caused ataxia in all the mice and researchers believe it is possible to suspect that the antibodies produced in those with CD could interact with the blood-brain barrier and cause altered permeability. This permeability of the blood-brain barrier could allow for an increase in likelihood for neurological disorders, such as ataxia. Other studies have shown that those with GA have anti-TGase2 antibodies on the brain vessels themselves. The immune response in the central nervous system could be causing damage to the neurons and therefore causing ataxia with those with CD (Boscolo & et al., 2007).

Because the circulating antibodies are the cause of the damage to the central nervous system, causing ataxia in patients, it is logical to assume that when a patient with CD adheres to a gluten-free diet, leading to a cessation in antibody formation, then the ataxia will resolve. A study done in the UK sought to prove this in an experimental setting (Hadjivassiliou, Davies-Jones, Sanders, Grunewald, 2003). There were 40 patients selected with gluten ataxia and 26 of them were placed on a strict gluten-free diet. Strict adherence to the diet is necessary, to see results from diet change. The remaining 14 patients refused the diet change. Both groups had similar baseline ataxia symptoms. Those with the gluten-free diet had a significant improvement in their

symptoms and it was concluded that a gluten-free diet was sufficient treatment for most cases of GA (Hadjivassiliou, Davies-Jones & et al., 2003). However, if after a year of a strict gluten-free diet and there has been no change in the ataxia, an immunosuppressant or intravenous immunoglobulin may be used (Hadjivassiliou, David, Woodroffe, Williamson, Richard, 2008).

Autism

Autism is a social and mental disorder that affects 1 out of 150 children in the United States, according to a study in 2002 (Genius & Bouchard, 2009). This is a chronic disorder with no known cure and the prognosis of autism is very grim. It is estimated that 85% of the outcomes are not favorable to the patient and families. The disorder manifests as difficulty in socialization and communication, a selection and obsession with just a few interests, and stereotyped behaviors. Some manifest with aggression, irritability, self-injury, and hyperactivity (Genius & et al., 2009).

In a case study performed by Dr. Stephen Genius, he studied a 5-year-old boy who was diagnosed with severe autism disorder (Genius & et al., 2009). He had severe communication and socialization difficulties, would experience sensory processing delay, had marked language delay, experienced fatigue, confusion, could not tolerate bright lights and experience ringing in his ears to the point that he would constantly have his fingers in his ears. He also had bloating and abdominal pain with nausea, vomiting, and diarrhea. He had many tests performed in order to see if any treatments could be done to assist with his diagnosis. It was found that he had deficiencies in fat-soluble vitamins (A, D, E), coenzyme Q10, and folate. His anti-TG2ase and EMA levels were extremely high at over 450 times the normal levels. Because these levels are sometimes indicative for

CD, he was placed on a gluten-free diet as well as an increase in the nutrients he was missing in his body. In one month, his gastrointestinal symptoms were gone and his autistic behavior was significantly decreased. He was also able to communicate at a much higher level than previously. In three months, he was able to go back to his normal school classroom with no aides or special education. In a follow up 2 ½ years later, he is still doing “incredibly well”, his mother says (Genius & et al., 2009).

As successful as this story is, there have been many experimental studies performed with negative findings. A study with 120 patients with CD had no findings of autism in the population and a study of 11 patients with autism found no CD in the population (Pavone, Fiumara, Bottaro, Mazzone, Coleman, 1997). These populations however may have been too small to have any statistical significance (Pavone & et al., 1997).

A study performed retrospectively chose 150 random children with autism, pervasive developmental disorder (not otherwise specified), childhood disintegrative disorder, and Asperger disorder (Barcia, Posar, Santucci, Parmeggiani, 2008). They were all tested for CD and five out of 150 or 3.33% of the children were diagnosed with CD. In general, the pediatric population has a 1 out of 106 or 0.94% chance of having CD. Those performing this study and also those who performed the case study discussed earlier (Genius & Bouchard, 2009) both recommend screening all children with autism for CD. If they test positive, they should have gluten restricted in their diet and any nutrients that are diminished should be replaced (Barcia & et al., 2008).

Another study took a population of only ten autistic children and increased their folate, fatty acids, cod liver oil, and coenzyme Q10 (Patel & Curtis, 2007). They did this

because findings have shown that those with autism sometimes have these nutritional deficiencies. The study also added behavioral therapy to the treatment and decreased any risk of heavy metal exposure. The results were extremely positive. All ten children improved their autistic symptoms. Since correcting a potential nutritional deficiency treated the autism, it is logical to link those with nutritional deficits who also have autistic symptoms to CD, since CD causes decreased nutrient absorption. This study should push others to further research this issue (Patel & et al., 2007).

There has also been research done with placing all those with autism on a gluten-free diet without knowledge of CD. In a single blind study, researchers randomly assigned half to a gluten-free and casein-free diet and the others to a regular diet (Knivsborg, Reichelt, Hoiem, Nodland, 2002). Those placed on the special diet had improvement in the areas of the autistic-spectrum (Knivsborg & et al., 2002).

Epilepsy

The issue of CD being associated with epilepsy is much debated. Some studies have found that the prevalence of epilepsy with those diagnosed with CD is merely 1% while others claim 21.5% (Barera, Mora, & Parma, 2008). There are many reasons for these discrepancies, including type and location of seizures seen. Occipital epilepsy is generally highly associated with CD (Gobbi, 2005). Another study found that 9% of patients with occipital epilepsy had CD from a 72 patient population with epilepsy. Of the patients studied with epilepsy from centrotemporal spikes, none had CD (Gobbi, 2005).

As CD goes untreated, there is a higher likelihood for cerebral calcifications that are usually located in the occipital region of the brain in patients with CD (Gobbi, 2005). Cerebral calcifications are associated with epilepsy. An Italian study performed in 1997 recorded many cases of patients with epilepsy and cerebral calcifications seen on a CT scan. It is thought that silent or latent CD that goes too long untreated could affect patients by causing cerebral calcifications and epilepsy. Another study reported that those with CD who had an average of 5.9 years before diagnosis and treatment of CD, there was a 0.79% likelihood of them presenting with epilepsy and cerebral calcifications. However, after an average of 10 years before diagnosis and treatment of CD, there was a 3.5% likelihood of epilepsy and a 1.7% likelihood of cerebral calcifications. While this study just shows a correlation and does not prove definitively of any direct causes of CD, it shows a strong link between the age of diagnosis and treatment and possible damage to the neurological system (Gobbi, 2005).

There is much discussion on why there seems to be a higher amount of calcification and seizure activity in the occipital region of the brain. Some have speculated that it is an autoimmune inflammatory response, similarly seen in other neurological disorders associated with CD, such as ataxia (Licchetta, Bisulli, Vito, Morgia, Naldi, Volta & et al., 2011). Chronic inflammation caused by the immune response can increase calcium deposits, leading to the calcification of the occipital lobe. However, there are other disease processes that present with cerebral calcifications and are not autoimmune related, an example being Sturge-Weber syndrome. Others say both the calcification and the epilepsy could be caused by vascular abnormalities, caused by the autoimmune response, which then leads to deterioration of the blood brain barrier.

However, some suggest that the calcifications are formed after the seizure occurs. A patient in a case study at the University of Bologna had an excision of a calcified lesion, yet still had episodes of seizing. There is still much research that needs to be done before there is a better understanding between the relationship of CD, cerebral calcifications, and epilepsy (Licchetta & et al., 2011).

Depression

A meta-analysis performed in 2011 reviewed 18 studies on depression and CD (Smith, 2012). This analysis has shown that there are more accounts of depression in CD adult populations than in healthy adult populations. Not only is depression more prevalent in CD patients, but also it is commonly more severe in those with CD than those who are healthy. However, based on the studies, there was not much difference in the prevalence of depression in patients with CD and those with other chronic illnesses. This might lead to the belief that the depression is due to a more difficult lifestyle and disabilities caused by CD rather than any pathological cause of depression from CD. This belief is also supported by the fact that when a patient diagnosed with CD and depression starts a gluten-free diet, there is often little change in their depression. There is also not a correlation between CD and anxiety, another emotional disorder that is commonly associated with depression. This could also be because there might not be a pathological relationship with emotional disorders and CD. However, there are some who believe that depression is caused by the autoimmune response in the body that could damage the nervous system. Depression could also be caused by the low amounts of nutrients the body has available, due to the damage in the small intestine. There is still

much room for research this area. Many of the studies performed have only been questionnaires and do not include experimental data (Smith, 2012).

Schizophrenia

Similar to many other psychiatric disorders, the cause of schizophrenia is vaguely understood. Because of this hazy understanding, there have been various studies to seek if a link between schizophrenia and CD exists (Kalaydjian, Eaton, Cascella, Fasano, 2006). Some studies have confirmed a possible link, while other studies deny such association (Kalaydjian, Eaton, Cascella, Fasano, 2006).

A literature review in 2006 claimed that it was beneficial for those with schizophrenia to be screened for CD due to the high prevalence of those with the mental disorder to also have CD (Kalaydjian, Eaton, Cascella, Fasano, 2006). While it is unclear what the association between the two diseases is, some studies have found that some schizophrenics have found it beneficial to their symptoms to adhere to a gluten-free diet. The hypothesized reason for the higher incidence of CD in schizophrenia is that the antibodies interact with various chemicals in the brain, causing the psychiatric symptoms. Another hypothesis stems from the fact that it has been found that those with schizophrenia have a higher reported amount of opioid peptides that form exorphine, which can cross the blood-brain barrier and activate the region of the brain that is associated with schizophrenia. Studies have shown that schizophrenia patients that have these peptides removed using dialysis have a reduction in their symptoms. These peptides are seen in high amounts in gluten and casein foods. This may be why, when patients eat only gluten-free and casein free foods, their symptoms decrease (Kalaydjian & et al., 2006).

One study in Maryland researched many different areas across the country and tested over 2,300 participants (Cascella & et al., 2011). In this study, 1,401 participants were clinically diagnosed with schizophrenia, while 900 participants had never been diagnosed with schizophrenia and consisted of the control group. Of those with schizophrenia, 23.1% had moderate to high levels of AGA and 5.4% of this population had moderate to high levels of tTGA in their blood. Only 3.1% of the control sample had moderate to high levels of AGA and 0.80% had moderate to high levels of tTGA (Cascella & et al., 2011). Other older studies found similar results as Cascella's study (Reichelt & Landmark, 1995).

In spite of this, not all researchers are in one accord. For example, study at John Hopkins found similar findings as the Cacella's study, however, this study claimed that the antibodies (IgG and IgA) found in greater percentages with the schizophrenic patients were different from those found in CD patients (Dickerson & et al., 2010). The antibodies in the CD patients are specific IgG antibodies to deaminated gliadin and IgA antibodies to GTGA, both of which were not found in higher numbers in the schizophrenic group. To summarize, this study claims those antibodies are different in schizophrenics and CD patients, which could lead to the conclusion that the etiology of schizophrenia is unrelated to CD (Dickerson & et al., 2010).

This leads to the question of whether the previous studies on schizophrenia and CD had extensively studied the specific sub-types of antibodies in order to be sure they were the ones diagnostic for CD. There is room for further study in the way of testing those with schizophrenia specifically for the genetic allele responsible for CD and also testing using the biopsy test (Dickerson & et al., 2010). This would better indicate

exactly how many patients with schizophrenia are clinically diagnosed with CD as opposed to the general population (Dickerson & et al., 2010).

Attention Deficit Hyperactivity Disorder

Attention Deficit Hyperactivity Disorder (ADHD) is a behavioral and psychiatric disorder that affects over 5% of children worldwide (Güngör, Celiloglu, Özcan, Raif, Selimoglu, 2013). Like other neurological disorders, results have been varied on the association. An Italian study tested 78 patients from age 3-57 with untreated CD (Niederhofer & Pittschieler, 2006). All 78 patients were assessed for ADHD symptoms. It was found that there were markedly more with ADHD symptoms in this CD sample than the worldwide average. These patients were then placed on a gluten-free diet. After six months, the patients and/or their caregivers reported that the ADHD behaviors were overwhelmingly decreased. Of those studied, 74% wished to continue on a gluten-free diet even after the study had been completed (Niederhofer & et al., 2006).

A study by pediatric physicians screened those with untreated CD for various psychiatric disorders, including ADHD, as well as screening a control group without CD for the same disorders (Zelnik, Pacht, Obeid, Lerner, 2004). It was found that over 20% of those with CD confirmed positive for ADHD, while only 10% of the control group confirmed positive (Zelnik & et al., 2004).

Like many research topics, the research is conflicting. A study in 2012 found that of the 362 ADHD children tested for CD, only four (1.1%) were confirmed positive for tTGA and only one (0.27%) was confirmed positive with the biopsy testing (Güngör, Celiloglu, Özcan, Raif, Selimoglu, 2013). In the control group of non-ADHD children tested for CD, three (0.8%) were confirmed positive for CD. These results are not

statistically significant to conclude there is an association between ADHD and CD.

Because of these varied reports, there is room for more research to be done (Güngör & et al., 2013).

Migraines

Migraines have been a mysterious phenomenon that has plagued many in the world and seem to have an elusive cause. While many cannot find relief, researchers have been busy seeking out connections. There have been a few studies recently that have seen a possible association between migraines and CD.

A study in Turkey by Alehan, Ozçay, Eroi, Canan, and Cemil (2008) researched children with migraine headaches. The study took 73 children with migraines and a control group of 147 children with minor respiratory illnesses. The control group children had no history of migraine headaches or gastrointestinal problems. The researchers tested each group for tTGA antibodies and IgA. Those who had positive antibodies, were asked to receive a biopsy in order to most effectively diagnose for CD. Four children (5.5%) in the study group were found to have positive tTGA antibodies, while only one patient (0.6%) in the control group had positive tTGA antibody test results. Three of the positively tested children were biopsy tested and showed that there could be potential for CD. All the positively tested children had an MRI and one of the children showed some white matter in the subcortex, which could be a lesion due to CD (Alehan & et al., 2008).

While this study has shown a substantial correlation between migraines and CD in children, there is another similar study that has shown no correlation between children with CD and migraines (Lehat, Broide, Leshem, Evans, Scapa, 2000). The study tested

the patients for both IgG antibodies and IgA. Of a study group with neurological dysfunctions, 13% tested positive for IgG antibodies and only 9% of the control group tested positive for the antibodies. However none of the patients in either group tested positive for IgA. This study claimed that this proves there is no need to further test for CD because the diagnostic test for CD is IgA antibodies. However, the study did not have as large of a sample size and was researching many different neurological symptoms and not just migraines specifically. While it was previously believed that elevated IgA antibodies was the only positive way to test for the disease, it has now been shown that testing for IgG antibodies can be more diagnostic for CD than testing for IgA antibodies (Hill & Holmes, 2008). Due to more recent findings on the diagnosis of CD, this study could in fact prove the link to CD in children with neurological disorders and migraines (Lehat & et al., 2000).

While these studies were exclusively performed on children, there are other studies reporting higher incidences of migraines among CD adult patients. Columbia University surveyed 324 patients with CD, inflammatory bowel disease (IBD), and gluten sensitivity (Dimitrova, Ungaro, Lebwohl, Green, Babyatsky, Green, 2012). There were 178 control patients who did not have any intestinal diseases or were not gluten-sensitive. The findings resulted in 30% of the CD patients reporting chronic headaches, 56% of those with a gluten sensitivity reporting chronic headaches, and 23% of those with IBD experiencing headaches. However, only 14% of those in the control group reported chronic headaches. This study also asked the participants if a gluten-free diet decreased the severity of the migraines. Most of the responders confirmed that before a gluten-free

diet the headaches were much worse. There is room for more research to test adults with migraines for CD (Dimitrova & et al., 2012).

Dementia

Due to the novelty of CD research and the commonality of misdiagnosis, there are a growing number of older adults over 60 years of age that are under diagnosed for CD (Lurie, Landau, Pfeffer, Oren, 2008). A retrospective study in Israel looked at seven patients diagnosed with CD after age 60. Of the seven, three also had neurological diagnoses along with CD. One had peripheral neuropathy and the two others had long-term cognitive decline. This decline was supposed to be related to Alzheimer dementia. After these patients were diagnosed with CD, they were placed on a gluten-free diet. This diet change completely resolved the symptoms of the peripheral neuropathy experienced by the first patient. The two with cognitive decline had complete reversals of the decline after adhering to a gluten-free diet. This response to a gluten-free diet could potentially be helpful for many who are hopelessly diagnosed with the dreaded Alzheimer's disease or dementia (Lurie & et al., 2008).

Another study in Italy found that an elderly population of 60 had an average time between symptoms starting and time of diagnosis of 17 years (Gasbarrini, Ciccocioppo, De Vitis, Corazza, 2001). The range was 0-58 years. Out of the 60 patients, 25 patients were over the age of 65 before they were diagnosed and 8.33% of the 60 had neurological disorders, including dementia, epilepsy, chorea, and Parkinson's disease. Most of these symptoms were resolved with a gluten-free diet. The percentage of those diagnosed with CD after age 70 from the CD population has increased from 4% in the 1960s to 27% in the 1980s. This is most likely from the increase in knowledge and screening for CD in

the recent years, or it could be an increase in the disease itself (Gasbarrini & et al., 2001). There has been little research done in the elderly populations to seek more understanding on CD and dementia, however these case studies, as well as others (Desplat-Jero, Bernard, Bagneres, Frances, 2003) and reports of the possible link are present.

Awareness

Many of the elderly in the previously mentioned study reported that the symptoms they had were life long and were quickly resolved by a gluten-free diet (Lurie & et al., 2008). These symptoms not only included the neurological disorders, but also osteoporosis, liver disorders, weight loss, iron deficiency anemia, and diarrhea. While there is joy in their new quality of life, there is also sadness that it took these men and women 60 years to find resolution to these very treatable symptoms. It is cases like these that reveal an extreme under awareness of CD and a need for a greater knowledge and teaching in order to prevent patients from living with their symptoms for a prolonged amount of time (Lurie & et al., 2008).

A study conducted by the Harbor-UCLA Medical Center, the West Los Angeles Veterans Administration Hospital, and the Celiac Disease Foundation investigated how much physicians in the United States knew about CD, as well as when and how those with CD are diagnosed (Zipser & et al., 2005). It was found that primary care physicians diagnosed only 11% of 2,440 patients with CD, while gastroenterologists diagnosed the majority. Patients who were diagnosed by a gastroenterologist usually had been symptomatic for an average of seven years. Those who were diagnosed by a primary

care physician were symptomatic for less than a year before diagnosis. Only 35% of the primary care physicians reported they had ever diagnosed a patient with CD in the average of 20 years they had been practicing. The results of this study can lead to the conclusion that primary care physicians who are more trained in knowing the symptoms of CD and how to diagnose could be preventing under-diagnosis of the disease and years of patients' suffering with the symptoms (Zipser & et al., 2005).

The disease is also under-diagnosed because many see CD as more rare than it actually is. CD is primarily a European disease and because America has a large number of European immigrants, it is also prevalent in the United States (King & et al., 2000). A study sought to determine the under-diagnosis of at-risk people groups, such as northern Europeans (Ivarsson & et al., 1999). This study showed that 5.3 out of 1000 adults in Sweden have CD and many of these were unaware of their disease. Other previous studies, which incorrectly diagnosed the disease, estimated that the prevalence was only 1 out of 1000 adult in Sweden. This emphasized the lack of awareness of CD. This study can be generalized to many other populations because of the wide sample used (Ivarsson & et al., 1999).

Mass Screenings

With the under-diagnosis of CD and the wide ranges of neurological disorders without the classic gastrointestinal symptoms of CD, there is a potential need for mass screening in the US for CD. However, as always, financing of such a procedure is in question. Health care programs are trying to determine whether these screenings would be cost-effective. One study attempted to measure the cost-effectiveness of mass screening for CD (Shamir, Hernell, Leshno, 2006). It was found that 1 out of 200 people

who were screened had CD. Taking into account the cost of treatment of CD (which is merely switching a diet), the probability of complying with a gluten-free diet, and the mortality rate of those with CD who go untreated, it was found that any screening approach resulted in approximately \$44,941 for the insurance companies for every year of life gained to projected mortality rate. This study used a standardized mortality ratio (SMR) (Shamir & et al., 2006). The ratio is found by dividing the observed deaths by the expected deaths (Lilienfeld & Stolley, 1994). If the SMR is greater than 100, the mortality rate is greater in that group of people. In those with undiagnosed CD, the projected SMR was 150 or higher (Shamir & et al., 2006). In those who are diagnosed with CD and adhere to a gluten-free lifestyle, the SMR was projected at even less than 100. This drop in mortality rate, paired with a monetary savings for every year of life saved, helps to prove a benefit to screening for CD (Shamir & et al., 2006).

In Italy, mass screenings are much more common than in the United States (D'Archivio & et al., 2004). A study in Italy, which tested 3188 school children for CD, confirmed 33 positive for the disease (Tommasini & et al., 2003). The overall cost of the mass-screening project was 46,000 Euros. Since 33 children were diagnosed, it is the equivalent of 1,400 Euros per case diagnosed in cost (this includes the screening costs of those without a diagnosis). The cost of a delayed or complicated diagnosis later in life for a person with CD was found to be 8,700 Euros. This is an average of 7,300 Euros in savings. Since the Italian government pays for the health care of its citizen, providing screenings dramatically saves government spending. The study also found that 18 of the 33 children who were diagnosed with the disease had symptoms that were not gastrointestinal. There were 21 children who had no symptoms at all. There were three

who had atopic dermatitis and recurrent arthralgia, and two who had chronic fatigue and anemia. This further shows the necessity to mass screen due to the variety of symptoms. All 33 of these children felt significantly better after adhering to a gluten-free diet (Tommasini & et al., 2003).

Italian physicians and researchers have been making great strides in early diagnosis of patients and knowledge about CD. There has been an increase in the diagnosis of patients who present with symptoms that are silent or non-gastrointestinal in Italy since they have started doing mass screenings throughout the country (D'Archivio & et al., 2004). This has allowed the patients to be diagnosed early in life, which lowers morbidity rates in CD populations.

Conclusion

There have been new strides in the medical research community to seek out the relationship between CD and neurological symptoms. The high prevalence of CD and especially atypical CD in America today requires a more aggressive approach to achieve diagnosis (Zipser & et al., 2005). Physicians and the general public need to be more aware of the disease and the vast array of symptoms that present (Zipser & et al., 2005). Mass screenings should be considered for implementation in high-risk people groups (Shamir & et al., 2006). The more health care professionals and the general public know about CD and how it affects health, especially in relation to health of the neurological system, the greater the general public's health will be.

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