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Intellectual and Attentional Characteristics of Children with Celiac Disease after Initiation of a Gluten-Free Diet

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Abstract The association of celiac disease (CD) with various cognitive and behavioral symptoms has been reported, but findings are mixed and inconclusive. This prospective study aimed to evaluate whether elimination of gluten in children with newly diagnosed CD leads to improvement in cognitive and behavioral functioning particularly related to attention after 6 months of a gluten-free diet (GFD). Thirty-three patients completed the study. Parent ratings of child behavior and direct assessment of child intelligence and attentional characteristics were collected. Parent reported scores on the Child Behavior Checklist (CBCL) demonstrated improvement in somatic symptoms and attentional characteristics after 6 months of GFD. Between 6-33% of the patients showed improvement in the 4 different attentional characteristics evaluated by the Conners Continuous Performance Test (CPT3). We conclude that parent ratings support improvement in somatic symptoms and attentional characteristics in celiac patients once on a GFD for 6 months.

Keywords: *Celiac disease, ADHD, behavior, IQ, cognitive, psychological*

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1. Introduction

Celiac disease (CD) is an immune-mediated disorder triggered by the ingestion of gluten. Testing for CD includes measuring tissue transglutaminase immunoglobulin A (TTG IgA) levels. [1] Definitive diagnosis of CD requires a small intestinal biopsy. Treatment is a strict gluten free diet (GFD). [1] The prevalence of CD in the United States in children is estimated to be 1:111. [2,3] CD is characterized by chronic small bowel mucosal inflammation which can lead to vitamin deficiencies and malnutrition. [4,5]

Patients with CD present with a wide array of somatic, cognitive and behavioral symptoms. [6,7] However, clear evidence of association of CD with these symptoms in children is poor. No prospective pediatric studies are using established cognitive and behavioral objective measures to assess for improvement following the implementation of a GFD in children with CD. Niederhofer and Pittschieler retrospectively assessed symptoms of attention deficit hyperactivity disorder (ADHD) in CD patients up to 57 years of age using the Hypescheme, a checklist for ADHD. [7] In that study patients were asked in retrospect 6 months after starting a GFD diet about symptoms that were present before making dietary changes. Multiple subsequent studies concluded that the GFD improved ADHD and neuropsychiatric symptoms in patients with CD and also that patients with CD are more prone to having neurologic disorders, including ADHD. [8,9,10] More recent studies have shown an increased prevalence of mental health concerns for patients with CD but no difference in attention between those with or without CD. [11,12] A review of this topic had mixed findings regarding the comorbidity of CD and ADHD or characteristics consistent with ADHD. [13]

The goal of this study is to prospectively determine if dietary elimination of gluten in children with confirmed CD improves cognitive and behavioral functioning. To our knowledge, this is the first prospective pediatric study examining the effect of a GFD on cognitive and behavioral functioning in pediatric patients with biopsy-confirmed CD using well-established objective measures.

2. Methods

2.1. Study Population

Recruitment was conducted in the Division of Pediatric Gastroenterology and Nutrition at Stony Brook Children's Hospital between June 2016 to August 2019, and in the Division of Pediatric Gastroenterology at Northwell Health from May 2017 to November 2018. Patients between 6 and 18 years of age who had both abnormal celiac serology and biopsy-proven CD were invited to enroll in the study. This age range of eligibility was selected because it allowed for the employment of psychometric measurement tools without shifting to a second form, validated for older or younger individuals. Patients with a diagnosis of ADHD taking medication for ADHD or on psychopharmacological agents at the time of diagnosis of CD were excluded because there was concern that medications might impact psychometric testing. Additional exclusion criteria included those who were untestable by a serious developmental disability or language or hearing deficit or patients and parents who were unable to comprehend or speak English as all psychometric testing was conducted exclusively in English.

Families were first informed of the study if there was a strong suspicion that the patient had CD after their endoscopy. They were then invited to participate in the study after an endoscopic biopsy confirmed the diagnosis.

The study was approved by the Institutional Review Board at Stony Brook University. Written informed consent and assent (when appropriate) were obtained.

A total of 43 patients were recruited from the Stony Brook site. Eight patients were withdrawn from the study, as they failed to keep their follow up appointment. For one patient, testing was not completed appropriately and thus data could not be counted. A total of 34 patients completed the study from the Stony Brook site.

At Northwell Health, a total of 13 patients were recruited. Nine were withdrawn from the study because they did not show up to their appointments. For three patients, testing was not completed appropriately and thus data could not be counted. One patient completed the study from the Northwell Health site.

2.2. Study Design

This is a prospective study of functioning and symptomatology conducted by the Division of Pediatric Gastroenterology and Nutrition and the Division of Developmental and Behavioral Pediatrics Stony Brook Children's Hospital and Northwell Health. The study assessed cognitive and behavioral characteristics in children with CD both before the initiation of a GFD and 6 months after starting the diet. Patients who had abnormal celiac serologies with CD confirmed on biopsies were recruited. Initial psychometric assessments were completed before the start of the GFD, and the same assessments were administered after 6 months on a GFD. Celiac serologies were repeated at the 6-month point as well, to assess adherence with the GFD.

2.3. Measures

Three neuropsychological and behavioral assessments were used. These included the Kaufman Brief Intelligence Test, Second Edition (KBIT2), a brief standardized assessment of intellectual status, measuring verbal and nonverbal intelligence. [14] All study participants were within the age range of this tool. It yields 3 scores: verbal, nonverbal and the overall score is known as the IQ composite. This assessment was completed by the child and administered by a qualified examiner.

The second assessment completed by the child was the Conners Continuous Performance Test 3rd Edition (CPT3), a standardized assessment of attention-related challenges in children across 14 minutes of interactive computer presentations. [15] The CPT3 assesses inattentiveness, impulsivity, sustained attention and vigilance. The CPT3 scores are interpreted as T-scores. The profile of scores and response pattern are further classified as no, some, or strong indication of each of the 4 categories.

The third assessment employed was the Achenbach Child Behavior Checklist for Ages 6-18 (CBCL). [16] The CBCL is a well-validated rating scale with age-specific rating forms. It comes in formats for parent and teacher completion. The parent rating form was used in this study. The rating scale requires a parent to respond to an array of possible behavioral concerns for which the parent reports whether that topic is 'not true or very rarely true,' 'sometimes or somewhat true' or 'often true' about the child. A subset of the rating scale items is computer-scored to identify characteristics consistent with the American Psychiatric Association's Diagnostic and Statistical Manual IV (DSMIV) as concern for problems in several categories. This study focused on the scoring related to concerns for somatic problems and attention-deficit/hyperactivity problems. Total scores, T-scores, and percentile scores are available for each of these categories. T-scores between 50 and 64are considered within a normal range. T-scores greater than or equal to 65 indicates borderline concerns and T-scores greater than or equal to 70 indicate clinical range concerns.

The breadth of these assessments was important to this study to provide indications of both parent ratings and directly assessed child characteristics in a prospective design both prior to and 6 months after dietary changes were made.

2.4. Statistical Analysis

Standard scores for the three different assessments were calculated. The IQ composite score, which is age-anchored, was used in the KBIT2. Categories of inattentiveness, impulsivity, sustained attention and vigilance in the CPT3 were scored as no indication, some indication or strong indication of each of those categories. The CBCL yielded T-scores that were used in analysis.

Statistical analyses were conducted using SPSS Statistics 26.0 (IBM Corp., Armonk, NY, USA). A paired t–test was used to compare KBIT2 composite scores pre and post-initiation of a GFD as well as comparing T-scores pre and post-initiation of a GFD on the CBCL for both somatic and attention-deficit/hyperactivity problems.

Descriptive statistics were used to analyze data pre and post-GFD on the 4 different CPT3 categories.

3. Results

Fifty-six patients were enrolled from the two institutions with 39 patients completing assessments both pre-GFD and 6 months after starting a GFD. The follow-up assessments were scheduled as close to the 6-month point as feasible. The average time from initial to follow up testing was 6 months19 days, ranging from 5 months 14 days to 8 months 12 days. Seventeen patients did not complete follow up testing because they did not follow up 6monthsafter starting the GFD, despite multiple reminders. Out of the 39 patients, testing for 4patients was not completed appropriately and thus data could not be considered. Patients were not included in the analysis of data unless all three assessments were completed appropriately.

Patients were also only included in the data analysis if they were adherent with the GFD for 6 months before reassessment. Celiac serologies pre and post-GFD were monitored. Two patients were excluded from the study because they disclosed to the provider that they were not compliant with the GFD. Five patients did not have follow-up labs but stated they were compliant with their diet during their follow up appointment. Studies by Vesci [17] and Husby/Bai [18] showed a limited value of serological follow up after starting GFD, especially in the short term. With those reports as context, these 5patients were included in the study. The rest of the 28 patients showed improvement in celiac serologies. Thus, data from a total of 33 patients entered into the analysis.

For the 33 cases entering our analysis, patients ranged from 6 to 17 years of age with a mean age of 10.7years (Table 1). Eleven patients were male (33.3%); 31were of Caucasian ethnicity (94.0%). The CBCL was completed by the same parent in both pre and post-testing in 27 of the 33 patients (81.2%) (Table 1).

Table 1. Demographics of our patient population, n =33

Gender	
Male	11 (33.3%)
Female	22 (66.7%)
Race	
Caucasian	31 (94%)
Asian	2(6.0%)
Age (in years)	
Range	6 to 17
Mean	10.7
Parents filling out CBCL	
Mother filled pre and post	24 (72.7%)
Father filled pre and post	3 (9.1%)
Different parent filled pre and post	6 (18.2%)

3.1. Intelligence

For the 33 patients completing the study, the KBIT2 IQ composite scores ranged from 88 to 142 at the start of initial evaluation (Figure 1). At the end of the 6-month evaluation, the KBIT2 IQ composite scores ranged from 88 to 144. There was no statistically significant difference between the score pre GFD and post GFD (t= -0.538, p=0.594) when analyzed with a paired t-test. Patients showed neither improvement nor worsening of intellectual status over the 6 month.

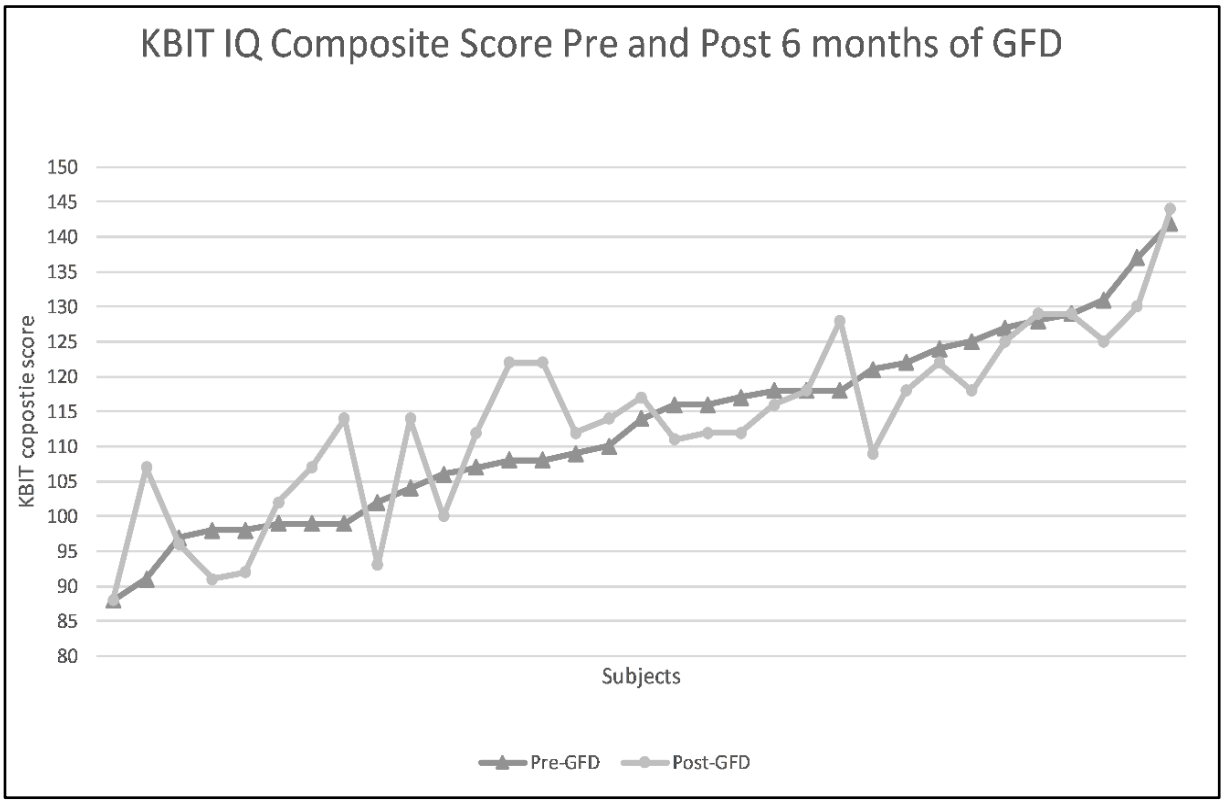

Figure 1. KBIT IQ Composite Scores Pre and Post 6 Months of GFD

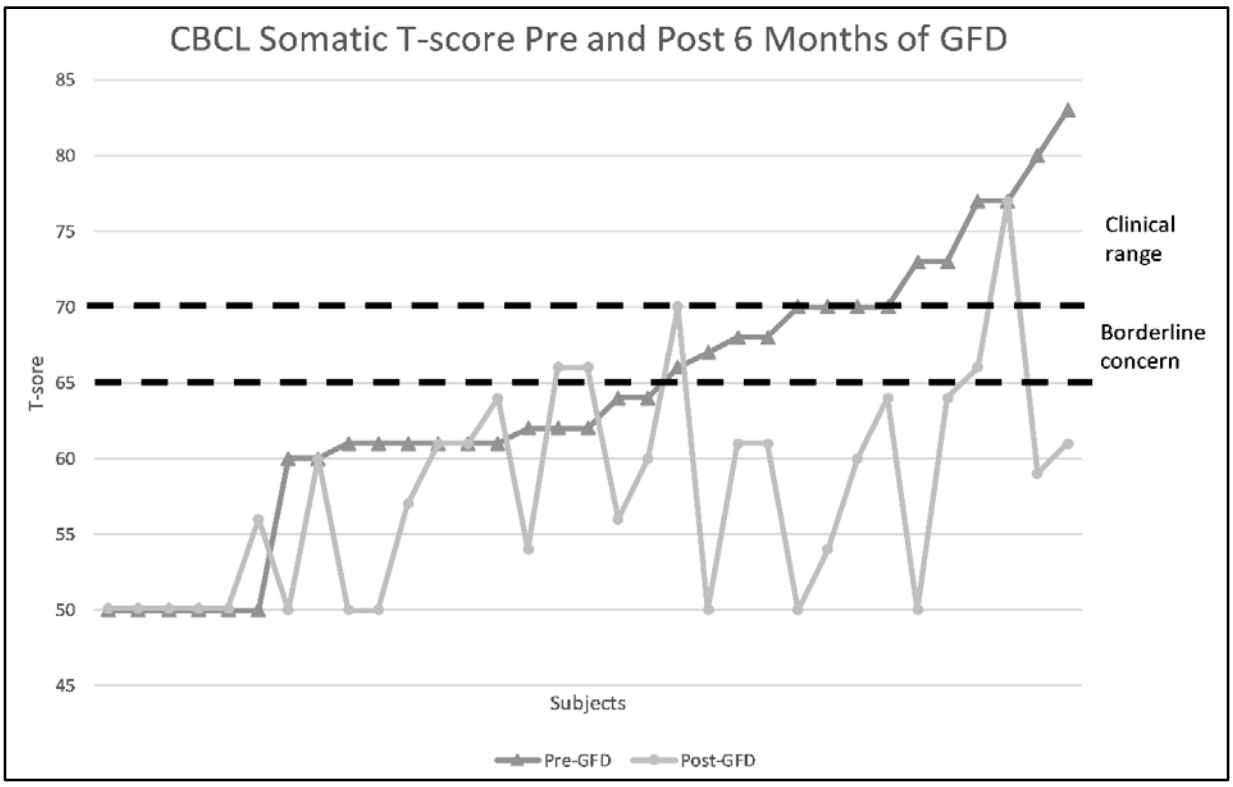

Figure 2. CBCL Somatic T-Scores Pre and Post 6 Months of GFD

3.2. Somatic Symptoms

The CBCL T-scores for somatic problems and attention-deficit/hyperactivity problems were also the focus of this study. Change in the T-score from pre-GFDto 6-month follow up for somatic concerns was significant, indicating a reduction in somatic symptoms at the 6-month follow up point ($t=4.313$, $p<0.01$) when using a paired t-test. Parents reported a decrease in somatic complaints. The average T-score pre-GFD diet was 64 and the average T-score post-GFD diet was 57.8. The T-scores before GFD ranged from 50 to 83 and T-scores post-GFD ranged from 50 to 77. Thirty percent (10/33) of the patients' scores were in clinical range pre-GFD. Nine of those 10 patients' scores improved to below clinical range after being on a GFD. One patient started and remained in the clinical range (see Figure 2 for patient movement in scores). Only 2 of 33 (6%) of patients' scores were in clinical range post-GFD.

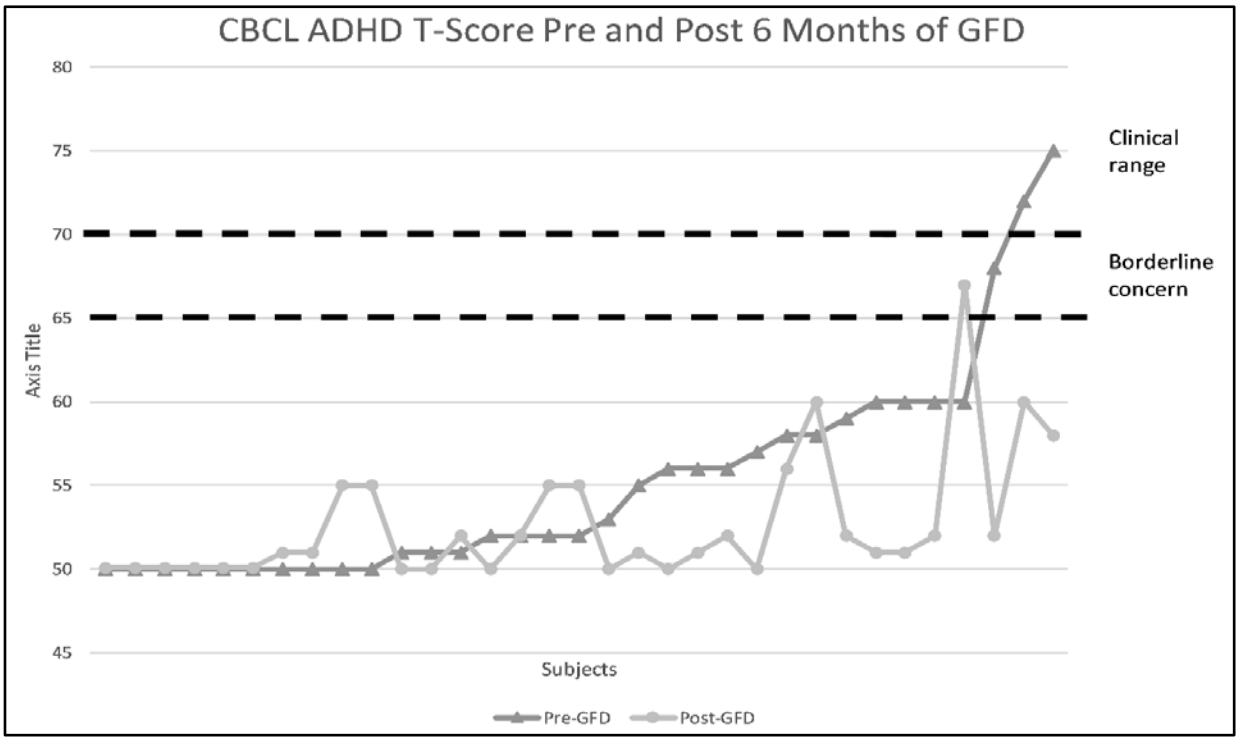

Figure 3. CBCL ADHD T-Scores Pre and Post 6 Months of GFD

3.3. Characteristics Consistent with ADHD

Parent ratings on the CBCL demonstrated a statistically significant reduction in ADHD symptomatology before initiation of dietary therapy to the 6-month follow up (t=2.608, p=0.014) using a paired t-test. Thus, parent-reported scores demonstrated an improvement in attentional characteristics consistent with DSM diagnosable ADHD. However, it is important to note that average T-scores on this rating measure both at pre-GFD and at follow up remained within the normal range, not the borderline or clinical range. Thus, the improvement was not from a score clinically consistent with ADHD to one below the clinical range. The average T-score pre-GFD was 55.3 and the average T-score post-GFD was 52.7. The T-scores before GFD ranged from 50 to 75 and T-scores post-GFD ranged from 50 to 67. Six percent (2/33) of the patients' scores were in clinical range pre-GFD. Both patients' scores improved to below clinical range after being on GFD (see Figure 3 for patient movement in scores). No patient scores were in clinical range post-GFD.

With direct patient testing on the CPT3, if a patient's score changed from strong to some indication, some to no indication or strong to no indication, this was considered an improvement from pre to post-GFD. If a patient's score changed from no indication to either some or strong indication or from some too strong indication, this was considered worsening from pre to post-GFD. For inattentiveness on the CPT3, 30.3% (10/33) improved, 15.2% (5/33) worsened, and 54.5% (18/33) had no change. For impulsivity, 6.1% (2/33) improved and 93.9% (31/33) had no change. For sustained attention, 33.3% (11/33) improved, 21.2% (7/33) worsened, and 45.5% (15/33) stayed the same. Lastly, for vigilance, 15.2% (5/33) improved, 24.4% (8/33) worsened and 60.6% (20/33) stayed the same.

4. Discussion

This is the first prospective pediatric study using multiple well-established cognitive and behavioral standardized measures to assess changes in functioning and symptomatology following the implementation of a GFD in patients with CD. Prior studies used fewer or less well established assessments or looked retrospectively at symptomatology after months of dietary change. [7,8,9,10] Those studies suggested preliminary evidence in favor of improved neuropsychiatric characteristics after initiation of a GFD in patients with CD. More recent studies evaluating attentional symptoms found no association to CD. [11,12] A systematic review of this topic had mixed findings regarding the comorbidity of ADHD and CD across several studies. [13]

In this prospective pediatric study, we found that in newly diagnosed CD, there was an improvement in somatic symptoms with parent reported rating. This is consistent with prior studies in which patients with CD show improvement of somatic symptoms on a GFD. Further, parents reported improvement in attentional characteristics in newly diagnosed celiac patients who have been on a GFD for 6 months. However the average pre and post-GFD T-scores for attentional concerns were both within the normal range. Our CPT testing showed about 50% or more of our patients' scores stayed the same in the 4 dimensions (inattentiveness, impulsivity, sustained attention and vigilance) of ADHD behavior. Between 6-33% of the patients showed improvement in scores in the 4 different dimensions. There was also no improvement or diminishment in intellectual status after 6 months of being on a GFD in our patients.

Our results are consistent with Niederhofer and Pittschieler's [7] retrospective study and Terrone et al's [10] study both showing improvement of ADHD-like symptoms in CD patients on a GFD. While there is an improvement in ADHD-like symptoms, our patient's average scores were within the normal range on pre and post-test. Normal range scores versus clinically concerning scores were not reported in the prior studies. Our additional direct patient testing using CPT3 showed some improvement in characteristics consistent with ADHD, but most patients' scores remained unchanged.

One possible explanation for parents reporting improvement in characteristics consistent with ADHD is that parents perceive their children to be focusing better when they were less hampered by somatic symptoms. This would suggest that attentional changes perceived by parents may have been impacted by shifts in children's somatic symptomatology.

Our patient demographics show a predominance of females and race was predominately Caucasian. This is not surprising since Mardini et al. found the prevalence of CD is 4-8 times higher among non-Hispanic white patients compared with other races in the US. [19] Chounget al. also used National Health and Nutrition Examination Survey2009-2014 and found the prevalence of CD was higher in women (0.9%) than in men (0.5%). [20]

There are some important limitations to our study. First, the sample is small, limiting generalizability until such work can be scaled up. Secondly, there is a lost-to-follow-up concern. We have no post-GFD behavioral or cognitive information on those who withdrew from the study. Longitudinal research such as this carries the risk of decline in participant/family interest, which could reflect improved well-being, poor adherence, or deteriorating well-being. There were also some patients who were withdrawn from the study due to the long length of time between testing visits and the limited window of testing. We also had no lab data for follow up for 5 patients to evaluate for compliance. Their data was utilized because they had endorsed compliance with the GFD at their follow up appointment when psychometric testing occurred. Finally, we limited the CBCL usage to parent ratings and did not include a measure of teacher ratings in this study. Since we were not specifically seeking to sample only children with diagnosed ADHD, the parent data seemed to be an appropriate first probe for this work.

5. Conclusions

This is the first prospective pediatric study using well-established cognitive and behavioral objective

measures to assess improvement in functioning following the implementation of a GFD with both direct and indirect assessment in pediatric patients with CD. Consistent with prior studies, our patients showed improvement in somatic symptoms while on a GFD. Parents reported improvement in characteristics consistent with ADHD; while this was statistically significant, it is important to recognize that this was not a sample of children diagnosed with ADHD. Furthermore, despite the improvement, the average pre and post-GFD T-scores were both within normal ranges and our CPT results showed 50% or more of our patients' scores stayed the same in the 4 dimensions (inattentiveness, impulsivity, sustained attention and vigilance) of ADHD behavior. Our study shows no change in intellectual status when newly diagnosed celiac patients begin and maintain a GFD for 6 months.

Several questions emerge from this work and deserve further study. For example, would children placed on a GFD but without CD show changes in attentional / behavioral characteristics? Would children with diagnosed ADHD and newly diagnosed CD, show improvement in attentional / behavioral characteristics? Is there further change in attentional characteristics or symptomatology when patients with CD maintain their GFD for a longer period? Such work might yield fuller insights into the relationships among elimination of gluten, improvement in the symptomatology of CD and children's attentional skills. Both parents and healthcare practitioners would benefit from the fullest understanding of the attentional / behavioral characteristics children under dietary management for CD might experience, and whether or not it is mediated by improvement in somatic symptomatology.

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Competing of Interest

The authors have no competing interests.

Abbreviations (in Order of First Appearance)

celiac disease (CD)
tissue transglutaminase immunoglobulin A (TTG IgA)
gluten free diet (GFD)
attention deficit hyperactivity disorder (ADHD)
Kaufman Brief Intelligence Test (KBIT2)
Conners Continuous Performance Test (CPT3)
Achenbach Child Behavior Checklist for Ages 6-18 (CBCL)
Diagnostic and Statistical Manual IV (DSM 4)

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