

Increased Prevalence of Antibodies Against Dietary Proteins in Children and Young Adults With Cerebral Palsy

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ABSTRACT

Objectives: Undernourishment is common in children with cerebral palsy (CP), but the reasons are unknown. We previously reported elevated levels of immunoglobulin (Ig) A and IgG antibodies against gliadin (AGA) and tissue transglutaminase (tTG) in 99 children and young adults with CP without characteristic findings of gluten enteropathy in small bowel biopsies. Our aim was to perform a case-control study of IgG antibodies against other dietary antigens, AGA, anti-tTG, and IgE antibodies against wheat and gluten.

Methods: Sera from 99 cases with CP and 99 healthy, age- and sex-matched controls were analysed with fluorescence enzyme-linked immunosorbent assay for detection of IgG antibodies against β -lactoglobulin, casein, egg white, IgG- and IgA-AGA, IgA-anti-tTG, and IgE antibodies against gluten and wheat.

Results: Compared with controls, the odds ratio in cases with CP for having elevated levels of IgG antibodies against β -lactoglobulin was 17.0 (95% confidence interval [CI] 2.3–128), against casein 11.0 (95% CI 2.6–46.8), and against egg white 7.0 (95% CI 1.6–30.8). The IgE responses for wheat/gluten were generally low. The tetraplegic and dyskinetic CP subtypes had significantly higher frequencies of elevated levels for all of the tested antibodies except IgG against egg white, and IgA-anti-tTG. A significantly lower weight was seen in cases with CP with positive versus negative serology.

Conclusions: Elevated levels of IgG against dietary antigens were more frequent in the CP group compared with controls, and particularly in the tetraplegic and dyskinetic CP subtypes with the most severe neurologic handicap and undernourishment. Hypothetically, malnourishment may cause increased intestinal permeability and thus immunization against dietary antigens.

Key Words: cerebral palsy, children, dietary antibodies, gluten sensitivity

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Children and young adults with severe cerebral palsy (CP) are often malnourished and have a retarded weight and height (1,2). Generally this has been regarded as a natural effect of the disease. Long-lasting starvation in early childhood has a negative effect on motor and brain development (3–6). It is therefore of great importance to give children with CP optimal nutrition to ensure growth and prevent further brain damage.

The reasons for poor growth in CP are not fully understood and are probably multifactorial. Spasticity per se requires more energy and feeding difficulties (ie, oral dysfunction) are probably partly responsible (7). Additional factors, such as gastroesophageal reflux disease, with or without aspiration, vomiting, delayed gastric emptying, constipation, or other gastrointestinal symptoms, may contribute and worsen the nutritional status. Much is still unknown about how CP influences gastrointestinal motility. Nutritional disorders are less frequently examined in CP than in other chronic diseases (8). The intestinal absorption of nutrients in CP is another question not yet thoroughly addressed. Poor growth is most pronounced in the tetraplegic (TP) and dyskinetic (DK) subgroups of CP, that is, in the most severe form of disability (1,9). Children and young adults with TP or DK CP are prone to aspirating food because of swallowing dysfunction (10). Therefore, it has been discussed whether such events could induce an immunoglobulin (Ig) E response against gluten; however, to our knowledge, no such studies have been presented.

Celiac disease (CD) is known to have a negative effect on growth and we have previously investigated the prevalence of CD in children and young adults with CP (9,11). We found that elevated levels of IgA and IgG anti-gliadin antibodies (AGAs) were common, as were slightly elevated levels of antibodies against tissue transglutaminase (tTG), but this was not associated with classic gluten enteropathy, according to routine small bowel histology (9,11). The interpretation of this finding was that they have increased immune reactivity to gluten and the finding was most pronounced in the TP and DK CP subtypes (11).

Whether this increased immune reactivity is restricted to gluten is not known. We therefore conducted a case-control study of this cohort to analyse the prevalence of IgG antibodies against other dietary antigens such as egg white and the milk proteins β -lactoglobulin and casein to investigate whether the antibody occurrence differs between different CP subtypes; compare levels of AGAs and anti-tTG with those in matched controls; and study the occurrence of IgE antibodies against wheat and gluten.

METHODS

This is a case-control study of 99 children and young adults with CP living in the Swedish counties of Värmland and

Örebro. It is the same cohort as in our previous publication (9), with addition of 9 young adults. For comparison, we included 99 controls matched for sex and age.

Cases

A total of 46 girls, median age 12 (range 2–24) years, and 53 boys, median age 9 (range 1.5–20) years, were studied. At the time of inclusion, none of them had comorbidity for CD such as diabetes mellitus or dermatitis herpetiformis. The nomenclature of CP and the classification of subgroups were based on a study by Hagberg et al (12). Weight and height were measured at the time of inclusion. Blood samples were collected from the end of 2003 until the beginning of 2005. Medical records were retrospectively reviewed by the first author (R.S.) concerning medical treatment at the time of inclusion.

Controls

Sera from 99 controls were available from previous studies (13,14). Blood samples from children younger than 7 years were collected at child health care centres during 2006; from children older than 7 years of age, they were collected in school health centres during 2008, in a nearby county, Dalarna. Exclusion criteria were asthma and/or atopic dermatitis, any other chronic disease, fever during the last 3 days, or vaccination during the week before blood sampling.

Data were available from a previous questionnaire on health and medications but not on weight, height, or body mass index (BMI). One child was receiving thyroid hormone treatment and another was receiving nonsteroidal anti-inflammatory drug (NSAID) treatment. The 99 children in the control group were matched to the study group by birth year and sex.

Laboratory Analyses

Sera from the CP group were stored at -20°C until analysed at the Department of Laboratory Medicine at the University Hospital in Örebro.

1. IgG against β -lactoglobulin, casein, and egg white were determined using a fluorescence enzyme immunoassay (FEIA) (Phadia 250; Phadia, Uppsala, Sweden). Cutoff levels were set at the 97.5th percentile of control levels.
2. IgG AGA was determined using a FEIA (Phadia 250). The manufacturer's recommended cutoff of 7 U/mL (weak positivity 7–10 U/mL) was used.
3. IgA AGA levels were determined using a FEIA, IgA-gliadin (Phadia 250). The manufacturer's recommended cutoff of 7 U/mL was used.
4. IgG tTG was analysed using a FEIA (Phadia 250). Again, we followed the manufacturer's recommendation of a cutoff at 7 U/mL (weak positivity 7–10 U/mL).
5. IgA tTG was determined using a FEIA (Phadia 250), with a cutoff at 7 U/mL, according to the manufacturer's recommendations.
6. IgE antibodies against wheat and gluten were assayed using a FEIA (Phadia 250). The manufacturer's recommended cutoff at 0.35 kUA/L was applied.
7. Total serum IgA concentrations were measured by an enzyme-linked immunosorbent assay for the controls and data on cases with CP were available from a previous study (9). IgA deficiency was defined as IgA concentration <0.07 g/L.

Anthropometric Data

Weight z scores, also referred to as weight $\pm$ standard deviation (SD), and height and BMI z scores were calculated for all of the cases with CP. z scores are standardised to the Swedish general population by age and sex and based on 3650 healthy children born at full term up to 18 years of age (15).

Statistical Methods

Age is summarised with medians (range) and other continuous variables with medians interquartile range (IQR) or means (SD), the latter if symmetrically distributed. Conditional (matched) logistic regression was used to evaluate the association of different antibodies between cases with CP and matched controls. The measure of association is odds ratio (OR), with 95% confidence intervals (CIs). The χ^2 test was used to compare categorical variables, and unpaired t test was applied for continuous symmetrical variables. An independent t test was used for BMI (z scores), height (z scores), and weight (z scores) using 2-tailed significance. A P value <0.05 was regarded as statistically significant. All of the statistical analyses were done in SPSS version 17 (SPSS Inc, Chicago, IL), except conditional logistic regression, where STATA release 11 (StataCorp LP, College Station, TX) was used.

Ethics

The study was approved by the regional ethical review board in Uppsala, Sweden. The parents gave written informed consent.

RESULTS

Cerebral Palsy Group

Results were obtained for 96 cases with CP regarding IgG antibodies against casein, β -lactoglobulin, and egg white. Sera were available from 90 cases with CP for IgG AGAs and for IgG tTG and 91 cases for IgA tTG and IgA AGA antibodies. Sera from 95 cases were analysed for IgE against wheat and gluten. The missing values from the children and young adults in the CP group were distributed randomly among different CP subtypes.

IgG Antibodies to β -Lactoglobulin, Casein, and Egg White

The levels of antibodies against β -lactoglobulin, casein, and egg white are shown in Figure 1A–C. The cutoff levels for β -lactoglobulin (34 U/mL), casein (40 U/mL), and egg white (23 U/mL) were set at the 97.5th percentile of the distribution in the control group.

Comparing the CP group with matched controls, statistically significant associations were found for IgG antibodies against β -lactoglobulin (OR 17.0; 95% CI 2.3–128), casein (OR 11.0; 95% CI 2.6–46.8), and egg white (OR 7.0; 95% CI 1.6–30.8) (Table 1). Presence of antibodies against β -lactoglobulin, casein, and egg white was influenced by AGA status in the CP group (Table 2). Positive AGA was associated with presence of antibodies to the other 3 dietary antigens.

AGA and tTG

IgG AGA and IgG tTG

Fifty-five of 90 (61%) individuals in the CP group had elevated levels of, IgG AGA compared with 22 of 99 (22%) in the control group, yielding a statistically significant association

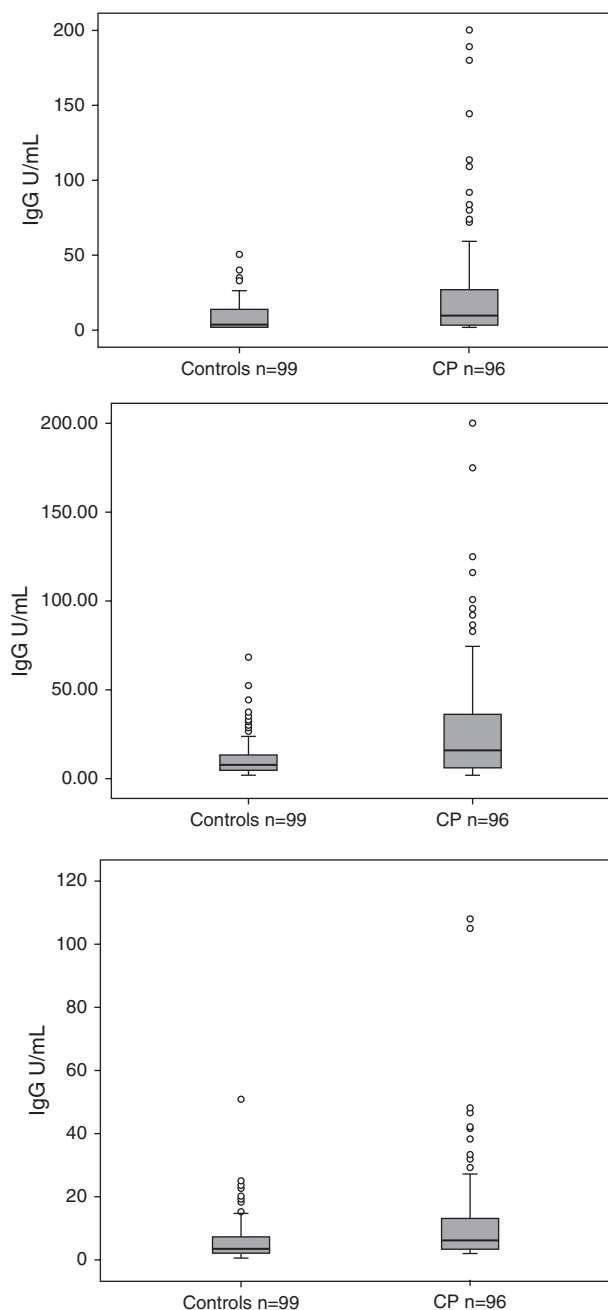


FIGURE 1. Top, Box plot showing the distribution of immunoglobulin G (IgG) antibodies to β -lactoglobulin in cases with cerebral palsy (CP) (median 9.4 U/mL, interquartile range [IQR] 2.8–27.6 U/mL) compared with healthy controls (median 3.7 U/mL, IQR 2.0–14.0 U/mL). The cutoff level was set to 34 U/mL, which is at the 97.5th percentile of control levels. Center, Box plot showing the distribution of IgG antibodies to casein in cases with CP (median 15.8 U/mL, IQR 6–37.7 U/mL) compared with healthy controls (median 7.8 U/mL, IQR 4.4–13.7 U/mL). The cutoff level was set to 40 U/mL, which is at the 97.5th percentile of control levels. Bottom, Box plot showing the distribution of IgG antibodies to egg white in cases with CP (median 6.1 U/mL, IQR 3.4–13.0 U/mL) compared with healthy controls (median 3.4 U/mL, IQR 2.0–7.6 U/mL). The cutoff level was set to 23 U/mL, which is the 97.5th percentile of control levels.

(OR 5.6; 95% CI 2.6–11.9). Significantly more cases with CP had elevated levels of IgG tTG: 14 of 90 (16%) compared with 3 of 99 (3%) of controls (OR 7.0; 95% CI 1.6–30.8) (Table 1).

IgA AGA and IgA tTG

Levels of IgA AGA were elevated in 20 of 91 (22%) in the CP group and 3 of 99 (3%) in the control group (OR 19.0; 95% CI 2.5–142). Only 1 case in the CP group and 2 cases in the control group had elevated levels of IgA tTG antibodies (Table 1). The patient with CP and IgA tTG antibodies has had a duodenal biopsy earlier and the routine biopsy showed a normal histology; however, as shown in a previous study (11), this child had IgA, colocalised with mucosal TG2, elevated numbers of $\alpha/\beta+$ and $\gamma/\delta+$ intraepithelial lymphocytes; CD3 staining; and also a slightly elevated serum level of anti-deamidated gliadin peptide. The child was human leukocyte antigen (HLA)-DQ2– and HLA-DQ8–positive.

IgE Antibodies Against Wheat and Gluten

There was low occurrence of IgE antibodies against wheat or gluten, without any difference between cases and controls (Table 1).

Clinical Data

Subtypes of CP

Of 99 children and young adults with CP, 43 were classified as diplegic, 16 as hemiplegic, 12 as DK, 17 as TP, and 11 as ataxic. In Table 3, the TP and DK subtypes of CP are presented together and compared with the other CP subtypes. We found a significantly higher frequency of elevated levels of all of the tested antibodies, except IgG against egg white and IgA tTG, in the TP and DK subgroups (Table 3).

Weight, Height, and BMI

The mean weight, height, and BMI, as measured in z scores $\pm$ SD, for individuals with CP were lower compared with normal Swedish children according to the national Swedish growth charts (see Methods). The mean (SD) z score in the whole CP group was -1.40 (1.96) for weight, -1.70 (1.66) for height, and -0.56 (1.84) for BMI (data not shown). The underweight was most pronounced in the TP and DK subtypes. When comparing these subtypes with the other subtypes of CP, we found even greater differences in the mean z scores for weight, -2.7 (2.07) compared with -0.88 (1.66) (Table 3).

In Figure 2, the association between weight and dietary antibodies is shown, in cases with CP positive for at least 1 antibody compared with cases negative to all of the antibodies.

In the group with negative antibodies, the mean weight z score was -0.77 , whereas in the group testing positive for ≥ 1 antibodies, the mean weight z score was -1.74 , yielding a difference of -0.97 SD (95% CI -1.8 to -0.1 ; $P = 0.03$).

Medical Treatment

Forty-two of 98 cases with CP were receiving some medical therapy, for example, treatment for constipation such as lactulose or enema ($n = 24$), proton pump inhibitors (PPIs) or H_2 receptor inhibitors for gastroesophageal reflux disease ($n = 11$), antiepileptic drugs ($n = 29$), NSAID ($n = 1$), aspirin ($n = 1$), or warfarin ($n = 1$). The medical record was missing for 1 case. Treatment with botulinum toxin and/or baclofen (intrathecal or peroral) was not

TABLE 1. Antibodies against dietary antigens in cases with CP and controls matched for age and sex, calculated using conditional logistic regression analysis

	CP cases, n = 99*, n (%)	Controls, n = 99, n (%)	OR	95% CI	P
IgG β -lactoglobulin	n = 96	n = 99			
Normal	76 (79)	95 (96)	1.0		
Elevated	20 (21)	4 (4)	17.0	2.3–128	0.006
IgG casein	n = 96	n = 99			
Normal	74 (77)	96 (97)	1.0		
Elevated	22 (23)	3 (3)	11.0	2.6–46.8	0.001
IgG egg white	n = 96	n = 99			
Normal	82 (85)	96 (97)	1.0		
Elevated	14 (15)	3 (3)	7.0	1.6–30.8	0.010
IgG AGA	n = 90	n = 99			
Normal	35 (39)	77 (78)	1.0		
Elevated	55 (61)	22 (22)	5.6	2.6–11.9	<0.001
IgA AGA	n = 91	n = 99			
Normal	71 (78)	96 (97)	1.0		
Elevated	20 (22)	3 (3)	19.0	2.5–142	0.004
IgG tTG	n = 90	n = 99			
Normal	76 (84)	96 (97)	1.0		
Elevated	14 (16)	3 (3)	7.0	1.6–30.8	0.010
IgA tTG	n = 91	n = 99			
Normal	90 (99)	97 (98)	1.0		
Elevated	1 (1)	2 (2)	1.0	0.1–16.0	1.0
IgE wheat	n = 95	n = 99	3.0	0.3–29.0	0.341
Normal	92 (97)	98 (99)			
Elevated	3 (3)	1 (1)			
IgE gluten	n = 95	n = 99	NE	NE	1.0
Normal	94 (99)	97 (100)			
Elevated	1 (1)	0			

AGA = anti-gliadin antibody; CI = confidence interval; Ig = immunoglobulin; OR = odds ratio; tTG = tissue transglutaminase; NE = not estimated.

* See the Results section, Cerebral Palsy Group, for the number of cases with CP included in each analysis.

recorded. Medication was mostly used by the TP and DK subtypes of CP.

Genetics

No correlation was found between positive HLA-DQ2 and/or -DQ8 and elevated levels of any of the antibody specificities in those 42 of 99 individuals in the CP group who had previously been HLA tested.

Sex

No sex differences were seen in the antibody-positive or antibody-negative groups.

DISCUSSION

Based on our previous findings of increased levels of serum AGA in CP but without histopathologic signs of enteropathy (9,11),

TABLE 2. Presence of IgG antibodies to β -lactoglobulin, casein, or egg white in cases with cerebral palsy (n = 90) with IgG AGA positivity or negativity

	Negative for IgG AGA, n = 36 (%)	Positive for IgG AGA, n = 54 (%)	P
β -Lactoglobulin	2 (6)	16 (30)	0.005
Casein	3 (8)	17 (31)	0.010
Egg white	0 (0)	14 (26)	0.001

AGA = anti-gliadin antibody; IgG = immunoglobulin G.

we now studied whether this immune reactivity is restricted to gluten. In this case-control study, we confirmed earlier findings of elevated serum levels of AGA and IgG-tTG in CP. Furthermore, we found elevated levels of IgG antibodies against β -lactoglobulin, casein, and egg white to be more frequent in cases with CP compared with matched controls, suggesting an immune reactivity against various dietary antigens (Table 1). These findings have not been previously reported in CP and suggest that a disturbed mucosal barrier may cause the specific antibody production. The proportion of elevated levels of all tested antibodies was higher in individuals with the most severe form of CP (TP and DK subtypes), although not statistically significant for IgG antibodies against egg white and IgA antibodies against tTG, when compared with the other subtypes of CP (Table 3). Children and young adults in the TP and DK subgroups of CP have lower weight, height, and BMI compared with the other subgroups of CP (Table 3) and particularly compared with normal children. The reason for this increased immune reactivity against various dietary antigens is unclear; however, malnutrition can affect the intestinal mucosa integrity and lead to increased gut permeability (16–18). For this reason, we looked at weight as a single factor in relation to elevated levels of antibodies, regardless of CP subtype, and found that low weight correlated to antibody positivity. The mean weight z score of the antibody-negative group was -0.77 SD, compared with -1.74 in the antibody-positive group (95% CI -1.8 to -0.10 ; $P = 0.03$) (Fig. 2).

Several studies from developing countries have reported that intestinal biopsies of severely undernourished children show villous atrophy with shortened villi, crypt hyperplasia, and epithelial lymphocyte infiltration. This damage has a negative effect on the small intestinal barrier and function, resulting in absorption of macromolecules, which may trigger a local and

TABLE 3. Weight, height, BMI, and antibody levels in cases with TP and DK CP, compared with the other CP subtypes in the studied group

	CP (TP+DK), n = 29	CP (DP, HP, A), n = 70	P
Mean weight, z score (SD)	−2.7 (2.07)	−0.88 (1.66)	<0.001
Mean height, z score (SD)*	−2.61 (1.91)	−1.34 (1.41)	0.001
Mean BMI, z score (SD)§	−1.63 (1.64)	−0.14 (1.74)	<0.001
Elevated IgG antibodies against β -lactoglobulin* n (%)	12/28 (43)	8/68 (12)	0.001
Elevated IgG antibodies against casein* n (%)	14/28 (50)	8/68 (12)	<0.001
Elevated IgG antibodies against egg white* n (%)	7/28 (25)	7/68 (10)	0.11
Elevated IgG antibodies against AGA† n (%)	21/25 (81)	33/65 (52)	0.004
Elevated IgG antibodies against tTG‡ n (%)	8/25 (32)	6/65 (9)	0.019
Elevated IgA antibodies against AGA‡ n (%)	10/25 (40)	10/66 (15)	0.011
Elevated IgA antibodies against tTG‡ n (%)	1/25 (4)	0/66 (0)	0.275

A = ataxic; AGA = anti-gliadin antibody; BMI = body mass index; CP = cerebral palsy; DP = diplegic; HP = hemiplegic; Ig = immunoglobulin; SD = standard deviation; TP = tetraplegic.

*Data and sera from 3 children were not available for analysis.

†Sera from 9 children were not available for analysis.

‡Sera from 8 children were not available for analysis.

§Data from 4 children not available.

systemic immune response and induce inflammatory processes that may further deteriorate the intestinal absorption and uptake of nutrients (19,20).

Intestinal permeability can be evaluated using the lactulose/mannitol test. Hossain et al (21) used this test in 77 Bangladeshi children with severe underweight. Compared with 17 non-malnourished controls, 84% of the undernourished children had abnormal intestinal permeability. After 3 months of food supplementation and psychosocial stimulation, this figure had decreased to 60%. Children whose intestinal permeability improved also gained more weight.

Lunn and Campbell (20,22) studied children in developing countries and found that malnutrition affects the intestinal mucosa, leading to increased permeability and mucosal enteropathy, which may remain throughout life, and may be the reason for poor growth. They also reported findings of high plasma concentrations of Ig (IgA, IgG, and IgM), which have been generally interpreted to reflect a chronic stimulation of the immune system as a consequence of highly contaminated environments, but the increased mucosal permeability is probably also of importance (20).

We found higher prevalence of antibodies to β -lactoglobulin, casein, and egg white in AGA-positive compared with AGA-

negative cases. Possibly, this may be related to a common underlying pathophysiologic alteration; however, gliadin has been shown to affect tight junctions, thereby causing increased intestinal permeability (23,24). Therefore, an alternative interpretation of our finding is that gliadin acts as an additional cofactor in breaking the mucosal structure and leads to increased passage of other dietary antigens (25). Drugs, especially NSAIDs, may also affect mucosal permeability (26); however, the use of such therapy was infrequent in our study population and may not account for our findings.

It may be discussed whether these children and young adults with CP have gluten sensitivity (GS) (27). They undoubtedly have increased immunological reactivity against gluten (not involving IgE antibodies against wheat or gluten). There have been efforts recently to clarify the definitions of “CD” and gluten-related disorders because clear definitions are lacking (28,29). Ludvigsson et al (28) list up to 13 terms of CD and 4 concern gluten-related diseases. They suggest that the term “gluten-related disorders” should be used as an umbrella term for all of the diseases triggered by gluten. Instead of using the term “GS,” the term “noncoeliac GS” should be used, meaning “a variety of immunological, morphological, or symptomatic manifestations that are precipitated by the ingestion of gluten” and excluding CD. Others use the term “GS” to refer to clinical symptoms related to ingestion of gluten, without signs of allergic or autoimmune mechanisms (29). Individuals with suspected GS have antibodies to AGA and gastrointestinal symptoms that improve with gluten withdrawal. The authors conclude that reactions to gluten are not limited to CD and that a spectrum of gluten-related disorders may be involved (29).

A study by Volta et al (30), of 78 patients with GS negative for CD and IgE-mediated wheat allergy, showed that the serological pattern was dominated by IgG AGA (56.4%) and, to a lesser extent, IgA AGA (7.7%). Only 1 patient was positive for IgG deamidated gliadin peptide and all were endomysial antibody-negative. HLA-DQ2 and/or -DQ8 positivity was found in 46%. The patients had both intestinal symptoms (diarrhoea, abdominal pain, and bloating) and extraintestinal symptoms (headache, joint/muscle pain, numbness in legs/arms, tiredness, rash, anaemia, and depression) after gluten ingestion and they promptly responded to a gluten-free diet. After gluten challenge the symptoms recurred. The small bowel biopsies showed normal mucosa in half of the patients and increased intraepithelial lymphocytes (Marsh Type 1) in 42% (30). The individuals in the study by Volta et al showed the same serological pattern as did the cases with CP in our study;

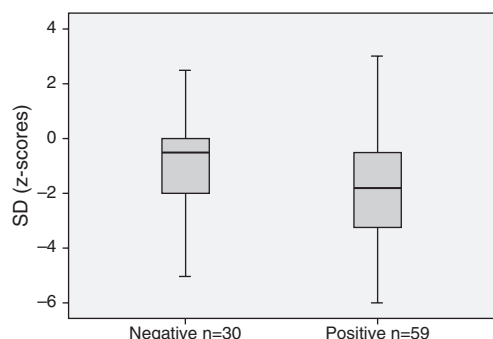


FIGURE 2. Box plot of weight z scores for cases with cerebral palsy (CP) with at least 1 positive dietary antibody compared with cases with CP with all of the negative dietary antibodies. In the group with negative antibodies, the mean weight z score was -0.77 , whereas in the group testing positive for one or more antibodies, the mean weight z score was -1.74 , yielding a difference of -0.97 standard deviation (SD) (95% confidence interval [CI] -1.8 to -0.1 ; $P=0.03$).

however, we lack data on clinical symptoms in our cohort, and gastrointestinal symptoms are difficult to assess, especially in the TP and DK CP subgroups owing to their severe neurological handicap. Presently, we do not have data to recommend a gluten-free diet and more studies are required in this respect.

The normal humoral response to food antigens consists of predominantly IgA and IgG antibodies, whereas development of IgE antibodies leads to allergy. Wheat allergy has been reported in bakers who inhale flour (31). Children and young adults with CP of the TP and DK subtypes are prone to aspirate food because of their swallowing dysfunction (10).

It is therefore possible that these children and young adults may develop IgE antibodies against gluten; however, in our study no subject in the TP or DK subgroups had IgE-mediated antibodies to wheat or gluten. The overall IgE antibody response was low.

In summary, in this case-control study, we report for the first time an increased occurrence of IgG antibodies to dietary antigens such as β -lactoglobulin, casein, and egg white in CP. Furthermore, we confirm an increased occurrence of antibodies against gliadin. The reason for this is unknown, but the findings suggest an underlying disturbance of intestinal permeability possibly related to their undernutrition. Further studies are needed to evaluate mucosal integrity in this group.

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REFERENCES

- Himmelman K, Beckung E, Hagberg G, et al. Bilateral spastic cerebral palsy—prevalence through four decades, motor function and growth. *Eur J Paediatr Neurol* 2007;11:215–22.
- Stallings VA, Charney EB, Davies JC, et al. Nutrition-related growth failure of children with quadriplegic cerebral palsy. *Dev Med Child Neurol* 1993;35:126–38.
- Stoch MB, Smythe PM. Does undernutrition during infancy inhibit brain growth and subsequent intellectual development? 1963. *Nutrition* 1996;12:569–71.
- Stoch MB, Smythe PM, Moodie AD, et al. Psychosocial outcome and CT findings after gross undernourishment during infancy: a 20-year developmental study. *Dev Med Child Neurol* 1982;24:419–36.
- Grantham-McGregor S, Ani C. Cognition and undernutrition: evidence for vulnerable period. *Forum Nutr* 2003;56:272–5.
- Fox JH, Fishman MA, Dodge PR, et al. The effect of malnutrition on human central nervous system myelin. *Neurology* 1972;22:1213–6.
- Dahlseng MO, Finbraten AK, Juliusson PB, et al. Feeding problems, growth and nutritional status in children with cerebral palsy. *Acta Paediatr* 2012;102:92–8.
- Campanozzi A, Capano G, Miele E, et al. Impact of malnutrition on gastrointestinal disorders and gross motor abilities in children with cerebral palsy. *Brain Dev* 2007;29:25–9.
- Stenberg R, Dahle C, Lindberg E, et al. Increased prevalence of anti-gliadin antibodies and anti-tissue transglutaminase antibodies in children with cerebral palsy. *J Pediatr Gastroenterol Nutr* 2009;49:424–9.
- Erasmus CE, van Hulst K, Rotteveel JJ, et al. Clinical practice: swallowing problems in cerebral palsy. *Eur J Pediatr* 2012;171:409–14.
- Stenberg R, Kaukinen K, Bengtsson M, et al. A study on early developing celiac disease in children with cerebral palsy. *J Pediatr Gastroenterol Nutr* 2011;53:674–8.
- Hagberg B, Hagberg G, Olow I. The changing panorama of cerebral palsy in Sweden. IV. Epidemiological trends 1959–78. *Acta Paediatr Scand* 1984;73:433–40.
- Ridefelt P, Aldrimer M, Rodoo PO, et al. Population-based pediatric reference intervals for general clinical chemistry analytes on the Abbott Architect ci8200 instrument. *Clin Chem Lab Med* 2012;50:845–51.
- Aldrimer M, Ridefelt P, Rodoo P, et al. Reference intervals on the Abbot Architect for serum thyroid hormones, lipids and prolactin in healthy children in a population-based study. *Scand J Clin Lab Invest* 2012;72:326–32.
- Albertsson-Wikland K, Karlberg J. Natural growth in children born small for gestational age with and without catch-up growth. *Acta Paediatr Suppl* 1994;399:64–70.
- Rodriguez P, Darmon N, Chappuis P, et al. Intestinal paracellular permeability during malnutrition in guinea pigs: effect of high dietary zinc. *Gut* 1996;39:416–22.
- Jeschke MG, Debroy MA, Wolf SE, et al. Burn and starvation increase programmed cell death in small bowel epithelial cells. *Dig Dis Sci* 2000;45:415–20.
- Song J, Wolf SE, Wu XW, et al. Starvation-induced proximal gut mucosal atrophy diminished with aging. *J Parenter Enteral Nutr* 2009;33:411–6.
- Sullivan PB, Marsh MN, Mirakian R, et al. Chronic diarrhea and malnutrition—histology of the small intestinal lesion. *J Pediatr Gastroenterol Nutr* 1991;12:195–203.
- Lunn PG. The impact of infection and nutrition on gut function and growth in childhood. *Proc Nutr Soc* 2000;59:147–54.
- Hossain MI, Nahar B, Hamadani JD, et al. Intestinal mucosal permeability of severely underweight and nonmalnourished Bangladeshi children and effects of nutritional rehabilitation. *J Pediatr Gastroenterol Nutr* 2010;51:638–44.
- Campbell DI, Lunn PG, Elia M. Age-related association of small intestinal mucosal enteropathy with nutritional status in rural Gambian children. *Br J Nutr* 2002;88:499–505.
- Fasano A. Zonulin and its regulation of intestinal barrier function: the biological door to inflammation, autoimmunity, and cancer. *Physiol Rev* 2011;91:151–75.
- Liden M, Kristjansson G, Valtysdottir S, et al. Gluten sensitivity in patients with primary Sjogren's syndrome. *Scand J Gastroenterol* 2007;42:962–7.
- Lammers KM, Lu R, Brownley J, et al. Gliadin induces an increase in intestinal permeability and zonulin release by binding to the chemokine receptor CXCR3. *Gastroenterology* 2008;135:194–204.
- Bjarnason I, Takeuchi K. Intestinal permeability in the pathogenesis of NSAID-induced enteropathy. *J Gastroenterol* 2009;44(suppl 19):23–9.
- Troncone R, Jabri B. Coeliac disease and gluten sensitivity. *J Intern Med* 2011;269:582–90.
- Ludvigsson JF, Leffler DA, Bai JC, et al. The Oslo definitions for coeliac disease and related terms. *Gut* 2013;62:43–52.
- Sapone A, Bai JC, Ciacci C, et al. Spectrum of gluten-related disorders: consensus on new nomenclature and classification. *BMC Med* 2012;10:13.
- Volta U, Tovoli F, Cicola R, et al. Serological tests in gluten sensitivity (nonceliac gluten intolerance). *J Clin Gastroenterol* 2012;46:680–5.
- Savolainen H. Flour protein antigens in occupational flour hypersensitivity. *Occup Med (Lond)* 1997;47:341–3.