ANTI-TRANSGLUTAMINASE 6 ANTIBODIES AS A SEROLOGICAL MARKER FOR GLUTEN RELATED NEUROLOGIC DYSFUNCTION IN CHILDREN WITH CEREBRAL PALSY

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ABSTRACT

Gluten sensitivity typically presents as celiac disease, a chronic, autoimmune mediated, small-intestinal disorder. Neurological disorders occur with a frequency of up to 10% in these patients. However, neurological disorders can also be the sole presenting feature of gluten sensitivity. Development of autoimmunity directed toward different members of the Transglutaminase gene family could offer an explanation for the diversity in manifestations of gluten sensitivity. Antibodies against Transglutaminase 6 (anti-TG6) represent a new marker associated with gluten-related neurological dysfunction. *The aim of this study* was to investigate the prevalence of anti-TG6 antibodies in this group of individuals with an early neurological injury resulting in CP. *Materials and Methods*: 60 children with different forms of cerebral palsy and 40 healthy control children were included and investigated for IgA/IgG class anti-TG6 by ELISA. *Results:* Anti-TG6 antibodies were found in 9/60 (15%) of patients with CP compared to 3/40 (7.5%) in controls. The quadriplegic subgroup of CP had a significantly higher prevalence of anti-TG6 antibodies 7/15 (46.7%) compared to the other subgroups and controls. *Conclusions:* An early brain insult and associated inflammation may predispose to future development of TG6 autoimmunity.

INTRODUCTION

Cerebral palsy is an umbrella term that refers to a group of disorders affecting a person's ability to move. It is due to damage to the developing brain either during pregnancy or shortly after birth (Panteliadis et al; 2013).

Cerebral palsy affects people in different ways and can affect body movement, muscle control, muscle coordination, muscle tone, reflex, posture and balance. Although cerebral palsy is a permanent life-long condition, some of these signs of cerebral palsy can improve or worsen over time. People who have cerebral palsy may also have visual, learning, hearing, speech, epilepsy and intellectual impairments (Novak et al; 2012).

While in certain cases there is no identifiable cause, typical causes include problems in intrauterine development (e.g. exposure to radiation, infection, fetal growth restriction), hypoxia of the brain (thrombotic events, placental conditions), birth trauma during labor and delivery, and complications around birth or during childhood(Nelson and Blair,2015).

Most people familiar with celiac disease know that gastrointestinal discomfort is one of the most common symptoms. The antibody most commonly associated with such discomfort is called anti-transglutaminase 1361 discomfort is called anti-transglutaminase 2 IgA. This is one of the main antibodies that doctors commonly look for when evaluating possible cases of celiac disease (Cascella et al; 2011).

Increasing numbers of studies have reported that gluten-related disorders include extra intestinal manifestations, for example, involving skin (dermatitis herpetiformis) and brain (gluten Ataxia) (Sárdy et al;2002). Such manifestations may occur in the absence of overt gastrointestinal involvement and patients may be sero-negative for anti-TG2 IgA auto-antibodies, the commonly used diagnostic marker for celiac disease (CD). Diagnosis of such cases is very difficult depending on family history of CD together with exclusion of other etiology (Hadjivassiliou et al; 2008).

Another enzyme in the transglutaminase family that is primarily expressed in the central nervous system is transgluta-minase 6 (TG6). Recent studies demonstrated the presence of circulating anti-TG6 antibodies in adults with gluten Ataxia, independent of intestinal involve-ment. This may suggest a bias of the immune response towards different TG isozymes in extra-intestinal manifestations (i.e., TG6 in gluten Ataxia and TG3 in dermatitis herpetiformis) (Thomas et al; 2013).

The aim of this study was to investigate the prevalence of antibodies against TG6 in patients with CP and to study the relation between TG6 and type and severity of CP.

MATERIAL AND METHODS

Patients:

The study recruited 60 children and with different forms of CP

visiting pediatric neurology unit and pediatric department at AL-Hussein university hospital in the period between March and November, 2014.

There were 28 girls and 32 boys. At the time of enrolment the age ranged from 18 months to 12 years (median age 6 years). There was no comorbidity for CD such as diabetes mellitus or dermatitis herpetiformis at the time of inclusion. The diagnosis of CP subgroups was based on studies by (Mutch et al.1992). A functional assessment of each child was made on the basis of the Gross Motor Function Classification System (GMFCS), graded I–V, where GMFCS V represent the most severe disability (Palisano et al; 1997). Medical data of the CP patients were reviewed retrospectively in medical files. Twelve children had treatment for gastro esophageal reflux disease (GERD).

All patients with CP in this study were subjected to:

- Full history taking including prenatal history, mode of delivery and suspected cause of CP.
- Detailed physical examination including full neurological assessment, assessment of growth and development, nutritional status and BMI.
- Revisions of the patient's file including findings of CT/MRI reports.

Controls:

40 children, aged 2–11 years (22 boys and 18 girls), were included in the serological analysis as controls. These children had no past history of neurological disorders, intestinal diseases and apparently healthy by clinical examination.

TG6 Antibody ELISA (Hadjivassiliou et al; 2013):

Enzyme-Linked Immuno-Sorbent Assay (ELISA) is intended for the quantitative or qualitative determination of IgA/ IgG antibodies in human serum, directed against TG6. The immobilized antigen is a highly purified preparation of human recombinant TG6. Plain solid phase is provided to assess the degree of unspecific binding. The test is fast (incubation time 30 / 30 / 30 minutes) and flexible (divisible solid phase, ready-to-use reagents). Six calibrators allow quantitative measurements; a negative and a

positive control check the assay performance.

The sample buffer, calibrators and controls contain Na-azide as preservative. The wash buffer contains bromonitrodioxane and the conjugate methylisothiazolone / bromonitrodioxane as preservative. The substrate contains 3, 3', 5, 5'-tetramethylbenzidine (TMB) and hydrogen peroxide (H2O2). The stop solution, 0,5 M sulfuric acid (H2SO4), is acidic and corrosive.

Principle of the test

The wells of the solid phase are coated with TG6.

1st reaction: TG6-specific antibodies present in the sample bind to the immobilised antigen, forming the antigen-antibody complex.

2nd reaction: A second antibody, directed at human IgA/ IgG antibodies and labeled with horseradish peroxidase (HRP), binds to the complex.

3rd reaction: The enzyme-labelled complex converts a substrate into a blue product. Samples containing IgA/ IgG antibodies against TG6 develop the blue color, whereas samples without these antibodies remain colorless.

Control wells without TG6 antigen are intended to determine unspecific binding of immune globulins. They are treated in the same way as the TG6-coated wells. The signal difference between TG6-coated and plain wells reflects the binding of TG6-specific IgA/ IgG antibodies.

***Preparation of the samples*:** Handle patient specimens as if capable of transmitting infectious agents. Prepare sera using normal laboratory techniques and dilute them 1/100, e.g. 10 µL serum + 990 µL sample buffer. Mix thoroughly. Take care to avoid any contamination of the buffer by serum.

Dispense the calibrators (2,0 mL each, ready-to-use, gradually blue), the negative and positive control (2,0 mL each, ready-to-use, green and red, respectively) and the diluted samples rapidly into the TG6-coated and control microwells; 100 µL per well.

***Quantitative evaluation*:** The data obtained are quantitatively evaluated with the standard curve. However, the depicted curve can only serve as a model. It can not substitute the measurement of the calibrators, together with the controls and actual samples. The

curve has been constructed with a conventional ELISA evaluation program, using a 4-parameter function. The Spline approximation is also appropriate.

***Qualitative evaluation*:** The test may also be evaluated in a qualitative manner. This requires measurement of only the positive control. Nevertheless, measurement and examination of the negative control is recommended.

A measurement >14 U/mL for IgA or >34 U/mL for IgG was considered positive.

Ethics:

The study was approved by AL-Azhar University Ethical Review Board .Parents of enrolled patients signed written informed consent.

Statistical Analyses:

All data were analyzed using the Statistical Package for the Social sciences (SPSS) program, version 15. Differences between groups were evaluated with Pearson's χ^2 test in cross tabulations and when appropriate Fisher's Exact Test. An independent *t*- test was used for body mass index (BMI) (standard deviation, SD), height (SD), and weight (SD), using 2-tailed significance (Bryman et al; 2011).

$P < 0.05$ was considered significant.

RESULTS

Sera from 60 patients with CP and 40 controls (children from same geographical area) were available for analysis of autoantibodies against TG6. We found elevated levels of anti-TG6 antibodies (IgG and/or IgA) in 9/60 (15%) in the CP-group and 3/40 (7.5%) in the control group and the difference between both groups was statistically significant (P= 0.03). (Figure 1) However, a positive test for TG6 antibodies was significantly more frequent in the quadriplegic subgroup of CP (46.7%) compared to the control group 7.5% (P=0.01). We also found statistical significance when the quadriplegic subgroup was compared to the other CP subgroups (P=0.006) (Figure 2). IgA anti-TG6 antibodies were found in 4/60 (6.6%) compared to 1/40 (2.5%) in the control group.(P=0.43) IgG anti-TG6 antibodies were found in 5/60 (8.3%) compared to 2/40 (5%) in the control group (P=0.64).

Figure 1: Analysis of serum for antibodies against transglutaminase type 6 (TG6) by ELISA.

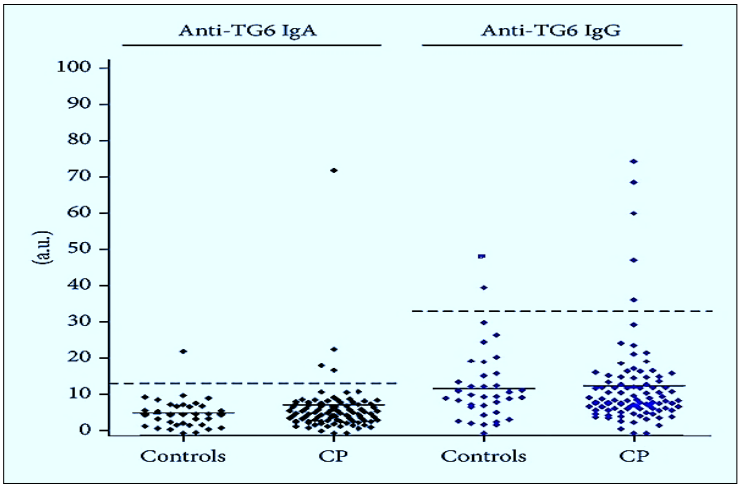


Figure (1): Analysis of serum for antibodies against transglutaminase type 6 (TG6) by ELISA. Relative concentration of antibodies in children (n=60) with cerebral palsy (CP) and controls (n=40) is given in arbitrary units. Bolded line represents the mean titre of the group and dotted line the threshold for a positive test.

Figure 2: Percentage of patients testing positive for IgA/IgG antibodies to TG6 in different CP subgroups and in a control group.

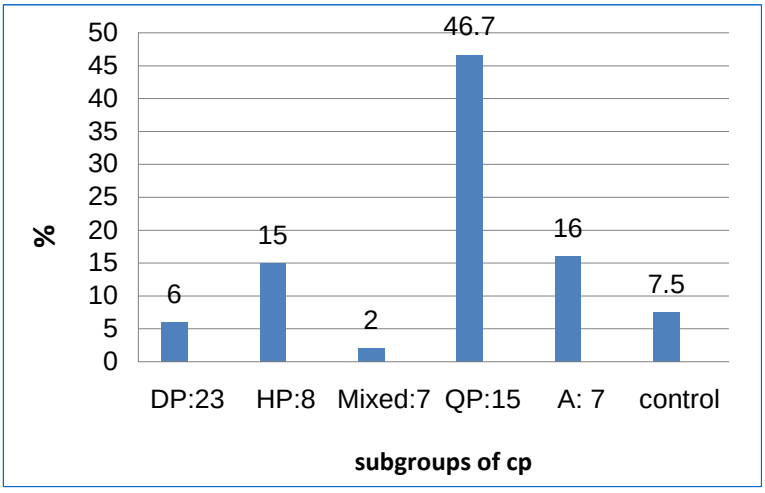


Figure 2: Percentage of patients testing positive for IgA/IgG antibodies to TG6 in different CP subgroups and in a control group. The quadriplegic subgroup compared to the other CP subgroups (p=0.006) and to controls (p=0.01)
HP: CP-Hemiplegia, DP: CP-Diplegia, QP: CP-qudriaplegia and A: CP-Ataxia.

In the present study, 77.8% of the patients with positive TG6 antibody had history of perinatal asphyxia in contrast to 74.5% in TG6 antibody negative group and the difference between both groups was statistically insignificant(P= 0.322).

All patients with positive TG6 antibodies (100%) has variable degrees of mental retardation and positive finding in CT/MRI while in negative group, 96.1% were mentally retarded and 88.2% had CT/MRI changes and the difference between both groups were statistically insignificant (p value 0.380 and 0.189 respectively)

8 patients in TG6 positive group were on regular antiepileptic drugs (88.9%) while in negative group, they were 39(76.5%)(p=0.035).

Patients in both groups were underweight and BMI in TG6 positive group was (17.3±0.528) and in TG6 antibody negative group (15.9±0.549) and the difference was statistically insignificant (p= 0.285).

There was a significant statistical difference between TG6 antibody positive and negative groups as regard GERD, 11.1% in positive group and 21.6% in negative group (P=0.03)(table 1).

Table (1): Clinical and radiologic characteristics of TG6 antibody positive and TG6 antibody negative groups.

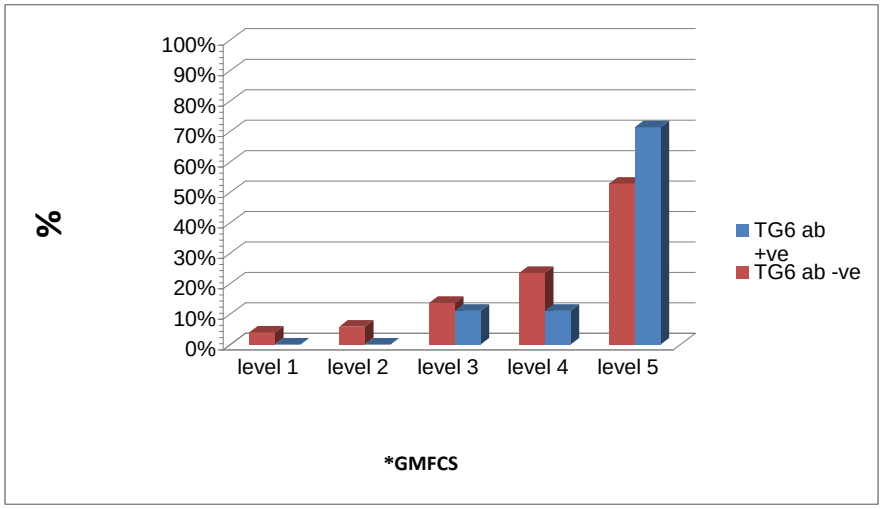
	TG6 antibody positive 9/60 (15%)	TG6 antibody negative 51/60 (85%)	*P* value
Perinatal asphyxia	7(77.8%)	40(74.5%)	0.322
MR	9(100%)	49(96.1%)	0.380
CT/MRI findings	9(100%)	45(88.2%)	0.189
Regular anti-epileptics	8(88.9%)	39(76.5%)	0.035
BMI	15.9±0.528	17.3±0.549	0.285
GERD	1(11.1%)	11(21.6%)	* 0.03

Table 1 clinical and radiologic characteristic of TG6 antibody positive and negative groups.
Abbreviations: GERD: gastroesophageal reflux disease; MRI: magnetic resonance imaging; CT: computer tomography.
* Significant difference.

Patients were classified according to GMFCS classification of motor functions in both groups, the statistical difference between patients as regard levels I,II,III were in- significant while this difference between TG6 antibody

positive and TG6 antibody negative group were significant as regard level IV(p=0.01) and level V(p=0.02)(figure3).

Figure (3): Gross motor function classification system in TG6 positive and TG6 negative groups.



*GMFCS: gross motor function classification system.

DISCUSSION

Cerebral palsy (**CP**) is a group of permanent movement disorders that appear in early childhood. Signs and symptoms vary among people. Often, symptoms include poor coordination, stiff muscles, weak muscles, and tremors. There may be problems with sensation, vision, hearing, swallowing, and speaking. Often babies with cerebral palsy do not roll over, sit, crawl, or walk as early as other children their age. Difficulty with the ability to think or reason and seizures each occurs in about one third of people with CP. While the symptoms may get more noticeable over the first few years of life, the underlying problems do not worsen over time (*Panteliadis* et al.; 2013).

In a large European study including 818 children, *Beckung et al 2002* report intellectual disabilities in 53%, seizures of the latest year in 21%, and blindness or no useful vision in 7% of the children. Communication problems of varying degrees were found in 42%. Pain was related to CP type, severity of motor function both gross and fine, feeding disabilities and seizures. Hearing impairment

was found in 2%. Twenty percent of individuals with CP have psychosocial and behavioral problems and 9% have an autistic spectrum disorder, (Pakula et al 2009).

Children with CP have many gastro intestinal problems. Gastrointestinal motility disorders result in various problems such as constipation, oral motor dysfunction, rumination, delayed gastric emptying, and especially gastro-esophageal reflux disease (GERD). In studies of children with neurological impairments, GERD has been reported in a range of 14- 75%.This indicates the difficulties in diagnosing this disease in neurologically impaired children (Sullivan et al; 2002).

Coeliac disease is an immune-mediated small bowel disorder precipitated by ingestion of gluten and related prolamines in genetically susceptible individuals, affecting approximately 1% of the general population (Husby et al; 2012).

Gluten sensitivity is thought to be due to gluten-mediated mechanisms that are different from the immune reactions in CD. However, due to lack of a clear definition and criteria, this field is controversial and confusing. Only a few years ago, researchers stated that gluten is harmful only with regard to CD pathology, i.e. enteropathy. It has, however, become apparent that gluten can have a negative impact on organs other than the gut, which may explain extra-intestinal manifestations (Hadjivassiliou et al; 2010).

Transglutaminase family involved in the neuronal process is the newly identified TG6. It is expressed in humans where the enzyme is probably associated carcinoma cell line with neuronal characteristics and with neurogenesis in mouse brain. *In situ* hybridization of newborn and embryonal mouse brain has shown that TG6 is wide spread in the brain and most commonly in the cerebral cortex, olfactory lobe and cerebellum. TG6 mRNA expression has been found to be prominent in regions undergoing neuronal differentiation (Thomas et al; 2011).

Elevated levels of antibodies were found in patients with cerebral palsy rather than apparently healthy group, the relation between higher levels of this gliadin seromarker and brain injury may be attributed to autoimmunity which developed due to severe hypoxia in early life.

Patients with quadriplegic type of CP showed higher levels of TG6 antibodies than other types

and this explained by the relation of this type of autoimmunity to the severity of CP which may be due to the extensive inflammation and hypoxia which with time leads to this autoimmunity. Another study done by *Stenberg et al., 2009*, showed children with dyskinetic and quadriplegic type CP have significantly higher levels of gliadin related seromarker**.**

This was supported by study the level of gross motor function classification system (GMFCS), Patients with marked motor disability as level IV and V GMFCS Classification has significantly higher levels of TG6 antibodies than milder levels I,II,III and the differences between group with high levels of TG6 and lower levels were statistically significant

Patients with positive TG6 antibodies are underweight have lower BMI than other group but the difference was insignificant. In Another study by *Sullivan* et al;2002, The children with elevated levels of gluten-related seromarkers had significantly lower weight, height and BMI than the children with low levels and this can be explained either by severe disability which interfere with feeding or gluten auto-immunity worsen the neurological dysfunction.

Gastrointestinal manifestations as abdominal pain, distension, persistent vomiting and GERD are characteristics of celiac disease. In patients with higher levels of TG6 antibodies GERD was lower than other group and this may be due to early manifestations of celiac disease in this group also excluding celiac disease in the group with high levels of TG6.

The interpretation of this data may indicate that an early brain insult and associated inflammation may predispose to future development of TG6 autoimmunity. More studies, however, are required to address the interpretation and clinical relevance of these findings.

CONCLUSION/ RECOMMENDATIONS

This study group of children with CP has more frequent immuno-reactivity to gluten. Here, we report significantly increased prevalence of anti-TG6 auto-antibodies in the quadriplegic subgroup of patients with CP and also in patients with severe motor dysfunction. This antibody response seems not to be correlated with low body weight but GERD were prominent in patients with low levels of TG6. The etiology of anti-TG6 antibodies in this CP subgroup remains unclear, but the results

could support the hypothesis of a primary brain insult leading to TG6 autoimmunity.

It is recommended to repeat this study on larger scale of patients and also follow up these patients for many years for development of celiac disease or other neurological complications.

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دور مضادات الترانسجلوتاميناز 6 كدلالة على إصابات الجهاز العصبي المرتبطة بالجلوتين في الأطفال مرضى الشلل الدماغي

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الحساسية للجلوتين الموجود بالقمح تظهر عادة في شكل داء الزلاقي والذي هو عبارة عن مرض مزمن له خلفية مناعية تصيب الأمعاء الدقيقة.

10% من المرضى المصابين بداء الزلاقي يعانون من اضطرابات بالجهاز العصبي وقد ظهرت بعض الحالات كانت إصابات الجهاز العصبي هي الممثل الوحيد للحساسية من مادة الجلوتين.

الشلل الدماغي عبارة عن مرض يصيب الجهاز العصبي والحركي أثناء مراحل نمو المخ سواء في مرحلة النمو الجنيني أو في مراحل النمو المبكرة وله أسباب عديدة أشهرها نقص الأكسجين وكذلك التلوث الوليدي وغيرها وعلى الرغم من أن نتائج هذا المرض غير مبشرة إلا أنه سجلت بعض الحالات التي حدث فيها بعض التحسن في الأداء الحركي أو بعض الوظائف الذهنية.

مضادات الترانسجلوتاميناز هي أجسام مضادة لأنواع مختلفة من هذا الأنزيم تظهر في المرضى المصابين بالحساسية للجلوتين مثل تراسجلوتاميناز 1-2-3.....الخ.

مضادات ترانسجلوتاميناز 6 ظهرت بنسب عالية مؤخرا في بعض امراض الجهاز العصبي المزمنة مثل مرض الترنح وكذلك إلتهاب الأعصاب الطرفية وبعض الأمراض النفسية مثل انفصام الشخصية

من هنا كان الغرض من الدراسة هي محاولة اكتشاف علاقة وجود هذه المضادات في المرضى المصابين بالشلل الدماغي بحساسية الجلوتين في المرضى الذين لا يعانون من داء الزلاقي.

وقد اشترك في هذه الدراسة 60 طفلا مريضا بالشلل الدماغي بأنواعه ودرجات الإصابة المختلفة وكذلك 40 طفلا من الأصحاء إكلينيكيا كمجموعة ضابطة حاكمة.

وقد تمت هذه الدراسة بقسم الأطفال ووحدة أعصاب الأطفال بمستشفى الحسين الجامعي في الفترة ما بين مارس ونوفمبر 2015.

وقد تم أخذ التاريخ المرضى لحالات الشلل الدماغي وشمل ذلك تاريخ الحمل والولادة وأسباب حدوث المرض.

كما تم فحص المرضى سريريا وشمل ذلك فحص الجهاز العصبي والحركي والحالة التغذوية للمرضى وكذلك نوع الإصابة وشدتها.

وقد أظهرت هذه الدراسة أن عدد مرضى الشلل الدماغي ذوي مستويات مضادات الترانسجلوتاميناز 6 العالية 9 حالات بنسبة 15%في مقابل 3 حالات فقط من المجموعة الضابطة بنسبة 75%.

هناك اختلاف ذو دلالة إحصائية بين ارتفاع مضادات الترانسجلوتاميناز 6 في الأطفال المصابين بالشلل الرباعي وكذلك الحالات المرضية الشديدة وبين بقية أنواع المرضى وكذلك مستويات الإصابة الحركية الأقل حدة.

وجد أيضا أن الإصابة بارتجاع المرئ كانت أكثر في المرضى ذوي النتائج السلبية لمضادات الترانسجلوتاميناز 6 مما يشير إلى احتمالية إصابة هؤلاء في المستقبل بداء الزلاقي دون بقية المرضى.

ونستخلص من هذه الدراسة أن مرضى الشلل الدماغي وخاصة الحالات الشديدة لديهم درجات متفاوتة من الحساسية للجلوتين هذه الحساسية تظهر في شكل اضطرابات بالجهاز العصبي والحركي وليس في داء الزلاقي هذه الحساسية ربما تكون سببا في تدهور المرض وربما تنتج من نشوء حالة من حالات المناعة الذاتية ضد خلايا الجهاز العصبي المرتبطة بحساسية الجلوتين.

كما توصي تلك الدراسة بعمل دراسات أخرى على أعداد أكبر من المرضى لدعم تلك النتائج وكذلك متابعة المرضى لعدة سنوات لبحث إمكانية ظهور علامات مرضية أخرى لداء الزلاقي.