



Original  
Artículo inglés

## Can gluten contribute to degenerative and neuronal diseases? Still no evidence based results.

### ¿Contribuye el gluten a las enfermedades degenerativas y neuronales? Sin resultados basados en la evidencia.

Ismael San Mauro-Martín<sup>1,2</sup>, Elena Garicano-Vilar<sup>1</sup>, Luis Collado-Yurrita<sup>2</sup> and María José Ciudad-Cabañas<sup>2</sup>

<sup>1</sup> CINUSA Group. C/ Artistas, 51. 28020, Madrid, Spain.

<sup>2</sup> Medicine Department, Complutense University of Madrid. Plaza Ramón y Cajal. 28040, Madrid, Spain.

#### Abstract

**Introduction:** Gluten not only affects humans by causing celiac disease or non-celiac sensitivity to gluten, but also contributes to other pathologies associated with glycoproteins. Gluten can cause neurologic damage through a combination of cross-reactive antibodies, complex immune diseases, and direct toxicity.

**Aim:** The aim of our study is to review scientific literature related to gluten ingestion in neuronal and mental pathologies, and to analyse the evidence that supports this hypothesis. Several search strategies were designed, including PubMed and other scientific databases, and combining keywords according to the study, aiming to the highest-quality scientific evidence possible.

**Results:** Patients suffering from ataxia, schizophrenia, bipolar disorder, anxiety and mental disorder, or headache due to gluten, have experienced significant relief of their symptoms after being on a gluten-free diet. It has also been suggested that the peptides of both gluten and casein can play a role in the origin of autism. The cause of neurologic symptoms is not known but it has been suggested that the autoimmunity resulting of the molecular mimicry between gliadin and proteins, of the nervous system has a relevant role.

**Conclusion:** There is a possible association between progressive cognitive deterioration and gluten. Removal of gluten from the diet has improved or stabilized the cognitive condition of studied patients.

#### KEYWORDS

*Antigliadin; Autism Spectrum Disorder; Bipolar disorder; Gluten; Neurologic disease; Review; Schizophrenia.*

#### Resumen

**Introducción:** El gluten no sólo afecta a los seres humanos causando la enfermedad celíaca o la sensibilidad al gluten no celíaca, sino que también contribuye a otras patologías asociadas con las glicoproteínas. El gluten puede causar daño neurológico a través de una combinación de anticuerpos de reacción cruzada, de enfermedades inmunitarias complejas, y mediante toxicidad directa.

**Objetivo:** El objetivo de nuestro estudio es revisar la literatura científica relacionada con la ingestión de gluten en patologías neuronales y mentales, y analizar la evidencia que apoya esta hipótesis. Varias estrategias de búsqueda fueron diseñadas, incluyendo PubMed y otras bases de datos científicas, combinando palabras clave según el estudio, en busca de pruebas científicas el mayor grado de evidencia posible.

**Resultados:** Los pacientes que sufren de ataxia, esquizofrenia, trastorno bipolar, ansiedad y trastorno mental o dolor de cabeza debido al gluten, han experimentado un alivio significativo de los síntomas después de seguir una dieta libre de gluten. También se ha sugerido que los péptidos tanto de gluten como de caseína pueden desempeñar un papel en el origen del autismo. La causa de los síntomas neurológicos no se conoce pero se ha sugerido que la autoinmunidad resultante de la mímica molecular entre gliadina y proteínas, del sistema nervioso, tiene un papel relevante.

**Conclusión:** Existe una posible asociación entre el deterioro cognitivo progresivo y el gluten. La eliminación del gluten de la dieta ha mejorado o estabilizado la condición cognitiva de los pacientes estudiados.

#### PALABRAS CLAVE

*Antigliadina; Trastorno del Espectro Autista; Trastorno bipolar; Gluten; Enfermedad neurológica; Review; Esquizofrenia.*

\* Autor para correspondencia.

Correo electrónico: [collado@med.ucm.es](mailto:collado@med.ucm.es) (Dr. Luis Collado).

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## Abbreviations

- AA; antigliadin antibodies
- ASCA; anti-*Saccharomyces cerevisiae* Antibodies
- ASD; autism spectrum disorder
- CD; celiac disease
- GABA; gamma-aminobutyric acid
- GFD; gluten free diet
- NASPGHAN; North American Society for Pediatric Gastroenterology, Hepatology and Nutrition
- IgA; immunoglobulin A
- IgG; immunoglobulin G
- NCGS; non-celiac gluten sensibility
- tTG; tissue transglutaminase

## Contribution to scientific literature

The contribution of this work is a comprehensive review of the scientific literature about gluten and how it can modulate and be implicated in neurological diseases. It is of great interest for researchers and general population and society, and therefore the manuscript would be of interest to Journal of Negative & No Positive Results.

## Introduction

Gluten is a glycoprotein formed by two other glycoproteins: gliadin and glutenin. These glycoproteins are found in some cereals of usual consumption, such as wheat, barley, rye, and in other cereals of a less frequent consumption, like spelt (dinkel wheat) or triticale (hybrid of wheat and rye)<sup>(1)</sup>. The *North American Society for Pediatric Gastroenterology, Hepatology and Nutrition* (NASPGHAN) also includes in this list the following grains or derivatives: bulgur, couscous, durum wheat, emmer wheat, flour, farro, graham flour, khorasan wheat, matzo, panko, seitan, semolina, udon, wheat seed and wheat starch<sup>(2)</sup>.

Although a number of studies relate some toxicity and allergen to gluten, it is of broad use on food industry due to its physical and chemical characteristics, giving great viscosity to food cooking. Nowadays, the use of cereals worldwide for 2013-2014 is expected to reach 2.42 billion tons<sup>(3)</sup>.

While less than 2% of the world's population has been diagnosed with celiac disease (CD) or wheat allergy (previously it was only considered to be 1%)<sup>(4-6)</sup>, more than 6% can suffer from non-celiac sensibility to gluten (NCSG)<sup>(7)</sup>. A wide range of the existing market for this demand can respond to the fact that the consumers simply feel better avoiding gluten in their diet<sup>(7)</sup>. The prevalence of disruptions related to gluten, including CD, is increasing. Pathologies traditionally distant from an aetiology or treatment for a gluten-free diet (GFD) are nowadays rising on internet and it is not difficult to find recommendations to several diseases which are easily accessible to society without any control or supervision. The profound rate of changes in human life provokes that the environmental factors<sup>(8-9)</sup>, instead of the changes on human genetics, can probably be considered as the cause for this aetiology. According to *U.S News and World Report* estimations, between 15% and 25% of the consumers are accustomed to buy free-gluten products, which increased the sale of this products considerably in 2012<sup>(10)</sup>. Although a GFD is recommended for this kind of disorders and many consumers believe that it is healthier, it has been proved that this is not always the case or that the scientific evidence is sometimes contrary to this belief<sup>(7)</sup>.

But gluten does not only causes in humans CD or NCSG. It also interferes in other pathologies sensible to glycoprotein, such as neurological diseases, indicating the evidence of the positive effect associated to the removal of gluten from a patient's diet. Gluten can cause neurological damage through a combination of antibodies of crossed-reaction, causing complex immune diseases and direct toxicity<sup>(11)</sup>. These effects on the nervous system include: cerebellar ataxia, underdevelopment, learning problems, migraine and headache<sup>(11)</sup>. A wide range of symptoms and neuropsychiatric disorders have also been associated with sensitivity to gluten, such as anxiety, depressive disorder and schizophrenia<sup>(12)</sup>.

## Objectives

- Our aim is to review scientific literature related to the ingestion of gluten in psychiatric-neuronal disorders, and to analyse the evidence that supports this hypothesis.
- It is not the aim of this study to review literature related to these disease: celiac or wheat-allergy, at the same time.

## Methods

### Search strategy:

The present study is a systematic review. It focuses on reviewing scientific literature about gluten (ingestion and sensibility) in different neuronal diseases. Thus, a bibliographic search has been made on PubMed's data base and other scientific data bases (Scielo, Embase).

The studies undertaken on gluten and neuronal diseases were systematically reviewed in September 2015. The search was done by two independent researchers who subsequently corroborated the results found. The exact electronic search strategy is outlined in Figure 1, below.

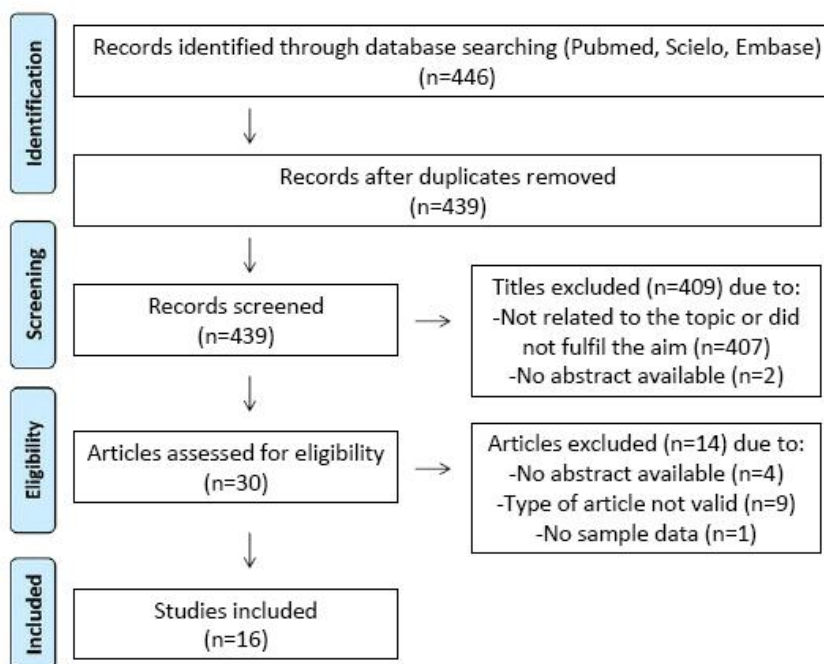


Figure 1: PRISMA diagram of literature search strategy and meta-analysis and its results.

### Search terms:

In order to recover the most relevant studies, several search strategies were designed, combining keywords according to the study that was aimed for, with the highest scientific evidence possible. The search strategy was as follows: (("glutens"[MeSH Terms] OR "glutens"[All Fields] OR "gluten"[All Fields]) AND ("cognitive"[MeSH Terms] OR "cognitive"[All Fields])) AND "humans"[MeSH Terms]. Following this process, the same search strategy was taken for the other descriptors ("neurologic", "neuro\*", "mental", "schizophrenia", "depressive", "depression", "anxiety", "cephalea/headache", etc.).

### Inclusion/Exclusion criteria:

The following types of studies were included: related to the aims, case reports, clinical trial, clinical trial, phase I, clinical trial, phase II, controlled clinical trial, multicenter study, observational study, overall, pragmatic clinical trial, randomized controlled trial, twin study, humans.

The exclusion criteria were as follows: duplicated studies or non-related with the topic, studies that reported presence of CD in patients, controversial biomarkers to get and support results or conclusions, reviews, opinions, expert's opinions, letters, conference papers and editorial papers.

## Results

### Search results:

A total of 446 articles were retrieved in this systematic review. After reading all the articles we were led to the exclusion of 430 of them for not following the proposed criteria. Thus, only 16 studies were considered legible for systematic review and have been included after a double revision. The characteristics of those, directly related with gluten and neuronal diseases are described in Table 1.

Table 1. Characteristics of gluten and neuronal diseases related studies included in the literature review and meta-analysis.

| AUTHORS   | YEAR | METHODOLOGY                                      | N SAMPLE | PATHOLOGY           | CONCLUSION  | POSITIVE RESULTS | EVIDENCE |
|---|------|--|----------|---------------------|---|------------------|----------|
| 1. Severance EG, Gressitt KL, Alaedini A, et al. [16]   | 2015 | Cross-sectional study                            | 166      | Schizophrenia       | They found striking correlations in the levels of IgG response to dietary proteins between serum and cerebrospinal fluid (CSF) of schizophrenia patients, but not controls; and the CSF-to-serum albumin ratio, was significantly elevated in cases compared to controls. Thus, the selective diffusion of wheat gluten antibodies between serum and CSF in schizophrenia may be the function of a low-level anatomical barrier dysfunction.                                  | Yes              | 2+       |
| 2. Stewart PA, Hyman SL, Schmidt BL, et al. [24]        | 2015 | Cross-sectional study                            | 288      | Autism              | Children receiving gluten/casein-free diet had similar micronutrient intake but were more likely to use supplements (78% vs 56%; P=0.01).   | Yes              | 2+       |
| 3. Hyman SL, Stewart PA, Foley J, et al. [26]           | 2015 | Double-blind, placebo-controlled challenge trial | 14       | Autism              | Being placed on a gluten/casein-free diet did not have statistically significant effects on measures of physiologic functioning, behavior problems, or autism symptoms.   | No               | 2+       |
| 4. Peters SL, Biesiekierski JR, Yelland GW, et al. [29] | 2014 | Randomised clinical trial                        | 22       | Depression          | Short-term exposure to gluten specifically induced current feelings of depression with no effect on other indices or on emotional disposition. Patients with non-coeliac gluten sensitivity feel better on a gluten-free diet despite the continuation of gastrointestinal symptoms.  | Yes              | 2+       |
| 5. Herbert MR, Buckley JA. [23]                         | 2013 | Case report                                      | 1        | Autism and epilepsy | Placed on a gluten-free, casein-free, ketogenic diet, the child showed marked improvement in autistic and medical symptoms. The child's Childhood Autism Rating Scale score decreased from 49 to 17, representing a change from severe autism to nonautistic, and her intelligence quotient increased 70 points. The child was essentially seizure free and the electroencephalogram showed only occasional 1-1.5 second spike-wave activity without clinical accompaniments. | Yes              | 3        |

Table 1 (cont.). Characteristics of gluten and neuronal diseases related studies included in the literature review and meta-analysis.

| AUTHORS  | YEAR | METHODOLOGY           | N SAMPLE | PATHOLOGY  | CONCLUSION   | POSITIVE RESULTS | EVIDENCE |
|--|------|-----------------------|----------|--|--|------------------|----------|
| 6. Carr AC. [30]                                       | 2012 | Case report           | 1        | Depression   | Placed back onto a strictly gluten-free diet and within 1 week the overall mood had improved significantly and suicidal statements were no longer verbalised. Depression, anger, fatigue, tension and confusion scores (Profile of Mood States) dropped, while vigour score rose, following her placement on the gluten-free diet. | Yes              | 3        |
| 7. Oztas E, Ozin Y, Onder F, et al [32]                | 2010 | Case report           | 1        | Mitochondrial neurogastrointestinal encephalomyopathy syndrome | After being advised a therapeutic trial of gluten free regimen, because of equivocal findings associated with celiac disease, his syndromes' symptoms were not resolved.   | No               | 3        |
| 8. Mittelbronn M, Schittenhelm J, Bakos G, et al. [28] | 2010 | Case report           | 1        | Ataxia and dementia  | Results, showing an absence of B- or plasma cells but multiple CD8(+) as well as granzyme B and perforin expressing cells in ataxia-associated brain areas, suggested that there are also prominent cytotoxic effects in neuropathogenesis after gluten ingestion.   | Yes              | 3        |
| 9. Samaroo D, Dickerson F, Kasarda DD, et al. [18]     | 2010 | Observational study   | 62       | Schizophrenia  | An association between the anti-gliadin immune response and anti-TG2 antibody or HLA-DQ2 and -DQ8 markers was not found in individuals with schizophrenia. In addition, the majority of individuals with schizophrenia and anti-gliadin antibody did not exhibit antibody reactivity to deamidated gliadin peptides.               | No               | 2-       |
| 10. Pascual J, Leno C. [27]                            | 2005 | Case report           | 1        | Migraine and idiopathic epileptic fits                         | Daily headaches returned to one every two to three months after stopped taking biscuits made of enriched wheat flour (51%), whole wheat flour (11%), vegetable oils, sugar, raising agents (sodium bicarbonate and tartaric acid) and salt.  | Yes              | 3        |
| 11. Serratrice J, Disdier P, Kaladjian A, et al. [31]  | 2002 | Case report           | 1        | Down's syndrome  | After 12 months of gluten-free diet a spectacular and lasting improvement of both psychotic and depressive symptoms was obtained.  | Yes              | 3        |
| 12. Reichelt KL, Landmark J. [17]                      | 1995 | Cross-sectional study | 61       | Schizophrenia  | More schizophrenics than controls showed IgA antibody levels above the upper normal limit to gliadin, beta-lactoglobulin, and casein.  | Yes              | 2+       |



Table 1 (cont.). Characteristics of gluten and neuronal diseases related studies included in the literature review and meta-analysis.

| AUTHORS  | YEAR | METHODOLOGY                 | N SAMPLE | PATHOLOGY                                       | CONCLUSION  | POSITIVE RESULTS | EVIDENCE |
|--|------|-----------------------------|----------|---|---|------------------|----------|
| 13. Sponheim E. [25]                           | 1991 | Double-blind and open study | 7        | Autism  | No connection was observed between gluten and behaviour typical for these patients. On the contrary, the gluten-free diet seemed to be another negative factor leading to further social isolation in this group.   | No               | 2+       |
| 14. Vlissides DN, Venulet A, Jenner FA. [20]   | 1986 | Double-blind control trial  | 24       | Psychotic disorders, particularly schizophrenia | There were beneficial changes in the whole group of patients between pre-trial and gluten-free period in five dimensions of the Psychotic In-Patient profile. Two patients improved during the gluten-free period and relapsed when the gluten diet was reintroduced.   | Yes              | 2+       |
| 15. Jansson B, Kristjánsson E, Nilsson L. [21] | 1984 | Case report                 | 1        | Schizophrenia                                   | Schizophrenic psychosis disappearing after patient is given gluten-free diet.   | Yes              | 3        |
| 16. Storms LH, Clopton JM, Wright C. [19]      | 1982 | Cross-sectional study       | 26       | Schizophrenia                                   | Tests and rating scales before and after the ten-day study period showed no greater improvement for those receiving the gluten-free cookies than for those receiving the gluten-added cookies. Contrary to expectations, the group receiving gluten-added cookies showed significantly greater improvement of Profile on Mood States measures of tension-anxiety and anger-hostility. | No               | 2-       |

## Discussion

### *Methods and hypothesis suggested in literature*

Gluten-sensitivity can be associated with neurological symptoms in patients who do not have any mucosal gut damage (that is, without celiac disease) <sup>(13)</sup>.

The cause of neurological manifestations regarding gluten is still unknown, but it has been suggested that the resulting autoimmunity of the molecular mimicry between gliadin and proteins on the nervous system has an important role <sup>(14)</sup>.

Gluten can cause neurological harm through a combination of cross reacting antibodies, immune complex disease and direct toxicity. These nervous system conditions include: dysregulation of the autonomic nervous system, cerebella ataxia, hypotonia, developmental delay, learning disorders, depression, migraine, and headache <sup>(13)</sup>.

Schizophrenia, for example, is a complex brain disorder that may be accompanied by idiopathic inflammation. Excessive production of interleukin-2 and IL-2 receptors by gastrointestinal T-lymphocytes is hypothesized as the cause of schizophrenia. It is based on: 1) Interleukin-2 given to human volunteers can cause all the symptoms of schizophrenia; 2) gastrointestinal lymphocytes in nonhuman primates produce much more interleukin-2 and interleukin-2 receptors when stimulated than peripheral blood lymphocytes; 3) the gastrointestinal tract is the largest lymphoid 'organ' in the body. The hypothesis appears to: 1) explain the protective effect of rheumatoid arthritis on schizophrenia; 2) make mechanistically plausible the findings on wheat and schizophrenia; 3) be consistent with and explain many of the known immunological abnormalities in schizophrenia <sup>(15)</sup>.

Other classic central nervous system (CNS) inflammatory disorders such as viral encephalitis or multiple sclerosis can be characterized by incongruent serum and cerebrospinal fluid (CSF) IgG. This is due in part to localized intrathecal synthesis of antibodies. The dietary antigens, such as wheat gluten, can induce a humoral immune response in susceptible individuals with schizophrenia, but the correlation between the food-derived serological and intrathecal IgG response is not known (16). Severance EG et al. <sup>(16)</sup> measured IgG to wheat gluten and bovine milk casein in matched serum and CSF samples from 105 individuals with first-episode schizophrenia ( $n = 75$  antipsychotic-naïve), and 61 controls. They found striking correlations in the levels of IgG response to dietary proteins between serum and CSF of schizophrenia patients, but not controls (schizophrenia,  $R^2 = 0.34-0.55$ ,  $p < 0.0001$ ; controls  $R^2 = 0.05-0.06$ ,  $p > 0.33$ ). A gauge of blood-CSF barrier permeability and CSF flow rate, the CSF-to-serum albumin ratio, was significantly elevated in cases compared to controls ( $p < 0.001-0.003$ ). Thus, the selective diffusion of bovine milk casein and wheat gluten antibodies between serum and CSF in schizophrenia may be the function of a low-level anatomical barrier dysfunction or altered CSF flow rate.

Other antibodies levels in serum, such as IgA were examined in two groups of schizophrenic patients by Reichelt KL et al. <sup>(17)</sup>. One group of 36 males and 12 females were compared to historical controls. The other group consisted of 13 males off drugs for at least 3 months; these were compared to age -and sex-matched controls. An increase in specific IgA antibodies was found. More schizophrenics than controls showed IgA antibody levels above the upper normal limit to gliadin, beta-lactoglobulin, and casein.

Obtaining contrary results, Samaroo D et al. <sup>(18)</sup> sought to examine the molecular specificity and mechanism of the anti-gliadin immune response in a subset of individuals with schizophrenia. Blood samples from individuals with schizophrenia and elevated anti-gliadin antibody titer were examined including antibodies to transglutaminase 2 (TG2) enzyme and deamidated gliadin peptides, as well as the HLA-DQ2 and -DQ8 MHC genes. An association between the anti-gliadin immune response and anti-TG2 antibody or HLA-DQ2 and -DQ8 markers was not found in individuals with schizophrenia. In addition, the majority of individuals with schizophrenia and anti-gliadin antibody did not exhibit antibody reactivity to deamidated gliadin peptides. These findings indicate that the anti-gliadin immune response in schizophrenia has a different antigenic specificity from that in celiac disease and is independent of the action of transglutaminase enzyme and HLA-DQ2/DQ8. Meanwhile, the presence of elevated levels of antibodies to specific gluten proteins points to shared immunologic abnormalities in a subset of schizophrenia patients.

Previous studies have suggested that a cereal- and milk-free diet may be beneficial to schizophrenics and that the gluten in regular diets is harmful to schizophrenics <sup>(19)</sup>. This was demonstrated by a double-blind control trial, by Vlissides DN et al. <sup>(20)</sup>, of gluten-free versus a gluten-containing diet was carried out in 24 patients for 14 weeks. Most suffered from psychotic disorders, particularly schizophrenia. There were beneficial changes in the whole group of patients between pre-trial and gluten-free period in five dimensions of the Psychotic In-Patient profile, maintained during the gluten challenge period; these changes could be attributed to the attention the patients received. Two patients improved during the gluten-free period and relapsed when the gluten diet was reintroduced. Similar results were obtained by Jansson B et al. <sup>(21)</sup>.

However, Storms LH et al. <sup>(19)</sup>, in an effort to replicate these findings, got some patients on a cereal- and milk-free diet. Thirteen schizophrenics were given gluten-free peanut-flour supplementary cookies and 13 were given virtually identical cookies with gluten added. Tests and rating scales before and after the ten-day study period showed no greater improvement for those receiving the gluten-free cookies than for those receiving the gluten-added cookies. Contrary to expectations, the group receiving gluten-added cookies showed significantly greater improvement of Profile on Mood States measures of tension-anxiety and anger-hostility. Previous findings were not supported.

Other neuronal diseases, such as autism, could also be caused by gluten. In typical functioning gastrointestinal tracts, enzymatic activity breaks proteins into peptides, and transforms peptides into amino acids. The intestinal lining then absorbs the amino acids into the blood stream, which carries the amino acids to the rest of the body, providing nutrition.

Theory alleges that autism spectrum disorder can result from disruptions to this process. According to the theory, some individuals suffer from inadequate production of gluten- and casein-related digestive enzymes, and increased gut permeability. Without adequate levels of digestive enzymes, peptides derived from gluten and casein fail to become amino acids in large numbers. Increased gut permeability then allows the peptides to leak into the blood stream, where they circulate and eventually cross the brain–blood barrier. Symptoms of autism spectrum disorder are theorized to result from peptides' attaching to opioid neuro-receptors<sup>(22)</sup>.

Different researchers investigating aspects of this theory have obtained troublesome results. Herbert MR et al.<sup>(23)</sup> reported the history of a child with autism and epilepsy who, after limited response to other interventions following her regression into autism, was placed on a gluten-free, casein-free diet, after which she showed evident improvement in autistic and medical symptoms. The child's Childhood Autism Rating Scale score decreased from 49 to 17, representing a change from severe autism to nonautistic, and her intelligence quotient increased 70 points. Stewart PA et al.<sup>(24)</sup> added that those children receiving gluten/casein-free diet had similar micronutrient intake but are more likely to use supplements (78% vs 56%; P=0.01).

In contrast to what Herbert MR et al. experienced, Sponheim E<sup>(25)</sup> gave seven patients with infantile autism a gluten-free diet. Three children were provoked with gluten/placebo in a double-blind study. Four young patients participated in an open study and were given a gluten-free diet in six months. Behaviour changes were registered before, during and after the period with a gluten-free diet. Visual Analogue Scale and Real Life Rating Scale were used to register changes in behaviour. No connection was observed between gluten and behaviour typical for these patients. On the contrary, the gluten-free diet seemed to be another negative factor leading to further social isolation in this group of highly socially handicapped patients and families. Hyman SL et al.<sup>(26)</sup> could not find either enough evidence to support general use of the gluten/casein-free diet. After placing the children with autism on the diet for 4-6 weeks and then conducting a double-blind, placebo-controlled challenge trial for 12 weeks while continuing with the diet, dietary challenges did not have statistically significant effects on measures of physiologic functioning, behaviour problems or autism symptoms.

As said before, nervous system causes cerebella ataxia, depression, migraine, and headache, among others. In that regard, Pascual J et al.<sup>(27)</sup> presented the case of a 48-year-old woman who experienced a transformation of her episodic migraine attacks into daily headache episodes due to the ingestion of biscuits containing wheat as their main ingredient. Daily headaches returned to one every two to three months after the removal of those biscuits made of enriched wheat flour (51%), whole wheat flour (11%), vegetable oils, sugar, raising agents (sodium bicarbonate and tartaric acid) and salt. While Mittelbronn M et al.<sup>(28)</sup> reported the case of a 68-year-old male patient suffering from progressive ataxia and dementia associated with chronic diarrhoea and both elevated IgG and IgA antigliadin-antibodies. At autopsy, frequent argyrophilic glial and neuronal inclusions within the basal nucleus of Meynert were considered as the structural correlative for the cognitive decline. Significant neuronal loss in the cerebellar cortex and the inferior olives was accompanied by infiltrating CD8(+)/perforin(+)/granzyme B(+) cells as well as reactive astrogliosis and microglial activation. These CD8(+) cytotoxic T and natural killers cells are likely to act as effector cells responsible for neuronal cell death in patients with gluten sensitivity and neurological disease and might therefore at least partly be responsible for cerebellar symptoms in gluten ataxia. Peters SL et al.<sup>(29)</sup> and Carr AC<sup>(30)</sup> concluded that short-term exposure to gluten specifically induced frequent feelings of depression and that patients feel better on a gluten-free diet.

Another group at risk of gluten affection is people with Down's syndrome. Serratrice J et al.<sup>(31)</sup> exposed the case of a 41-year-old woman, who presented with Down's syndrome and suddenly experienced some esthetic hallucinations, depression, anorexia, affective flattening and autistic behaviour. Biological evaluation revealed macrocytosis, polyclonal IgA and IgG hypergammaglobulinemia and strong positivity for anti-gliadin antibodies of IgG and IgA isotypes. Brain scan was normal. Since digestive specimen biopsies did not evidence villous atrophy, we concluded that she suffered from a silent coeliac disease. After 12 months of gluten-free diet a spectacular and lasting improvement of both psychotic and depressive symptoms was obtained.

Finally, results for mitochondrial neurogastrointestinal encephalomyopathy syndrome were found. It is a rare and life-threatening, autosomal recessive, multisystem disorder, caused by the mutations in the thymidine phosphorylase gene. It was Oztas E et al.<sup>(32)</sup> who reported a case of a 21 year-old male with a long history of intestinal pseudo-obstruction who was diagnosed with the syndrome. After being advised a therapeutic trial of gluten free regimen, because of equivocal findings associated with celiac disease, his syndromes' symptoms were not resolved.

## Limitations

The initial intent of the review is to exclude those studies which treated NCGS patients. It was complicated because NCGS is a very recent syndrome<sup>(33-34)</sup>, and there is still lack of NCGS biomarkers for its diagnosis confirmation<sup>(35)</sup>. We do not know if, despite not being celiac, patients met or not the diagnostic criteria for NCGS. This made more complicated the exclusion of these studies, which were finally included due to the controversies.



## Conclusions

The effects of abnormal interaction between the immune system and gluten can be expressed not only in the gut (coeliac disease) but also in the brain (psychosis) in genetically predisposed patients.

Gluten ingestion could be the cause in the aetiology of some revised neuronal diseases, in which it is being postulated and sustained increasingly with more studies the pathologic and symptomatology benefits of starting a GFD.

Although not wholly affirmative, the majority of published studies indicate statistically significant positive changes to symptom presentation following dietary intervention, with a level of evidence between 2+ and 3. More studies, with a more clinical design, should be undertaken to analyse each one of the different diseases individually regarding its coexistence with a GFD.

## Conflicts of Interest

The authors have no conflicts of interest or any financial involvement.

## References

1. cmed.es [web site]. Madrid: Centro médico – quirúrgico de enfermedades digestivas. [Updated 2014 May 12; accessed 2014 June 3]. Available from: <http://www.cmed.es/sensibilidad-gluten.php>
2. Children's Digestive Health and Nutrition Foundation; North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Gluten-Free Diet Guide for Families. Pennsylvania (USA). Available from: <http://www.naspgan.org/user-assets/documents/pdf/diseaseinfo/glutenfreedietguide-e.pdf>
3. Fao.org [web site]. Organización de las Naciones Unidas para la Alimentación y la Agricultura. [Updated 2014; accessed 2014 March 27]. Available from: <http://www.fao.org/worldfoodsituation/csdb/es/>
4. Czaja-Bulsa G, Bulsa M. The natural history of IgE mediated wheat allergy in children with dominant gastrointestinal symptoms. *Allergy Asthma Clin Immunol* 2014; 10(1):12.
5. Coeliac.org.uk [web site]. England: Coeliac UK. [Accessed 2014 June 3]. Available from: <https://www.coeliac.org.uk/coeliac-disease/about-coeliac-disease-and-dermatitis-herpetiformis/>
6. csaceliacs.info [web site]. Nebraska: Celiac Support Association. [Accessed 2014 June 3]. Available from: [http://www.csaceliacs.info/coeliac\\_disease\\_defined.jsp](http://www.csaceliacs.info/coeliac_disease_defined.jsp)
7. Leonard MM, Vasagar B. US perspective on gluten-related diseases. *Clinical and Experimental Gastroenterology* 2014; 7:25–37.
8. Corouge M, Loridant S, Fradin C, Salleron J, Damiens S, Moraques MD, et al. Humoral immunity links candida albicans infection and celiac disease. *PLoS One* 2015; 10(3):e0121776.
9. Namatovu F, Strömberg M, Ivarsson A, Lindgren U, Olsson C, Lindkvist M, et al. Neighborhood conditions and celiac disease risk among children in Sweden. *Scand J Public Health* 2014; 42(7):572-80.
10. Celiaccentral.org [web site]. USA: National Foundation for Celiac Awareness. [Updated 2014 June 3; accessed 2014 June 3]. Available from: <http://www.celiaccentral.org/SiteData/docs/The%20gluten/13ec19c2616ddac0/The%20gluten%20free%20diet.pdf>
11. Ford RP. The gluten syndrome: a neurological disease. *Med Hypotheses* 2009; 73(3):438-40.
12. Jackson JR, Eaton WW, Cascella NG, Fasano A, Kelly DL. Neurologic and psychiatric manifestations of celiac disease and gluten sensitivity. *Psychiatr Q* 2012; 83(1): 91–102.
13. Kinvig Ford RP. The gluten syndrome: A neurological disease. *Medical Hypotheses* 2009; 73(3): 438-40.
14. Alaedini A, Okamoto H, Briani C, Wollenberg K, Shill HA, Bushara KO, et al. Immune cross-reactivity in celiac disease: anti-gliadin antibodies bind to neuronal synapsin I. *J Immunol* 2007; 178(10):6590-5.
15. Smith RS. Is schizophrenia caused by excessive production of interleukin-2 and interleukin-2 receptors by gastrointestinal lymphocytes? *Medical Hypotheses* 1991; 34(3): 225-9.
16. Severance EG, Gressitt KL, Alaedini A, Rohleder C, Enning F, Malte Bumb J, et al. IgG dynamics of dietary antigens point to cerebrospinal fluid barrier or flow dysfunction in first-episode schizophrenia. *Brain, Behavior, and Immunity* 2015; 44:148-58.
17. Reichelt KL, Landmark J. Specific IgA antibody increases in schizophrenia. *Biological Psychiatry* 1995; 37(6):410-13.
18. Samaroo D, Dickerson F, Kasarda DD, Green PHR, Briani C, Yolken RH, et al. Novel immune response to gluten in individuals with schizophrenia. *Schizophrenia Research* 2010; 118(1-3):248-55.
19. Storms LH, Clopton JM, Wright C. Effects of gluten on schizophrenics. *Arch Gen Psychiatry* 1982; 39(3):323-7.
20. Vlissides DN, Venulet A, Jenner FA. A double-blind gluten-free/gluten-load controlled trial in a secure ward population. *Br J Psychiatry* 1986; 148:447-52.
21. Jansson B, Kristjánsson E, Nilsson L. Schizophrenic psychosis disappearing after patient is given gluten-free diet. *Lakartidningen* 1984; 81(6):448-9.
22. Mulloy A, Lang R, O'Reilly M, Sigafoos J, Lancioni G, Rispoli M. Gluten-free and casein-free diets in the treatment of autism spectrum disorders: a systematic review. *Research in Autism Spectrum Disorders* 2010; 4(3):328-39.

23. Herbert MR, Buckley JA. Autism and dietary therapy: case report and review of the literature. *J Child Neurol* 2013; 28(8):975-82.
24. Stewart PA, Hyman SL, Schmidt BL, Macklin EA, Reynolds A, Johnson CR, et al. Dietary supplementation in children with autism spectrum disorders: common, insufficient, and excessive. *J Acad Nutr Diet*. 2015; 115(8):1237-48.
25. Sponheim E. Gluten-free diet in infantile autism. A therapeutic trial. *Tidsskr Nor Laegeforen* 1991; 111(6):704-7.
26. Hyman SL, Stewart PA, Foley J, Cain U, Peck R, Morris DD, et al. The gluten-free/casein-free diet: a double-blind challenge trial in children with autism. *J Autism Dev Disord* 2015. [Epub ahead of print].
27. Pascual J, Leno C. A woman with daily headaches. *J Headache Pain* 2005; 6(2):91-2.
28. Mittelbronn M, Schittenhelm J, Bakos G, de Vos RA, Wehrmann M, Meyermann R, et al. CD8(+)/perforin/granzyme B(+) effector cells infiltrating cerebellum and inferior olives in glutenataxia. *Neuropathology* 2010; 30(1):92-6.
29. Peters SL, Biesiekierski JR, Yelland GW, Muir JG, Gibson PR. Randomised clinical trial: gluten may cause depression in subjects with non-coeliac glutensensitivity - an exploratory clinical study. *Aliment Pharmacol Ther*. 2014; 39(10):1104-12.
30. Carr AC. Depressed mood associated with gluten sensitivity--resolution of symptoms with a gluten-free diet. *N Z Med J*. 2012; 125(1366):81-2.
31. Serratrice J, Disdier P, Kaladjian A, Granel B, Azorin JM, Laugier R, et al. Psychosis revealing a silent celiac disease in a young women with trisomy 21. *Presse Med* 2002; 31(33):1551-3.
32. Oztas E, Ozin Y, Onder F, Onal IK, Oguz D, Kocaeefe C. Chronic intestinal pseudo-obstruction and neurological manifestations in early adulthood: considering MNGIE syndrome in differential diagnosis. *J Gastrointestin Liver Dis* 2010; 19(2):195-7.
33. Mansueto P, Seidita A, D'Alcamo A, Carroccio A. Non-coeliac gluten sensitivity: literature review. *J Am Coll Nutr* 2014; 33(1):39-54.
34. Czaja-Bulsa G. Non celiac gluten sensitivity – a new disease with gluten intolerance. *Clinical Nutrition* 2015; 34(2):189-94.
35. Catassi C, Elli L, Bonaz B, Bouma G, Carroccio A, Castillejo G, et al. Diagnosis of non-coeliac gluten sensitivity (NCGS): The Salerno Experts' Criteria. *Nutrients* 2015; 7(6):4966-77.