“Let Food Be Thy Medicine”: Gluten and Potential Role in Neurodegeneration

Aaron Lerner * and Carina Benzvi

Chaim Sheba Medical Center, The Zabludowicz Research Center for Autoimmune Diseases, Tel Hashomer 5262000, Israel; carina.ben.zvi@gmail.com
* Correspondence: aaronlerner1948@gmail.com; Tel.: +972-525-919484

Abstract: Wheat is a most favored staple food worldwide and its major protein is gluten. It is involved in several gluten dependent diseases and lately was suggested to play a role in non-celiac autoimmune diseases. Its involvement in neurodegenerative conditions was recently suggested but no cause-and-effect relationship were established. The present narrative review expands on various aspects of the gluten-gut-brain axes events, mechanisms and pathways that connect wheat and gluten consumption to neurodegenerative disease. Gluten induced dysbiosis, increased intestinal permeability, enteric and systemic side effects, cross-reactive antibodies, and the sequence of homologies between brain antigens and gluten are highlighted. This combination may suggest molecular mimicry, alluding to some autoimmune aspects between gluten and neurodegenerative disease. The proverb of Hippocrates coined in 400 BC, “let food be thy medicine,” is critically discussed in the frame of gluten and potential neurodegeneration evolution.

Keywords: gluten; nutrients; intestine; brain; neurodegeneration; gut-brain axis; cross-reactivity; sequence homology; BLAST

1. Introduction

The gut–brain axes connote a very complex and a challenging topic that tries to decipher the cross-talks between the two extrema, hence functionally dependent compartments. For decades, the brain dominated the arena. However, the increased knowledge on gut performances, mucosal and luminal eco-events, and immune surveynance and regulation have flipped the dogma [1]. It appears that one can’t without the other. Facing the environment, the primary immune function of the intestine is to induce tolerance and to negate the non-self for a long-term homeostasis.

Neurodegenerative diseases are characterized by the progressive loss of structure or function of neurons, finally resulting in their death. The most frequent ones are Parkinson’s (PD) and Alzheimer’s diseases (AD). They are genetically mediated but, the role of environmental factors is constantly unraveled. More specifically, the place of the nutrients, dysbiome and its metabolome, luminal enzymatic modification of naïve proteins, increased permeability and the resulting leaky gut is gaining knowledge [2,3]. In parallel, brain–gluten cross-reactive antibodies and peptides’ sequences identity between gliadin peptides and cerebral antigens are constantly reported. Hence, strengthening the autoimmune processes of molecular mimicry in neurodegenerative conditions [4]. In this regard, the present narrative review describes the potential detrimental effects of gluten ingestion on neurodegenerative disease evolution.

The first part of this review addresses the relationship between gluten and neurodegenerative diseases, while the second part screen the cross-reactivity and the sequence homology between gluten peptides and human central nervous systems’ antigens. The literature search covered the period 2000–2020 and included studies that describe gluten/gliadin association with neurodegenerative disorders. Research studies, reviews, and case–control series were included, while case reports were excluded. The literature search was performed.
using the PubMed, MEDLINE, Embase, Scopus, and Cochrane Database of Systematic Reviews databases to identify the most relevant information. The following search keywords were used “gluten” or “gliadin” AND “Neurodegenerative” or “neuroinflammatory” or “neuropsychiatric” AND “Alzheimer disease” or “Parkinson’s disease” or Amyotrophic Lateral Sclerosis, and Multiple Sclerosis, were searched. Additional studies were identified by examining the reference list of the retrieved articles. The search was limited to articles published in English. Relevant articles were selected for full-text review on the basis of screened titles and abstracts. Since primary and personal data were not included, human rights approval was not necessary. Sequence homologies between related human brain antigens and Gluten/Gliadin peptides were explored. The UniProt Knowledgebase (www.uniprot.org/, accessed on 15 December 2020) was used to extract α/β-Gliadin MM1, (UniProt: P18573). The NIH/US National Library of Medicine’s Basic Local Alignment Search Tool (BLAST) sequence matching program, (blast.ncbi.nlm.nih.gov/Blast.cgi, accessed on 24 December 2020) was used to identify sequence homology between Gliadin epitopes and central nervous system (CNS) antigenic sequences. The Immune Epitope Database (www.iedb.org, accessed on 21 March 2021) was searched to extract all human antigens epitopes that are implicated in central neuronal diseases. This included Alzheimer disease, Parkinson’s Disease, Amyotrophic Lateral Sclerosis, and Multiple Sclerosis. The aggregated epitopes were “Linear Epitopes” of “B cells” OR “HLA I” OR “HLA II” AND were rated as “Positive Assays”. In addition, neuronal epitopes that were found in the literature search to have cross reactivity or sequence homology with Gliadin, were included in this epitopes list [5–11]. Following this, a pairwise local alignment tool was used, EMBOSS Matcher (www.ebi.ac.uk/Tools/psa/emboss_matcher/, accessed on 4 October 2019). This tool implements an algorithm that is based on the Bill Pearson’s Lalign application, version 2.0u4 (February 1996). Using a Python script, the EMBOSS Matcher was executed on each of the neuronal epitopes against the Gliadin sequence and the following cutoff parameters were used to express the results: peptide length ≥ amino acids, similarity ≥50% and identity ≥50%.

2. Gluten and Tissue Transglutaminase Potential Involvement in Neurodegeneration

The world market of wheat surpasses all other crops combined and gluten is its major protein, comprising 80% of the wheat’s proteins. It is the most favored staple food worldwide and a major food additive in the processed food industries [12]. Gluten essentiality, its protein’s quality and consumption necessity for human health is debatable. However, there is no doubt regarding its inductive role in gluten dependent disease like celiac disease (CD), dermatitis herpetiformis, gluten ataxia, gluten allergy, and potentially in non-celiac wheat sensitivity [13,14].

The two most frequent conditions are non-celiac wheat sensitivity and CD with incidences of 1–6% and 1–1.5%, respectively. Dermatitis herpetiformis, gluten allergy and gluten ataxia are much less frequent with an prevalence of 1:10,000, 0.2–0.5%, and very rare, respectively [15].

Its potential role in extraintestinal manifestation of CD and remote organs’ pathologies is well reported [16,17]. In addition, its place in the enteric eco-events in the trajectory of the gut-brain axis was recently described [18]. After ingestion, gluten is digested by luminal proteases to various gliadin peptides which are the offending molecules in the gluten-related diseases [19].

Most recently, gluten’s potential role in neurodegeneration was suggested by Mohan et al. [20]. The authors comprehensibly described and suggested that dysregulated microbiome, anti-tissue transglutaminase (tTG) 6 in celiac ataxia, various gut derived biomolecular condensates or extracellular microbial vesicles might play parts in neurodegenerative evolvement. Furthermore, the authors alluded to various therapeutical strategies to prevent or treat those brain conditions. Not only gluten withdrawal, but probiotics, and some nutraceuticals, such as phyto and synthetic cannabinoids, were suggested to mitigate dietary gluten-induced neurodegeneration [20]. The clinical basis for gluten as-
associated CNS diseases comes from the numerous neurological, psychiatric and behavioral manifestations, extensively describes in gluten induced conditions in Table 1 [16,21–30].

Table 1. Neuro and psychiatric manifestations in gluten related diseases.

| Disease                  | Neuro/Psychiatric Manifestations                                                                 | References         |
|-------------------------|-------------------------------------------------------------------------------------------------|--------------------|
| Celiac disease          | peripheral neuropathy, inflammatory myopathies, myoclonus, myelopathies, headache, migraine, and gluten encephalopathy, epilepsy and seizure disorders, restless legs syndrome. Anxiety, depressive and mood disorders, attention deficit hyperactivity disorder, autism spectrum disorders, schizophrenia | [16,21,24–29]     |
| Non-celiac wheat sensitivity | foggy mind’, headache, leg or arm numbness, epilepsy and seizure disorders, gluten ataxia, gluten neuropathy and gluten encephalopathy, depression, anxiety psychosis, schizophrenia, autism, and hallucinations | [27–30]            |
| Dermatitis herpetiformis | Rarely essential tremor, chorea, migraine.                                                    | [22]               |
| Gluten ataxia           | Mainly gait and limb ataxia. rarely, myoclonus, palatal tremor, opsoclonus, chorea, Gaze-evoked nystagmus and other ocular marks of cerebellar dysfunction. | [27–29]            |
| Gluten allergy          | None                                                                                            | [23]               |

Substantial reinforcements for the gluten-brain axis are coming from epidemiological, biochemical, pathophysiological and nutritional scientific sources. Epidemiologically, gluten consumption, gluten dependent diseases and neurodegenerative/neuroinflammatory diseases’ incidences are rising, at least in the last decades [12,13,31–34]. Intriguingly, the autoantigen of CD, the tTG, also called TG2, is a pleiotropic enzyme expressed ubiquitously and abundantly, in all tissues in the body, including the human cerebrospinal fluid and brain [35,36]. Interestingly, it can occupy a cytoplasmic, trans membranous or extracellular position and recently specific inhibitors were suggested as a new therapeutic strategy to treat neurodegenerative conditions [37]. Gluten/gliadins, being tTG preferred substrate can be deamidated or transamidated [38,39]. This post translational modification of the naïve proteins, turns them to immunogenic molecules, accompanied by loss of tolerance. Notably, not only tTG is everywhere in the body. Gluten and gliadin peptides, as well, are dispersed extra-luminally to reach the systemic blood circulation [40] and are secreted even in the urine [41]. It is postulated that those urinary gliadin peptides are filtered from the systemic circulation. In many human chronic diseases, the gut is leaking and gluten/gliadin peptides can reach the sub-epithelial compartment in their way to the systemic circulation. Quite recently, trans epithelial transport of gluten was demonstrated, thus facing the local sub-epithelial immune systems [42].

The antibody’s cross reactivity between gliadin peptides and brain/cerebellar proteins is not less interesting and might allude to antigenic mimicry between gluten/gliadin peptides and human brain constituents in brain diseases [43,44]. The gut-brain axes are interesting but not less intriguing with much hidden over the visible [16,18]. Ingested gluten/gliadins are playing part in brain pathologies. Following are several gluten-related detrimental effects and pathways that might impact neurodegenerative conditions. On the systemic aspect, gluten is proinflammatory and proapoptotic and impacts epigenetics [45]. On the gut level, it enhances intestinal permeability by compromising functional tight junction integrity resulting in a leaky gut [12,16,18,45].

Interestingly, increased intestinal permeability was reported, not only in active CD and CD in remission [46], but in the other gluten dependent conditions, namely dermatitis herpetiformis [47], non-celiac gluten sensitivity and non-celiac wheat sensitivity, wheat
allergy [48]. When exposed to gliadin/gluten, biopsies from non-CD patients demonstrated a lower, limited, transient zonulin release, paralleled by an enhanced intestinal permeability that never reached the level of increased permeability seen in untreated CD [46–48]. Intriguingly, gliadin affects tight junction functional integrity also in normal controls [46].

Gluten consumption affects microbiome/dysbiome composition and diversity [38,45,49]. Reduction of diversity with a significant increase of Proteobacteria and an expansion of Neisseria, especially in active adult patients, while treated celiacs showed an intermediate profile between active disease and controls [50]. The ratio between anti-inflammatory bacteria such as Lactobacillus-Bifidobacterium to proinflammatory Bacteroides-Enterobacteriaceae in decreased in untreated CD children [51]. The corresponding metabolome revealed altered levels of free amino acids and volatile organic components. To our knowledge, the effects of gluten/gliadin on the intestinal microbiota, its metabolomic effects and the gut-brain relationships in neurodegenerative conditions is still lacking. Down to the cellular level, it decreases viability and cell differentiation, induces apoptosis, and suppresses DNA, RNA, and glycoproteins synthesis [45]. Gluten has substantial effects on the immune performances. It increases neutrophils migration, Th17 cells activity, NKG2D expression and TLR signaling pathway. It affects adaptive and innate immune systems and T reg cells functions [45]. However, a word of caution is advised since most of those side effects were describe in vitro and on animal models and there are not enough studies performed in human [45]. There are no defined recommendations to start gluten-free diet (GFD) in non-celiac gluten dependent disease, nor in other autoimmune diseases or neurodegenerative condition, unless gluten related diseases are associated and properly diagnosed [45,52,53]. On the other hand, before implementing gluten withdrawal, one has to consider the difficulties in compliance and the various gluten free-diet side effects [54,55].

3. Potential Involvement of Tissue and Microbial Transglutaminase in Neurodegeneration

A total new aspect that might apply to the present topic is the bacterial member of transglutaminase family, namely the microbial transglutaminase. Despite having low sequence homology, its functional imitation of the tTG, to modify gluten/gliadin peptides, is similar [56]. Both avidly deamidate or transamidate those molecules [38,39]. Being a survival factor that is secreted by various prokaryotes including the luminal microbiome it is widely used as a process food additive. Its enzyme gluten modifying capacity in the food industries and intestinal compartment was extensively reported [56–60]. More so, most recently the microbial transglutaminase was suggested as a new environmental factor for CD induction [59–61]. Since the microbial and the tTGs share similar enzymatic activity on gluten and brain tTG is involved in brain diseases and since trans epithelial transport of microbial transglutaminase was recently demonstrated [42], not surprising is that the bacterial transglutaminase was hypothesized to be involved in human neurodegeneration [62].

4. Gut–Brain Axes

The pathways connecting the gut luminal eco-events with the brain and the mechanisms by which ingested nutrients protect or induce neuroinflammatory/neurodegenerative diseases are far from being understood. Blood and lymphatic vessels can carry gut originated immune cells, antibodies, immunogenic proteins, immune complexes, cytokine and lymphokines. The local immune system can transfer systemically autoantibodies and proinflammatory cytokines. The enteric nervous systems are connected to the brain via the vagal nerve and the para-spinal neuronal routs. In fact, multiple epithelial (enterocytes, enteroendocrine) and sub-epithelial (dendritic and entero-glial) interconnected sensing cells are surveying the luminal events and can mediate the information upwards to the cephalic compartment [16–18]. However, there is still plenty to explore in this Pandora enigmatic puzzle.
5. Gluten Withdrawal in Neurodegenerative, Neuropsychiatric and Brain Autoimmune Diseases

As a preliminary proof of concept, GFD was reported to be beneficial in some of those neurodegenerative, neuroinflammatory, autoimmune and neuropsychiatric brain diseases (Table 2). However, in some of Table 2 cited references the patients were additionally diagnosed with CD and it is difficult to distinguish between the differential effects of GFD through CD or directly on the brain. Secondly, it should be stressed that gluten restriction is an adjuvant therapy in those brain conditions and doesn’t represent the main or the exclusive therapy.

Table 2. Brain diseases that might benefit gluten withdrawal.

| Disease Category | Disease Name                                | Reference |
|------------------|---------------------------------------------|-----------|
| Neurodegenerative| Alzheimer disease, Cognitive impairment     | [63]      |
| Parkinson’s disease |                                              | [20,29,64]|
| Anxiety          |                                              | [65]      |
| Depression       |                                              | [20,65,66]|
| “foggy mind”     |                                              | [15,66]   |
| Schizophrenia    |                                              | [65]      |
| Autism           |                                              | [20,65,67]|
| Psychosis        |                                              | [20,68]   |
| Bipolar disorder |                                              | [65]      |
| Neuropsychiatric | Dementia                                    | [65]      |
| Autoimmune       | Multiple sclerosis                          | [69]      |
| Autoimmune hypopituitarism |                                        | [70]      |
| Gluten ataxia    |                                              | [20,71]   |
| Autoimmune uveitis |                                            | [72,73]   |
| Miscellaneous    | Migraine                                    | [74]      |
| Chorea           |                                              | [75]      |
| Epilepsy         |                                              | [76]      |
| Headache         |                                              | [77]      |

6. Cross-Reactivity between Wheat/Gluten and Brain Tissue Components

Cross-reactive antibodies between self-components and environmental epitopes are a well described biologic phenomenon, as schematically illustrated in Figure 1. In this regards, molecular mimicry between anti-wheat/gluten and brain tissue component were shown by cross-reactive antibodies [8–10, 78, 79]. For example, when autistic children were checked, an eight amino acids sequence similarity of gliadin and cerebellar neural tissue was detected [8]. The authors suggested that cross-reactive antibodies against gliadin peptides and Purkinje cells might play a role in some neurological manifestations in childhood autism. More so, when anti-food antibody derived from six common foods were checked against 65 different tissue antigens, anti-wheat antibody cross-reacted with 15 tissue antigens. Concentrating on brain components, the anti-wheat antibodies reacted against dopamine receptor, neurotropin, alpha enolase and not surprisingly also against tTG which is the autoantigen of CD [10,79]. Interestingly, anti-gliadin antibodies also reacted against glutamic acid decarboxylase (GAD65), an enzyme involved in the production of γ-aminobutyric acid (GABA), which is a prime inhibitory neurotransmitter that, when dysregulated, is implicated in both depression and anxiety [65,78].
Figure 1. A schematic presentation of cross-reactive antibodies between two separated antigenic determinants. The specific antibody that reacted with each is cross-reacting to both of them. (A) Anti-gluten/gliadin antibodies. (B) Anti-brain autoantibodies. (C) Anti-gluten/gliadin and brain epitopes cross-reactive antibodies.

The cross-reactivity of anti-gluten/-gliadin/-wheat antibodies with cerebral molecules father attest for the gut-brain axes connecting those heavily consumed nutrients to chronic brain conditions. Being more updated and contemporaneous, the current SARS-Cov-2 was recently defined as an auto immunogenic virus [80–82]. In fact, 17 autoimmune diseases and 13 various autoantibodies associated with COVID-19 infection, were reported and the list is continuously expanding [80]. Zooming on the brain, multiple immunogenic epitopes of SARS-CoV-2 have high degree of homology with human brain proteins [83]. Most recently, screening 55 different human tissue antigens, Vojdani A et al., reported on SARS-CoV-2 cross-reactivity with brain tissue antigens like myelin basic protein, neurofila-ment protein, amyloid-beta, alpha-synuclein, synapsin, GAD65 and tTG-6 [84]. Antibodies against those neural protein targets are depicted in patients with neuroautoimmune and neurodegenerative conditions such as AD, PD, multiple sclerosis (MS), and ataxia [85,86]. Indeed, the current covid-19 pandemic put the PD patients at increased risk for deterioration, worsening their motor as well as non-motor symptoms [87]. The same holds for AD with negative impact on the patients’ cognitive and psychiatric functions [88].

Intriguingly, cross-reactivity between amyloid-Beta 1-42 and tTG and microbial trans-glutaminase were observed [86]. The author suggested that those cross-reactive antibodies may contribute to intraneuronal deposition of A-Beta-P-42 in AD. It should be stressed that both enzymes, the human tTG and the microbial transglutaminase were described as potential drivers of systemic autoimmunity and gluten is a prime substrate for both of the enzymes [38,39,62]. Finally, most recently, sequence homology between wheat and tTG and alpha synuclein was observed (Vojdani Aristo, personal communication), suggesting molecular mimicry between nutrients, self-tissue antigens and alpha synuclein in PD development.

Taken together, environmental factors, be it nutrients like gluten or infections like the covid-19, might impact neurodegenerative disorders. Cross-reactive antibodies might play a role in neuroinflammatory, neuropsychiatric or neurodegenerative condition. Cross-reactive antibodies allude for autoimmune molecular mimicry, but antigenic sequence identity might strengthen the gliadin-degenerative brain relationship.

7. Sequence Homology between Gluten and Brain Tissue Components

Encouraged by the cross reactivity between gluten epitopes and human brain antigens, a Blast search was conducted to identify significant peptides’ sequences identity/similarity between both components. The Glutamate Receptor Ionotropic NMDA-Associated Protein 1 (GRINA) belongs to the Lifeguard family and is involved in calcium homeostasis [89]. This Protein Lifeguard 1, (UniProt: Q7Z429) was identified to have high sequence homology with Gliadin epitopes at identity level of 85.7% (Table 3). Based on this homology, Gliadin peptides may interact with GRINA and interfere with its functionality, which is relevant in many of the extraintestinal manifestations, such as schizophrenia [6]. In a recent study, about one third of the patients with schizophrenia harbor elevated inflammation and IgG
antibodies against gliadin (anti-AGA). They showed an increased gut permeability and higher levels of anti-GRINA antibodies that were associated to anti-AGA levels [90].

Table 3. Sequence homology between gluten/gliadin peptides and brain antigen.

| Parent Protein | Disease Name | Reference | UniProt | Protein Epitope | Gliadin L | Sim% | Id% |
|----------------|--------------|-----------|---------|----------------|-----------|------|-----|
| Protein lifeguard 1 | Alzheimer disease, multiple sclerosis | [6,89,90] | Q7Z429 | PQGPYPQ | PQQPYPQ | 7 | 85.7 | 85.7 |
| | Bipolar disorder, psychosis | | | TAAAT | TTARIA | 6 | 66.7 | 66.7 |
| | Schizophrenia | | | QRRAGPQQ | QQQFPFFPQ | 8 | 75 | 62.5 |
| | Depressive disorder | [7,9,91,92] | P17600 | PQGPQPQPQ | PQQQQPQPQPQ | 16 | 62.5 | 56.2 |
| | Huntington’s disease | | | PQGPQPQPPQ | PQQPQPQPQPQ | 9 | 66.7 | 55.6 |
| | ALS | | | PQQGYPQ | PQQPYPQ | 7 | 85.7 | 85.7 |
| | Autism epilepsy | | | PQQPYPQ | PQPQPYPQ | 6 | 66.7 | 66.7 |
| | Amyloid-beta precursor protein | Alzheimer disease | [10,85,93] | P05067 | LALLAIVAT | LALLLA1AW | 18 | 72.2 | 61.1 |
| | | Parkinson’s disease, dementia with Lewy bodies, multiple system atrophy | [94] | P37840 | VVHGV | VVHAI | 5 | 80 | 60 |
| | Alpha-synuclein | Late-onset Alzheimer disease | [95] | Q7Z5R6 | QATHSV | QAIHNV | 6 | 83.3 | 66.7 |
| | Amyloid beta A4 precursor protein-binding family B member 1-interacting protein | | | VPELE | VPQRL | 5 | 100 | 60 |
| | | | | SKTS | STYQ | 5 | 60 | 60 |
| | | | | QFEN | QFEE | 5 | 80 | 60 |
| | | | | PAPVP | PQQP | 5 | 60 | 60 |
| | | | | LMKAL | LILAL | 5 | 80 | 60 |
| | | | | IYVGT | IAYGS | 5 | 60 | 60 |
| | | | | FKNIPQ | FOQP | 5 | 80 | 60 |
| | | | | YPELQI | YPOQP | 6 | 83.3 | 50 |
| | | | | QKESQY | QSOPQY | 6 | 66.7 | 50 |
| | | | | QHMKYK | QHISAY | 6 | 83.3 | 50 |
| | | | | PELQERF | PLYQPQF | 5 | 80 | 60 |
| | | | | NVVESL | NVVHAI | 6 | 66.7 | 50 |
| | | | | LITQSL | LIIQQQL | 6 | 66.7 | 50 |
| | | | | AGASLR | ARIAVR | 6 | 66.7 | 50 |
| | Cerebellar degeneration-related antigen 1 | Alzheimer disease, paraneoplastic cerebellar degeneration, autism | [8] | P51861 | EDVPLLE | EQVPLVQ | 7 | 85.7 | 57.1 |
| | Microtubule-associated protein tau | Alzheimer disease, Parkinson’s disease | [93,96,97] | P10636 | YSSPGSP | YSQQPQP | 7 | 57.1 | 57.1 |
| | Myelin-associated glycoprotein | Multiple sclerosis | [98] | P20916 | VSLLC | VQQC | 5 | 60 | 60 |
Table 3. Cont.

| Parent Protein                                      | Disease Name              | Reference | UniProt | Protein Epitope | Gliadin | L | Sim% | Id% |
|-----------------------------------------------------|---------------------------|-----------|---------|-----------------|---------|---|------|-----|
| Myelin Oligodendrocyte Glycoprotein Precursor       | multiple sclerosis        | [98]      | Q16653  | EIEEL           | EIRNL   | 5 | 80   | 80  |
| Myelin Proteolipid Protein                          | multiple sclerosis        | [98]      | P60201  | TSASIG          | TIAPVG  | 6 | 66.7 | 50  |
| Myelin basic protein                                | multiple sclerosis        | [98]      | J3QKL5  | LCNMY           | MCNVY   | 5 | 100  | 60  |
| Myelin-oligodendrocyte glycoprotein                 | multiple sclerosis        | [98,99]   | Q5SSB8  | EELRN           | EEIRN   | 5 | 100  | 80  |
| Reticulon-4 Receptor                                | multiple sclerosis        | [98,100]  | Q9BZR6  | GPGLFR          | GQGFSQ  | 6 | 66.7 | 50  |
| Spectrin alpha chain, non-erythrocytic 1            | multiple sclerosis        | [98]      | Q13813  | SQLLANS         | SQVLQQS | 7 | 71.4 | 57.1|
| Phosphoglycerate Mutase 1                           | multiple sclerosis        | [101]     | P18669  | IRHGES          | IAYGSS  | 6 | 66.7 | 50  |
| Alpha-enolase                                       | schizophrenia             | [102,103] | P06733  | LVVGLC          | LVQQLC  | 6 | 66.7 | 66.7|
| Glutamic acid decarboxylase GAD65                   | stiff-person syndrome    | [104,105] | Q9UGI5  | MCNVYIPP        | VCFWYIPP| 8 | 75   | 62.5|

As summarized in Table 3, multiple human brain antigens share sequence homology with gluten epitopes. Using the Immune Epitope Database and the EMBOSS Matcher tool, the number of proteins that had sequence homology at identity level ≥50% with Gliadin epitopes came down to 17, and the number of identified epitopes was 52. These proteins could be divided into the following categories.

8. Neurodegenerative

- Synapsin I is a major immunoreactive protein where 17 shared epitopes were identified. Synapsin is a neuron-specific cytosolic phosphoprotein, present in most of the nerve terminals and coats synaptic vesicles. It binds to the cytoskeleton, and is believed to function in the regulation of neurotransmitter release. It affects nitric-oxide functions at a presynaptic level. Anti-AGA from patients with CD identified epitopes from this protein. Although, the potential pathogenic role of SYN1-cross-reactive anti-gliadin antibodies is still unclear [7,9], increasing evidence substantiated the relevance of alterations in synapsins as a major determinant in many neurological disorders, including AD, MS, bipolar disorder, psychosis, schizophrenia, depressive
disorder, Huntington’s disease, amyotrophic lateral sclerosis, autism and epilepsy, as demonstrated by both genetic and functional studies [91,92].

- Amyloid-beta precursor protein is a key protein in AD and is considered one of the main components and inducers of the built-up plaque in the brain. Autoantibodies against this protein are detected in patients with AD and have been shown to cause neuronal degeneration in individuals with compromised blood brain barrier [10,85,93,106].

- Alpha-synuclein is a neuronal protein that plays several roles in synaptic activity such as regulation of synaptic vesicle trafficking and subsequent neurotransmitter release. This protein is a pathogenic hallmark of PD, and related to dementia with Lewy bodies, and multiple system atrophy [94].

- Amyloid beta A4 precursor protein-binding family B member 1 (APBB1IP) is another protein with a significant homology of 15 epitopes. It functions in the signal transduction from Ras activation to actin cytoskeletal remodeling. It is associated with Late-onset AD [95].

- Cerebellar degeneration-related antigen 1: Autoantibodies directed against this protein were found in some patients with paraneoplastic cerebellar degeneration, AD and autism [8].

- Microtubule-associated protein (Tau) has roles primarily in promoting microtubule assembly in axons, and in maintaining their stability. It is abundant in the CNS neurons, and might be involved in the establishment and maintenance of neuronal polarity. Tau is a key protein involved in many neurodegenerative diseases, including PD and AD [93,96,97,106].

9. Autoimmune

- Antibodies of the following four myelin proteins were reported in serum of patients suffering from MS [98]:
  1. Myelin-associated glycoprotein is an adhesion molecule that mediates interactions between myelinating cells and neurons.
  2. Myelin Oligodendrocyte Glycoprotein Precursor mediates homophilic cell-cell adhesion, and may be involved in maintenance of the myelin sheath and in cell-cell communication.
  3. Myelin Proteolipid Protein plays an important role in the formation or maintenance of the multilamellar structure of myelin.
  4. Myelin basic protein is the structural constituent of myelin sheath.

- Myelin-oligodendrocyte glycoprotein is a minor component of the myelin sheath. It may be involved in completion and/or maintenance of the myelin sheath, in cell-cell communication and it mediates homophilic cell-cell adhesion. Antibodies are associated with MS, psychosis, schizophrenia and depressive disorder [98,99].

- Reticulon-4 Receptor is a receptor for RTN4, OMG and MAG, and sialylated gangliosides GT1b and GM1. Proteomic analysis of cerebrospinal fluid in patient MS was found to contain these proteins significantly dysregulated [98,100].

- Spectrin alpha chain, non-erythrocytic 1 is a structural protein that ensures vital cellular properties including polarity and cell stabilization. In addition, it is involved in cell adhesion, cell-cell contact, and apoptosis. This protein was also found to be associated with MS [98].

- Phosphoglycerate Mutase 1 is a glycolytic enzyme that catalyzes step 8 of glycolysis. A proteomics-based analysis revealed high prevalence of autoantibodies against PGAM1 in patients with autoimmune CNS diseases, including MS and neuromyelitis optica [101].

10. Neuropsychiatric

- Alpha-enolase: This glycolytic enzyme is involved in various processes such as growth control, hypoxia tolerance and allergic responses [107]. It stimulates immunoglobulin production [108] and is a diagnostic marker for many tumors. It is often significantly
deregulated in schizophrenic patients compared with controls [102] and might have significance in CD [103].

- **GAD65** is the rate-limiting enzyme for the synthesis of GABA, the major inhibitory neurotransmitter in the CNS. Antibodies against GAD65 are seen in various CNS excitability disorders as well as autoimmune neurological conditions, including stiff-person syndrome, cerebellar ataxia, encephalitis, epilepsy, psychosis, bipolar disorder, depressive disorder, autism, mood dysfunction, anxiety, and behavioral dysfunction [104].

### 11. Discussion

Gluten is the offending nutrient in various gluten-dependent diseases like CD, dermatitis herpetiformis, gluten ataxia, gluten allergy and potentially in non-celiac sensitive conditions [13,14,45]. Despite being the major protein in wheat—the most frequently consumed staple food, it has some harmful effects on human health [13,45,52,53]. It plays a role in the extraintestinal manifestation of CD [16], including in brain pathologies [16–18,20,21,24–26], hence its involvement in neurodegenerative conditions has just started to be explored. The present review expands on two aspects, namely the cross reactivity and sequence homology between gluten and human brain epitopes, thus reinforcing the molecular mimicry between the two. The classification of the neurodegenerative conditions as ADs is debatable since they don’t fulfill the classical criteria of ADs. PD is an inflammatory condition with some autoimmune aspects [4]. Various autoantibodies against PD associated antigens were described suggesting non secondary, hence primarily causal relationship between the two, resulting in the dopaminergic neuronal loss [4,109–111]. Also, AD holds multiple autoimmune features. The vascular-derived anti-neuronal autoantibodies contained in specific brain neurons with degenerative and apoptotic features, including C1q and C5b-9 complement compounds and the permeable blood brain barrier, suggest autoimmunity-induced cell death in AD [112]. More specifically, autoantibodies targeting FcγR-mediated function, tau and ceramide in AD or FcγR-mediated function in PD, were observed to be pathogenic [113]. Most recently, putative 16 autoantibody biomarkers were detected in the cerebrospinal fluid of AD [114] So, not surprising is the above mentions gluten-brain cross-reactivity [8–10,78,79] and sequence homology between gluten/gliadin peptides and cephalic epitopes (Table 3). An interesting aspect is the similarity between cephalic antigens that were detected by both technics, namely, cross-reactivity and sequence homology in relation with wheat/gluten/gliadin components. Neuropsychiatric antibodies against alpha enolase and GAD65 cross-reacted and had sequence similarity with wheat and gliadin, respectively [10,65,78,79]. More so, anti amyloid-beta peptides and anti alpha synuclein antibodies exist in AD and PD [84] and both had sequence homology with gluten/gliadin peptides (Table 3). Anti Purkinje cells and alpha-synuclein antibodies cross-react with gliadin/wheat [8]. (Vojdani Aristo, personal communication), alpha synuclein accumulates in Purkinje cells in Lewy body [115] and have sequence homology with gliadin peptides (Table 3). Anti wheat antibodies reacted against dopamin receptors [10,79]. Despite the present lack of sequence homology between gliadin and dopamin receptors, gluten is the major protein in wheat and it is possible that the anti wheat antibodies contain anti gluten antibodies that cross react with the dopamin receptor. Since dopamin loss is a pivotal aspect in PD pathophysiology, one wonders if this cross reactivity might affect dopamin receptors functionality in PD. Based on the above, it is hypothesized that exploring the combined cross reactive antibodies and structure similarity between brain epitopes and gluten/gliadin peptide might shade novel aspects in human neurodegenerative conditions.

An additional interesting pathway by which gluten might affect the brain was summarized by Bressan and Kramer, 2016. It appears that gluten can generate exorphines, as shown in animal models [116]. Intriguingly, the gluten originated opioids have higher activity compared to those from casein and many Western societies consume as much as 50 g of gluten, daily [15]. The bad side of those exorphins, when reaching their brain receptors, is their behavioral effects as shown in autism, schizophrenia and psychosis [65].
Decrease social interaction, reduced pain sensitivity, uncontrolled motor activity, disruptive
effects on visual and auditory performances were described in mental illnesses as well
as in neurodegenerative conditions [65]. The case report illustrating the life-changing
amelioration, as achieved by gluten withdrawal in a patient with neuropsychiatric disorder
having long term auditory and visual hallucinations, is very intriguing [117]. Finally, some
cognitive impairment and “brain fog” associated with gluten-dependent diseases, may
respond to gluten elimination [63,118].

If the gluten involvement in neurodegenerative process evolvement is substantiated,
a more practical question will be: Will GFD be a novel nutritional therapeutic strategy in
preventing or suppressing those conditions? Since adhering to GFD is a tough ally [54,119],
several alternative ways to decrease gluten-brain exposure might be envisioned. GF-
Mediterranean diet [120], might be very rewarding as Mediterranean diet adherence
significantly correlated with 8.4 years of later onset of PD [121]. The dysbiosis in CD and
the gluten degrading microbial enzyme (glutenase) capacity might suggest probiotic
and lactobacilli enhancing prebiotic therapies [122]. Multiple microbial, fungi and plant
proteases were suggested to digest the luminal gluten [123], but it seems that they are not
efficient for complete remove of the detrimental gluten peptides, but can help as supple-
mental therapies. Since one of the drawbacks of GFD is its deficiency in fiber [55] and
indigestible polysaccharides are a major nutritional source for the healthy microbiome, pre-
biotics can boost a normal protective flora. Various functional food supplements, recently
summarized by Chander et al., 2018, might decrease gluten exposure. Nutraceuticals are
beneficial for PD and AD [93,94,124] and can potentially prevent or treat intestinal barrier
dysfunctions and decrease intestinal permeability, thus counteracting the gluten effects
on the tight junction functional integrity [12,13,16,45,52,53]. Since tTG and microbial TG
can turn naïve gluten peptide to immunogenic molecules [38,39], their specific inhibitors
might decrease the cross-linked gluten peptide load on the brain [62,125]. Due to their
involvement, transglutaminases were suggested as a therapeutic target for AD [126,127] as
well as for PD [128], both aiming to suppress their cross-linked substrate, including gluten
peptides, that are rich in proline and glutamine sites [38,39,56–62]. The harmful effects of
industrial processed food, a hallmark of the Western diet, on the gut eco-events and its
pro-inflammatory and pro-oxidative, favoring the development of neurodegenerative dis-
eases were recently summarized [129]. Notably, microbial transglutaminase and its gluten
peptides preferred substrates are frequently used as food additives [12,38,39]. The resulting
cross-linked gluten complexes were recently suggested as potential driver of autoimmunity,
not sparing neurodegenerative conditions [56–62]. Moreover, a trans-enterocytic transport of
gliadin and microbial transglutaminase [42] and anti-gluten cross-linked systemic antibodies
were recently reported [130,131]. Avoiding process nutrients might decrease the gluten load
and diminish its enzymatic cross-linking effects on the human brain. In addition, based on
the above, avoiding gluten–brain cross-reactive nutrients and abstaining from gluten–brain
sequence similar proteins to minimize molecular mimicry is suggested to be explored in
the future.

12. Conclusions

It is concluded that Hippocrates was holistically right. Gluten already existed in 400 BC
and even much earlier, but sometimes the food is not “thy medicine”, nor the solution.
Gluten might be a potential detrimental nutrient in neurodegenerative diseases evolvement.
Circulating systemically, being localized in the brain and being a prime substrate for
tissue and microbial transglutaminases posttranslational modifications, gluten/gluten
peptides should be thoroughly investigated for their pathophysiology in neurodegenerative
conditions. The anti-gluten antibodies cross-reactivity and the numerous epitope sequence
homologies with CNS peptides direct to the possible pathophysiological pathway of
molecular mimicry, operating in neurodegenerative diseases. Figure 2 summarizes the
gluten–brain relationship that might operate in neurodegenerative diseases. The quote
from Matthew 6:11, 13: “Give us this day our daily bread ( . . . .) but deliver us from evil”
might be actual in the frame of gluten induced neurodegeneration and mental illness [65]. The gluten–brain degeneration axis exploration is only in its infancy and deserves extensive research exploration. If substantiated, it could represent a new therapeutic strategy for neurodegenerative conditions.

Figure 2. Ingested gluten and gliadin’s peptides cross talks with brain epitopes in neurodegenerative diseases. (A) Wheat reach gluten is ingested and digested to gliadin peptides. (B) By deamidation and cross-linking, luminal and mucosal tissue and microbial transglutaminases post translate those peptides to immunogenic molecules. (C) In parallel, gluten affects the microbiome/dysbiome ratio, resulting in proinflammatory metabolome and harmful microbial constituents. (D) This mobilome finds its way, trans- or inter-enterocytically, through the failed tight junction to end up sub-epithelially. (E) In addition, the sensing epithelial and subepithelial cells are activated and deliver signals to the adjacent local or systemic blood, lymphatic and neuronal networks (E,F), respectively. (G) Finally brain neuroinflammatory and neurodegenerative processes are affected.
Author Contributions: A.L. and C.B. designed the study and screened the literature, carried out, and wrote this study. The two authors contributed to the article and approved the submitted version. All authors have read and agreed to the published version of the manuscript.

Funding: Not funded nor grant or institutional supported.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Acknowledgments: The author thanks Vered Raanan for the English revision of the manuscript. The figures were created with BioRender.com (accessed on 19 March 2021).

Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

Abbreviations
tTG-tissue transglutaminase; CD-celiac disease; GFD-gluten-free diet. PD-Parkinson’s disease; AD-Alzheimer’s disease; MS-multiple sclerosis; CNS-central nervous system; GAD-Glutamic acid decarboxylase.

References
1. Konjevod, M.; Nikolac Perkovic, M.; Sáiz, J.; Svob Strac, D.; Barbas, C.; Rojo, D. Metabolomics Analysis of Microbiota-Gut-Brain Axis in Neurodegenerative and Psychiatric Disorders. J. Pharm. Biomed. Anal. 2021, 194, 113681. [CrossRef]
2. Ghaisas, S.; Maher, J.; Kanthasamy, A. Gut Microbiome in Health and Disease: Linking the Microbiome-Gut-Brain Axis and Environmental Factors in the Pathogenesis of Systemic and Neurodegenerative Diseases. Pharmacol. Ther. 2016, 158, 52–62. [CrossRef]
3. Hirschberg, S.; Gisevius, B.; Duscha, A.; Haghiakia, A. Implications of Diet and the Gut Microbiome in Neuroinflammatory and Neurodegenerative Diseases. Int. J. Mol. Sci. 2019, 20, 3019. [CrossRef]
4. Jiang, T.; Li, G.; Xu, J.; Gao, S.; Chen, X. The Challenge of the Pathogenesis of Parkinson’s Disease: Is Autoimmunity the Culprit? Front. Immunol. 2018, 9, 2047. [CrossRef]
5. Vojdani, A.; Kharrrazian, D.; Mukherjee, P.S. The Prevalence of Antibodies against Wheat and Milk Proteins in Blood Donors and Their Contribution to Neuroimmune Reactivities. Nutrients 2013, 6, 15–36. [CrossRef]
6. Garcia-Quintanilla, A.; Miranzo-Navarro, D. Extraintestinal Manifestations of Celiac Disease: 33-Mer Gliadin Binding to Glutamate Receptor GRINA as a New Explanation. BioEssays 2016, 38, 427–439. [CrossRef] [PubMed]
7. Yu, X.B.; Uhde, M.; Green, P.H.; Alaedini, A. Autoantibodies in the Extraintestinal Manifestations of Celiac Disease. Nutrients 2018, 10, 1123. [CrossRef] [PubMed]
8. Vojdani, A.; O’Bryan, T.; Green, J.A.; McCandless, J.; Woeller, K.N.; Vojdani, E.; Nourian, A.A.; Cooper, E.L. Immune Response to Dietary Proteins, Gliadin and Cerebellar Peptides in Children with Autism. Nutr. Neurosci. 2004, 7, 151–161. [CrossRef]
9. Alaedini, A.; Okamoto, H.; Briani, C.; Wollenberg, K.; Shill, H.A.; Bushara, K.O.; Sander, H.W.; Green, P.H.R.; Hallett, M.; Latov, N. Immune Cross-Reactivity in Celiac Disease: Anti-Gliadin Antibodies Bind to Neuronal Synapsin I. J. Immunol. 2007, 178, 6590–6595. [CrossRef] [PubMed]
10. Vojdani, A.; Gushgari, L.R.; Vojdani, E. Interaction between Food Antigens and the Immune System: Association with Autoimmune Disorders. Autoimmun. Rev. 2020, 19, 102459. [CrossRef] [PubMed]
11. Gershteyn, I.M.; Ferreira, L.M.R. Immunodietica: A Data-Driven Approach to Investigate Interactions between Diet and Autoimmune Disorders. J. Transl. Autoimmun. 2019, 1, 100003. [CrossRef]
12. Lerner, A.; Matthias, T. Changes in Intestinal Tight Junction Permeability Associated with Industrial Food Additives Explain the Rising Incidence of Autoimmune Disease. Autoimmun. Rev. 2015, 14, 479–489. [CrossRef] [PubMed]
13. Lerner, A.; Matthias, T. Gluten and Autoimmunogenesis. In Mosaic of Autoimmunity: The Novel Factors of Autoimmune Diseases, 2nd ed.; Perricone, C., Shoenfeld, Y., Eds.; Elsevier: Amsterdam, The Netherlands, 2019; pp. 315–321.
14. Sergi, C.; Villanacci, V.; Carroccio, A. Non-Celiac Wheat Sensitivity: Rationality and Irrationality of a Gluten-Free Diet in Individuals Affected with Non-Celiac Disease: A Review. BMC Gastroenterol. 2021, 21, 1–12. [CrossRef] [PubMed]
15. Sapone, A.; Bai, J.C.; Ciacci, C.; Dolinsek, J.; Green, P.H.R.; Hadjivassiliou, M.; Kaukinen, K.; Rostami, K.; Sanders, D.S.; Schumann, M.; et al. Spectrum of Gluten-Related Disorders: Consensus on New Nomenclature and Classification. BMC Med. 2012, 10, 1–12. [CrossRef] [PubMed]
16. Lerner, A.; Matthias, T.; Wusterhausen, P. Autoimmunity in Celiac Disease: Extra-Intestinal Manifestations. Autoimmun. Rev. 2019, 18, 241–246. [CrossRef]
17. Lerner, A.; Matthias, T. GUT-the Trojan Horse in Remote Organs’ Autoimmunity. J. Clin. Cell. Immunol. 2016, 7, 1–10. [CrossRef]
18. Lerner, A.; Neidhöfer, S.; Matthias, T. The Gut Microbiome Feelings of the Brain: A Perspective for Non-Microbiologists. Microorganisms 2017, 5, 66. [CrossRef]
19. Lebwohl, B.; Rubio-Tapia, A. Epidemiology, Presentation, and Diagnosis of Celiac Disease. *Gastroenterology* 2021, 160, 63–75. [CrossRef]

20. Mohan, M.; Okeoma, C.M.; Sestak, K. Dietary Gluten and Neurodegeneration: A Case for Preclinical Studies. *Int. J. Mol. Sci.* 2020, 21, 5407. [CrossRef]

21. Trovato, C.M.; Raucci, U.; Valitutti, F.; Montuori, M.; Villa, M.P.; Cucciara, S.; Parisi, P. Neuropsychiatric Manifestations in Celiac Disease. *Epilepsy Behav.* 2019, 99, 106393. [CrossRef] [PubMed]

22. Wills, A.J.; Turner, B.; Lock, R.J.; Johnston, S.L.; Unsworth, D.J.; Fry, L. Dermatitis Herpetiformis and Neurological Dysfunction. *J. Neurol. Neurosurg. Psychiatry* 2002, 72, 259–261. [CrossRef] [PubMed]

23. Ortiz, C.; Valenzuela, R.; Lucero Alvarez, Y. Celiac Disease, Non Celiac Gluten Sensitivity and Wheat Allergy: Comparison of 3 Different Diseases Triggered by the Same Food. *Rev. Chil. Pediatr.* 2017, 88, 417–423. [CrossRef]

24. Slim, M.; Rico-Villademoros, F.; Calandre, E.P. Psychiatric Comorbidity in Children and Adults with Gluten-Related Disorders: A Narrative Review. *Nutrients* 2018, 10, 675. [CrossRef] [PubMed]

25. Zelnik, N.; Pacht, A.; Obeid, R.; Lerner, A. Range of Neurologic Disorders in Patients with Celiac Disease. *Pediatrics* 2004, 113, 1672–1676. [CrossRef] [PubMed]

26. Lerner, A.; Makhouli, B.F.; Eliakim, R. Neurological Manifestations of Celiac Disease in Children and Adults Affiliations Celiac Disease and Environmental View Project Neurological Manifestations of Celiac Disease in Children and Adults. *Eur. Neurol. J.* 2012, 4, 15–20.

27. Jackson, J.R.; Eaton, W.W.; Cascella, N.G.; Fasano, A.; Kelly, D.L. Neurologic and Psychiatric Manifestations of Celiac Disease and Gluten Sensitivity. *Psychiatr. Q.* 2012, 83, 91–102. [CrossRef] [PubMed]

28. Rouvroye, M.D.; Zis, P.; Van Dam, A.M.; Rozemuller, A.J.M.; Bouna, G.; Hadjivassiliou, M. The Neuropathology of Gluten-Related Neurological Disorders: A Systematic Review. *Neuropathol. Neurobiol.* 2020, 12, 822. [CrossRef]

29. Vinagre-Aragón, A.; Zis, P.; Grunevald, R.; Hadjivassiliou, M. Movement Disorders Related to Gluten Sensitivity: A Systematic Review. *Neuropathol. Neurobiol.* 2018, 10, 1034. [CrossRef]

30. Losurdo, G.; Principi, M.; Iannone, A.; Amoruso, A.; Ierardi, E.; DiLeo, A.; Barone, M. Extra-Intestinal Manifestations of Non-Celiac Gluten Sensitivity: An Expanding Paradigm. *World J. Gastroenterol.* 2018, 24, 1521–1530. [CrossRef]

31. Lerner, A.; Jeremias, P.; Matthias, T. The World Incidence and Prevalence of Autoimmune Diseases Is Increasing. *Int. J. Celiac Dis.* 2015, 3, 151–155. [CrossRef]

32. Hirsch, L.; Jette, N.; Frolkis, A.; Steeves, T.; Pringsheim, T. The Incidence of Parkinson’s Disease: A Systematic Review and Meta-Analysis. *Neuroepidemiology* 2016, 46, 292–300. [CrossRef] [PubMed]

33. Niu, H.; Álvarez-Alvarez, I.; Guíllén-Grima, F. Prevalence and Incidence of Alzheimer’s Disease in Europe: A Meta-Analysis. *Neurologia* 2017, 32, 523–532. [CrossRef] [PubMed]

34. Lerner, A.; Jeremias, P.; Matthias, T. The world incidence of celiac disease is increasing: A review. *Int. J. Recent Sci. Res.* 2015, 6, 5491–5496.

35. Lerner, A.; Neidhöfer, S.; Matthias, T. Transglutaminase 2 and Anti Transglutaminase 2 Autoantibodies in Celiac Disease and Beyond: TG2 Double-Edged Sword: Gut and Extraintestinal Involvement. *Immunome Res.* 2015, 11, 1–4. [CrossRef]

36. Schrödl, D.; Kahlenberg, F.; Peter-Zimmer, K.; Hermann, W.; Kühn, H.J.; Mothes, T. Intrathecal Synthesis of Autoantibodies against Tissue Transglutaminase. *J. Autoimmun.* 2004, 23, 335–340. [CrossRef]

37. Min, B.; Chung, K.C. New Insight into Transglutaminase 2 and Link to Neurodegenerative Diseases. *BMB Rep.* 2018, 51, 5–13. [CrossRef] [PubMed]

38. Lerner, A.; Aminov, R.; Matthias, T. Dysbiosis May Trigger Autoimmune Diseases via Inappropriate Post-Translational Modification of Host Proteins. *Front. Microbiol.* 2017, 8, 74. [CrossRef]

39. Lerner, A.; Aminov, R.; Matthias, T. Transglutaminases in Dysbiosis as Potential Environmental Drivers of Autoimmunity. *Front. Microbiol.* 2017, 8, 66. [CrossRef]

40. Severance, E.G.; Gressitt, K.L.; Halling, M.; Stallings, C.R.; Origoni, A.E.; Vaughan, C.; Khushalani, S.; Aledini, A.; Dupont, D.; Dickerson, F.B.; et al. Complement C1q Formation of Immune Complexes with Milk Caseins and Wheat Glutens in Schizophrenia. *J. Pediatr. Gastroenterol. Nutr.* 2012, 54, 205. [CrossRef] [PubMed]

41. Costa, A.F.; Sugai, E.; De La Paz Temprano, M.; Niveloni, S.I.; Vázquez, H.; Moreno, M.L.; Smeucul, E.; Stefanoi, J.P.; González, A.F.; Mauriño, E.; et al. Gluten Immunogenic Peptide Excretion Detects Dietary Transgressions in Treated Celiac Disease Patients. *World J. Gastroenterol.* 2019, 25, 1409–1420. [CrossRef]

42. Stricker, S.; de Lafolie, J.; Rudloff, S.; Komorowski, L.; Zimmer, K.-P. Intracellular Localization of Microbial Transglutaminase and Its Influence on the Transport of Gliadin in Enterocytes. *J. Pediatr. Gastroenterol. Nutr.* 2019, 68, e43–e50. [CrossRef]

43. Rudzki, L.; Szulc, A. “Immune Gate” of Psychopathology-The Role of Gut Derived Immune Activation in Major Psychiatric Disorders. *Front. Psychiatry* 2018, 9, 205. [CrossRef]

44. Diamond, B.; Honig, G.; Mader, S.; Brimberg, L.; Volpe, B.T. Brain-Reactive Antibodies and Disease. *Annu. Rev. Immunol.* 2013, 31, 345–385. [CrossRef]

45. Lerner, A.; Shoenfeld, Y; Matthias, T. Adverse Effects of Gluten Ingestion and Advantages of Gluten Withdrawal in Nonceliac Autoimmune Disease. *Nutr. Res.* 2017, 75, 1046–1058. [CrossRef] [PubMed]
46. Hollon, J.; Puppa, E.L.; Greenwald, B.; Goldberg, E.; Guererro, A.; Fasano, A. Effect of Gliadin on Permeability of Intestinal Biopsy Explants from Celiac Disease Patients and Patients with Non-Celiac Gluten Sensitivity. *Nutrients* 2015, 7, 1565–1576. [CrossRef] [PubMed]

47. Smecuol, E.; Sagui, E.; Niveloni, S.; Vázquez, H.; Pedreira, S.; Mazure, R.; Moreno, M.L.; Label, M.; Mauriño, E.; Fasano, A.; et al. Permeability, Zonulin Production, and Enteropathy in Dermatitis Herpetiformis. *Clin. Gastroenterol. Hepatol.* 2005, 3, 335–341. [CrossRef]

48. Di Lazzaro, V.; Capone, F.; Cammarota, G.; Di Giud, D.; Ranieri, F. Dramatic Improvement of Parkinsonian Symptoms after Gluten-Free Diet Introduction in a Patient with Silent Celiac Disease. *Int. J. Neurol.* 2018, 3, 443–445. [CrossRef] [PubMed]

49. Lerner, A.; Ramesh, A.; Matthias, T. Going Gluten Free in Non-Celiac Autoimmune Diseases: The Missing Ingredient. *Clin. Immunol.* 2019, 199, 37–43. [CrossRef]

50. Lerner, A.; Matthias, T. Gluten-Free Diet Tough Alley in Torrid Time. *Int. J. Celiac Dis.* 2017, 5, 50–55. [CrossRef]

51. De Angelis, M.; Vannini, L.; Di Cagno, R.; Cavallo, N.; Minervini, F.; Francavilla, R.; Aalberg, V.A.; Withoff, S.; Branchi, F.; Schumann, M. Intestinal Barrier Function in Gluten-Related Disorders. *Nutrients* 2019, 11, 2325. [CrossRef]

52. Sanz, Y. Microbiome and Gluten. *Ann. Nutr. Metab.* 2015, 67, 28–41. [CrossRef] [PubMed]

53. Lerner, A.; Ramesh, A.; Matthias, T. Microbial Transglutaminase: A New Potential Player in Celiac Disease. *Int. J. Clin. Med.* 2017, 389. [CrossRef]

54. Lerner, A.; Matthias, T. Microbial Transglutaminase Should Be Considered as an Environmental Inducer of Celiac Disease. *Int. J. Clin. Cases* 2019, 7, 3912–3914. [CrossRef] [PubMed]

55. Lerner, A.; Matthias, T. Don’t Forget the Exogenous Microbial Transglutaminases: It Is Immunogenic and Potentially Pathogenic in Pediatric Celiac Disease. *Front. Pediatr.* 2018, 6, 389. [CrossRef]

56. Panelli, S.; Capelli, E.; Lupo, G.F.D.; Schiepatti, A.; Betti, E.; Sauta, E.; Marini, S.; Pasi, A.; et al. Comparative Study of Salivary, Duodenal, and Fecal Microbiota Composition Across Adult Celiac Disease. *J. Clin. Med.* 2020, 9, 1109. [CrossRef]

57. De Angelis, M.; Vannini, L.; Di Cagno, R.; Minervini, F.; Francavilla, R.; Ercolini, D.; Gobetti, M. Salivary and Fecal Microbiota and Metabolome of Celiac Children under Gluten-Free Diet. *Int. J. Food Microbiol.* 2016, 239, 125–132. [CrossRef]

58. Lerner, A.; Matthias, T. Are Non-Celiac Autoimmune Diseases Responsive to Gluten-Free Diet? *Int. J. Celiac Dis.* 2017, 5, 164–167. [CrossRef]

59. Lerner, A.; Ramesh, A.; Matthias, T. Microbial Transglutaminase Is Beneficial to Food Industries but a Caveat to Public Health. *Nutrients Rev.* 2017, 38, 873–875. [CrossRef]

60. Lerner, A.; Matthias, T. Processed Food Additive Microbial Transglutaminase and Its Cross-Linked Gliadin Complexes Are Potential Public Health Concerns in Celiac Disease. *Clin. Immunol.* 2020, 21, 1127. [CrossRef] [PubMed]

61. Panelli, S.; Capelli, E.; Lupo, G.F.D.; Schiepatti, A.; Betti, E.; Sauta, E.; Marini, S.; Pasi, A.; et al. Comparative Study of Salivary, Duodenal, and Fecal Microbiota Composition Across Adult Celiac Disease. *J. Clin. Med.* 2020, 9, 1109. [CrossRef]

62. De Angelis, M.; Vannini, L.; Di Cagno, R.; MAV; Minervini, F.; Francavilla, R.; Ercolini, D.; Gobetti, M. Salivary and Fecal Microbiota and Metabolome of Celiac Children under Gluten-Free Diet. *Int. J. Food Microbiol.* 2016, 239, 125–132. [CrossRef]

63. Makhlouf, S.; Messelmani, M.; Zaouali, J.; Mrissa, R. Cognitive Impairment in Celiac Disease and Non-Celiac Gluten Sensitivity: Review of Literature on the Main Cognitive Impairments, the Imaging and the Effect of Gluten Free Diet. *Acta Neurol. Belg.* 2018, 118, 21–27. [CrossRef] [PubMed]

64. Hollon, J.; Puppa, E.L.; Greenwald, B.; Goldberg, E.; Guererro, A.; Fasano, A. Effect of Gliadin on Permeability of Intestinal Biopsy Explants from Celiac Disease Patients and Patients with Non-Celiac Gluten Sensitivity. *Nutrients* 2015, 7, 1565–1576. [CrossRef] [PubMed]

65. Bressan, P.; Kramer, P. Bread and Other Edible Agents of Mental Disease. *Front. Hum. Neurosci.* 2016, 10, 1–11. [CrossRef]

66. Pynnönen, P.A.; Isometsä, E.T.; Verkasalo, M.A.; Kähkönen, S.A.; Sipilä, I.; Savilahti, E.; Aalberg, V.A. Gluten-Free Diet May Alleviate Depressive and Behavioural Symptoms in Adolescents with Celiac Disease: A Prospective Follow-up Case-Series Study. *BMC Psychiatry* 2005, 5, 1–6. [CrossRef]

67. Liberto, D.D.; D’anneo, A.; Carlisi, D.; Emanuele, S.; De Blasio, A.; Calvaruso, G.; Giuliani, M.; Lauricella, M. Brain Sciences Review Brain Opioid Activity and Oxidative Injury: Different Molecular Scenarios Connecting Celiac Disease and Autistic Spectrum Disorder. *Brain Sci.* 2020, 10, 437. [CrossRef]

68. Serratrice, J.; Disdier, P.; Kaladjian, A.; Garel, B.; Azorin, J.M.; Laugier, P.; Berenguer, M.; Weillier, P.J. Psychose Révélatrice Une Maladie Coeliaque Silencieuse Chez Une Jeune Femme Ayant Une Trisomie 21. *Press. Med.* 2002, 31, 1551–1553.

69. Rodríguez, I.; Hernández-Lahoz, C.; Fuentes, D.; Mauri, G.; Álvarez, N.; Vega, J.; González, S. Randomised Clinical Trial Comparing the Efficacy of A Gluten-Free Diet Versus A Regular Diet in A Series of Relapsing-Remitting Multiple Sclerosis Patients. *Int. J. Neurol. Neurother.* 2014, 1, 1–6.

70. Bellastella, G.; Maiorino, M.I.; Cirillo, P.; Longo, M.; Pernice, V.; Costa, N.; Bellastella, A.; Esposito, K.; De Bellis, A. Remission of Pituitary Autoimmunity Induced by Gluten-Free Diet in Patients With Celiac Disease. *Clin. Endocrinol. Metab.* 2020, 105, 2252–2261. [CrossRef] [PubMed]

71. Hadjivassiliou, M.; Grünewald, R.A.; Sanders, D.S.; Shanmugarajah, P.; Hoggard, N. Effect of Gluten-Free Diet on Cerebellar MR Spectroscopy in Gluten Ataxia. *Neurology* 2017, 89, 705–709. [CrossRef] [PubMed]

72. Holmberg, J.; Pereira, R.M.R.; De Carvalho, J.F. Uveitis in Celiac Disease with an Excellent Response to Gluten-Free Diet: Third Case Described. *Rheumatol. Int.* 2011, 31, 399–402. [CrossRef]
101. Prabakaran, S.; Swatton, J.E.; Ryan, M.M.; Huffaker, S.J.; Huang, J.T.J.; Griffin, J.L.; Wayland, M.; Freeman, T.; Dudbridge, F.; Lilley, K.S.; et al. Mitochondrial Dysfunction in Schizophrenia: Evidence for Compromised Brain Metabolism and Oxidative Stress. *Mol. Psychiatry* 2004, 9, 684–697. [CrossRef] [PubMed]

102. Przybylska-Feluś, M.; Platek-Guziewicz, A.; Dynowski, W.; Zwaliriska-Wcislo, M.; Rozpondek, P.; Mach, T. Antibodies against Alfa-Enolase as an Indication of Inflammatory Process in Patients with Celiac Disease—Preliminary Results. *Przegląd Lek.* 2014, 71, 254–257.

103. Hecker, M.; Fitzner, B.; Wendt, M.; Lorenz, P.; Flechtner, K.; Steinbeck, F.; Schröder, I.; Thiessen, H.J.; Zettl, U.K. High-Density Peptide Microarray Analysis of IgG Autoantibody Reactivities in Serum and Cerebrospinal Fluid of Multiple Sclerosis Patients. *Mol. Cell. Proteom.* 2016, 15, 1360–1380. [CrossRef] [PubMed]

104. Sugahara, T.; Nakajima, H.; Shirahata, S.; Murakami, H. Purification and Characterization of Immunoglobulin Production Stimulating Factor-II Derived from Namalwa Cells. *Cyto technology* 1992, 10, 137–146. [CrossRef]

105. Huang, H.; Tang, S.; Ji, M.; Tang, Z.; Shimada, M.; Liu, X.; Qi, S.; Locasale, J.W.; Roeder, R.G.; Zhao, Y.; et al. EP300-Mediated Lysine 2-Hydroxysobutyrylation Regulates Glycolysis. *Mol. Cell 2018*, 70, 663–678.e6. [CrossRef]

106. De Virgilio, A.; Greco, A.; Fabbrini, G.; Inghilleri, M.; Rizzo, M.I.; Gallo, A.; Conte, M.; Rosato, C.; Cinciglio Appiani, M.; de Vincentis, M. Parkinson’s Disease: Autoimmunity and Neuroinflammation. *Autoimmun. Rev.* 2016, 15, 1005–1011. [CrossRef]

107. De Virgilio, A.; Greco, A.; Fabbrini, G.; Inghilleri, M.; Rizzo, M.I.; Gallo, A.; Conte, M.; Rosato, C.; Cinciglio Appiani, M.; de Vincentis, M. Parkinson’s Disease: Autoimmunity and Neuroinflammation. *Autoimmun. Rev.* 2016, 15, 1005–1011. [CrossRef]

108. De Virgilio, A.; Greco, A.; Fabbrini, G.; Inghilleri, M.; Rizzo, M.I.; Gallo, A.; Conte, M.; Rosato, C.; Cinciglio Appiani, M.; de Vincentis, M. Parkinson’s Disease: Autoimmunity and Neuroinflammation. *Autoimmun. Rev.* 2016, 15, 1005–1011. [CrossRef]

109. De Virgilio, A.; Greco, A.; Fabbrini, G.; Inghilleri, M.; Rizzo, M.I.; Gallo, A.; Conte, M.; Rosato, C.; Cinciglio Appiani, M.; de Vincentis, M. Parkinson’s Disease: Autoimmunity and Neuroinflammation. *Autoimmun. Rev.* 2016, 15, 1005–1011. [CrossRef]

110. De Virgilio, A.; Greco, A.; Fabbrini, G.; Inghilleri, M.; Rizzo, M.I.; Gallo, A.; Conte, M.; Rosato, C.; Cinciglio Appiani, M.; de Vincentis, M. Parkinson’s Disease: Autoimmunity and Neuroinflammation. *Autoimmun. Rev.* 2016, 15, 1005–1011. [CrossRef]

111. De Virgilio, A.; Greco, A.; Fabbrini, G.; Inghilleri, M.; Rizzo, M.I.; Gallo, A.; Conte, M.; Rosato, C.; Cinciglio Appiani, M.; de Vincentis, M. Parkinson’s Disease: Autoimmunity and Neuroinflammation. *Autoimmun. Rev.* 2016, 15, 1005–1011. [CrossRef]

112. De Virgilio, A.; Greco, A.; Fabbrini, G.; Inghilleri, M.; Rizzo, M.I.; Gallo, A.; Conte, M.; Rosato, C.; Cinciglio Appiani, M.; de Vincentis, M. Parkinson’s Disease: Autoimmunity and Neuroinflammation. *Autoimmun. Rev.* 2016, 15, 1005–1011. [CrossRef]

113. De Virgilio, A.; Greco, A.; Fabbrini, G.; Inghilleri, M.; Rizzo, M.I.; Gallo, A.; Conte, M.; Rosato, C.; Cinciglio Appiani, M.; de Vincentis, M. Parkinson’s Disease: Autoimmunity and Neuroinflammation. *Autoimmun. Rev.* 2016, 15, 1005–1011. [CrossRef]

114. De Virgilio, A.; Greco, A.; Fabbrini, G.; Inghilleri, M.; Rizzo, M.I.; Gallo, A.; Conte, M.; Rosato, C.; Cinciglio Appiani, M.; de Vincentis, M. Parkinson’s Disease: Autoimmunity and Neuroinflammation. *Autoimmun. Rev.* 2016, 15, 1005–1011. [CrossRef]

115. De Virgilio, A.; Greco, A.; Fabbrini, G.; Inghilleri, M.; Rizzo, M.I.; Gallo, A.; Conte, M.; Rosato, C.; Cinciglio Appiani, M.; de Vincentis, M. Parkinson’s Disease: Autoimmunity and Neuroinflammation. *Autoimmun. Rev.* 2016, 15, 1005–1011. [CrossRef]

116. De Virgilio, A.; Greco, A.; Fabbrini, G.; Inghilleri, M.; Rizzo, M.I.; Gallo, A.; Conte, M.; Rosato, C.; Cinciglio Appiani, M.; de Vincentis, M. Parkinson’s Disease: Autoimmunity and Neuroinflammation. *Autoimmun. Rev.* 2016, 15, 1005–1011. [CrossRef]

117. De Virgilio, A.; Greco, A.; Fabbrini, G.; Inghilleri, M.; Rizzo, M.I.; Gallo, A.; Conte, M.; Rosato, C.; Cinciglio Appiani, M.; de Vincentis, M. Parkinson’s Disease: Autoimmunity and Neuroinflammation. *Autoimmun. Rev.* 2016, 15, 1005–1011. [CrossRef]

118. De Virgilio, A.; Greco, A.; Fabbrini, G.; Inghilleri, M.; Rizzo, M.I.; Gallo, A.; Conte, M.; Rosato, C.; Cinciglio Appiani, M.; de Vincentis, M. Parkinson’s Disease: Autoimmunity and Neuroinflammation. *Autoimmun. Rev.* 2016, 15, 1005–1011. [CrossRef]

119. De Virgilio, A.; Greco, A.; Fabbrini, G.; Inghilleri, M.; Rizzo, M.I.; Gallo, A.; Conte, M.; Rosato, C.; Cinciglio Appiani, M.; de Vincentis, M. Parkinson’s Disease: Autoimmunity and Neuroinflammation. *Autoimmun. Rev.* 2016, 15, 1005–1011. [CrossRef]

120. De Virgilio, A.; Greco, A.; Fabbrini, G.; Inghilleri, M.; Rizzo, M.I.; Gallo, A.; Conte, M.; Rosato, C.; Cinciglio Appiani, M.; de Vincentis, M. Parkinson’s Disease: Autoimmunity and Neuroinflammation. *Autoimmun. Rev.* 2016, 15, 1005–1011. [CrossRef]

121. De Virgilio, A.; Greco, A.; Fabbrini, G.; Inghilleri, M.; Rizzo, M.I.; Gallo, A.; Conte, M.; Rosato, C.; Cinciglio Appiani, M.; de Vincentis, M. Parkinson’s Disease: Autoimmunity and Neuroinflammation. *Autoimmun. Rev.* 2016, 15, 1005–1011. [CrossRef]

122. De Virgilio, A.; Greco, A.; Fabbrini, G.; Inghilleri, M.; Rizzo, M.I.; Gallo, A.; Conte, M.; Rosato, C.; Cinciglio Appiani, M.; de Vincentis, M. Parkinson’s Disease: Autoimmunity and Neuroinflammation. *Autoimmun. Rev.* 2016, 15, 1005–1011. [CrossRef]

123. De Virgilio, A.; Greco, A.; Fabbrini, G.; Inghilleri, M.; Rizzo, M.I.; Gallo, A.; Conte, M.; Rosato, C.; Cinciglio Appiani, M.; de Vincentis, M. Parkinson’s Disease: Autoimmunity and Neuroinflammation. *Autoimmun. Rev.* 2016, 15, 1005–1011. [CrossRef]

124. De Virgilio, A.; Greco, A.; Fabbrini, G.; Inghilleri, M.; Rizzo, M.I.; Gallo, A.; Conte, M.; Rosato, C.; Cinciglio Appiani, M.; de Vincentis, M. Parkinson’s Disease: Autoimmunity and Neuroinflammation. *Autoimmun. Rev.* 2016, 15, 1005–1011. [CrossRef]

125. De Virgilio, A.; Greco, A.; Fabbrini, G.; Inghilleri, M.; Rizzo, M.I.; Gallo, A.; Conte, M.; Rosato, C.; Cinciglio Appiani, M.; de Vincentis, M. Parkinson’s Disease: Autoimmunity and Neuroinflammation. *Autoimmun. Rev.* 2016, 15, 1005–1011. [CrossRef]
126. Wilhelmus, M.M.M.; De Jager, M.; Bakker, E.N.T.P.; Drukarch, B. Tissue Transglutaminase in Alzheimer’s Disease: Involvement in Pathogenesis and Its Potential as a Therapeutic Target. *J. Alzheimers Dis.* **2014**, *42*, S289–S303. [CrossRef] [PubMed]

127. Wilhelmus, M.M.M.; De Jager, M.; Smit, A.B.; Van Der Loo, R.J.; Drukarch, B. Catalytically Active Tissue Transglutaminase Colocalises with Aβ Pathology in Alzheimer’s Disease Mouse Models. *Sci. Rep.* **2016**, *6*, 1–12. [CrossRef]

128. Junn, E.; Ronchetti, R.D.; Quezado, M.M.; Kim, S.Y.; Mouradian, M.M. Tissue Transglutaminase-Induced Aggregation of α-Synuclein: Implications for Lewy Body Formation in Parkinson’s Disease and Dementia with Lewy Bodies. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 2047–2052. [CrossRef]

129. Martínez Leo, E.E.; Segura Campos, M.R. Effect of Ultra-Processed Diet on Gut Microbiota and Thus Its Role in Neurodegenerative Diseases. *Nutrition* **2020**, *71*, 110609. [CrossRef]

130. Lerner, A.; Jeremias, P.; Neidhöfer, S.; Matthias, T. Comparison of the Reliability of 17 Celiac Disease Associated Bio-Markers to Reflect Intestinal Damage. *J. Clin. Cell Immunol.* **2017**, *8*, 486. [CrossRef]

131. Agardh, D.; Matthias, T.; Wusterhausen, P.; Neidhöfer, S.; Heller, A.; Lerner, A. Antibodies against Neo-Epitope of Microbial and Human Transglutaminase Complexes as Biomarkers of Childhood Celiac Disease. *Clin. Exp. Immunol.* **2020**, *199*, 294–302. [CrossRef] [PubMed]