The neurology of coeliac disease in childhood: what is the evidence? A systematic review and meta-analysis

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LIST OF ABBREVIATIONS

AGA	Anti-gliadin antibody
GFD	Gluten-free diet
Ig	Immunoglobulin
I	Incosistency
OR	Odds ratio
RD	Risk difference
RR	Relative risk

AIM The aim of this article was to review and conduct a meta-analysis of the paediatric literature on the neurology of coeliac disease.
METHOD We conducted a review of paediatric studies published in English assessing neurological illness in coeliac disease identified through a MEDLINE search (1950–2009). Calculation of computed relative risk, odds ratio, and risk difference was performed using the fixed effect method if applicable.
RESULTS Fifteen studies were analysed (11 772 participants). The meta-analysis showed that (1) the relative risk of epilepsy in individuals with coeliac disease, and of coeliac disease in individuals with epilepsy, compared with the general population, was 2.1 and 1.7, respectively, and the risk difference was close to zero, indicating that it was probably a chance association; and (2) the relative risk of headache in individuals with the disease compared with comparison groups was 3.2. In two studies, cerebellar ataxia was documented in 2.7 to 5.4% of participants; in two further studies, the risk of cerebellar dysfunction was zero. Two studies found an association between coeliac disease and peripheral neuropathy. Brain white matter lesions were recorded in two other studies. An association between autism and coeliac disease is disputed.
INTERPRETATION Children with coeliac disease are at risk of developing neurological complications, but the risk is lower than in adulthood. The discrepancy might be due to short disease duration, early elimination of gluten from the diet, stricter adherence to diet, or different susceptibility to immune-mediated disorders.

Coeliac disease is a chronic, immune-mediated, inflammatory disorder triggered by the ingestion of grains containing gluten by genetically susceptible individuals expressing the HLA class II molecules DQ2 or DQ8.[1] The clinical manifestations of the disease vary greatly, and range from typical gastrointestinal manifestations to absent, minimal, or unusual intestinal complaints with extraintestinal manifestations or disorders.[1]

The overall prevalence of coeliac disease varies between 0.7% and 2% in the general population, and between 0.4% and 1.3% in the childhood population.[2] In adults, among the numerous extraintestinal manifestations and/or disorders of coeliac disease, the wide spectrum of neurological and psychiatric conditions reported includes peripheral neuropathy, cerebellar ataxia, myelopathy, myopathy, brainstem encephalitis, epilepsy, headache, and autism.[3] The prevalence of neurological complications in adults with the disease has been estimated to be as high as 26%.[3] Further data suggest that antibodies associated with the disease occur in 16 to 57% of individuals with neurological dysfunction.[3]

The pathogenesis of neurological manifestations in coeliac disease is multifactorial. The disease is characterized by malabsorption, and some neurological complications may, therefore, be secondary to vitamin B_{12} deficiency (e.g. myelopathy and neuropathy), vitamin D malabsorption (e.g. myopathy), or vitamin E deficiency (e.g. cerebellar ataxia and myopathy).[3] However, neurological complications are also frequently reported in individuals without malabsorption, leading to the hypothesis that other factors may play a role in the pathogenesis of neurological defects. Emerging evidence suggests possible humoral mechanisms for both neuropathy and ataxia. Immunoglobulin (Ig) G antibody reactivity to peripheral nerve antigens has been recorded in individuals with coeliac disease and peripheral neuropathy.[4] A humoral mechanism has also been postulated for gluten ataxia. Hadjivassiliou et al.[5] detected antibodies against Purkinje cells in sera from individuals with coeliac ataxia as well as cross-reactivity between anti-gliadin antibodies and epitopes on Purkinje cells. However, other authors did not confirm these findings.[6] Whether

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these antibodies are pathogenic or only a non-specific marker is still unclear. Few evidence-based data (mostly anecdotal) are available for these issues in children, the incidence varying according to the selection criteria and the individual's characteristics. In this article we provide a meta-analysis and systematic review of the existing paediatric literature on the neurology of coeliac disease, and we try to answer the question of whether there is evidence of a causal relationship between the disease and neurological conditions.

What this paper adds

- We provide a meta-analysis and a systematic review of the paediatric literature on the neurology of coeliac disease.
- Our data shows that children with coeliac disease are at risk of developing neurological complications, but the risk is lower than in adulthood.

METHOD

Protocol

Before review and meta-analysis we developed a protocol, including eligibility criteria, search strategies, criteria for study selection, methods for extracting related data, and methods for assessing study quality and statistical methodology.

Eligibility criteria

All types of study design (e.g. cross-sectional, cohort, case–control, and case series), except case reports, were considered for inclusion in this review. Children with coeliac disease were the focus of our search. The disease was defined according to the modified criteria of the European Society for Paediatric Gastroenterology and Nutrition.[7] The prevalence of neurological disorders in children with coeliac disease and the prevalence of coeliac disease in children with neurological disorders were our primary outcome measures. Search results were limited to paediatric studies published in the English language. No publication date or publication status restrictions were imposed.

Information sources

Studies were identified by searching electronic databases and scanning reference lists of articles, and by consultation with experts in the field.

Search

This search was applied to the Medline database using PubMed by combining search terms for neurological disorders (ataxia, autism, epilepsy, febrile seizures, headache, neurology, neurological disorders, neuropathy, peripheral neuropathy, seizures, white matter lesions) with keywords for coeliac disease (coeliac disease, coeliac, gluten intolerance, gluten sensitivity). All studies described in this review were published between 1950 (start of Medline) and May 2009.

Study selection

Eligibility assessment was performed independently in an unblinded standardized manner by two reviewers (EL and MR). Disagreements between reviewers were resolved by consensus.

Data collection process

We developed a data extraction sheet (based on the Cochrane Consumers and Communication Review Group's data extraction template), pilot tested it on three randomly selected included studies, and refined it accordingly. One author (EL) extracted the data from included studies, and the second author (MR) checked the extracted data.

Data items

Information was extracted from each included study on (1) characteristics of participants, including number, age, method of diagnosis of coeliac disease, age at diagnosis, gluten-free diet (GFD), and compliance with a GFD; and (2) the presence and type of neurological disease, and its clinical, laboratory and imaging features.

Summary measures

To assess the correlations between coeliac disease and epilepsy and between the disease and headache we performed the meta-analysis by using meta package of the R system. We computed relative risks (RR), odds ratios (OR), and risk differences (RD) using the fixed-effect method. The Mantel–Haenszel inverse variance was used for pooling.[8] In the case of correlation between coeliac disease and epilepsy, the available samples did not yield a statistically significant meta-analysis, owing to the lack of comparison data and the small sample size. Therefore, to obtain a statistically significant analysis, a randomized bootstrap on comparison samples (using the known historic comparison) was applied.[9] The meta-analysis was not applied to other diseases (e.g. ataxia, neuropathy, autism, white matter lesions) as data from the literature were not sufficient.

Planned method of analysis

As a measure of heterogeneity, we computed the statistic I^2, defined as the percentage of total variance across studies attributable to heterogeneity rather than chance. Measures were computed on subsamples with low heterogeneity values ($I^2<33\%$).

Risk of bias

To ascertain the validity of the eligible studies, the study design, the size and representativeness of the study population (i.e. the presence of selection bias), the validity of outcomes (risk of confounding or bias), and the quality of the statistical analysis were taken into account. We assessed the methodological quality of included studies in accordance with the guidelines of the Cochrane Consumers and Communication Review Group, adapted for the current review concerning observational non-intervention studies. In all cases, two authors (EL and MR) independently assessed the quality of the studies included, with any disagreements resolved by discussion and consensus. Where necessary, study authors were contacted for additional information or for clarification of the study methods.

RESULTS

Study selection

Figure S1 (available online only) presents a flow diagram, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,[10] that summarizes the results of the literature search.

Study characteristics

We did not find any paediatric systematic reviews. The characteristics of the 15 studies included in the review are summarized in Table I; four were comparative observational cohort prospective studies,[11–14] two were comparative observational case–control studies,[15,16] and eight were descriptive cross-sectional studies.[17–25] The included studies involved 11 772 participants. The primary inclusion criteria entailed children (median age 10 years 6 months) with a diagnosis of coeliac disease. None of the articles reported a power calculation to determine the population size necessary to answer the research question. Because 95% confidence intervals (CIs) for prevalence of neurological disorders were not reported in any study, these were calculated by using the reported size of the study population, so as to provide valuable additional information for evaluating the validity of the reported outcomes.

All studies included were at low risk of selective reporting bias but at risk of other potential bias as a result of the specific study design used or because insufficient information to assess whether an important risk of bias existed. Three studies categorized as paediatric studies (and/or labelled as studies focusing solely on children) involved a mixed population of children, adolescents, and young adults.[15,20,23] The ages of participants ranged between 3 months and 21 years,[20] between 2 years 8 months and 24 years 2 months,[23] and between 11 years 2 months and 29 years.[15] In one investigation, the study population with neurological illness was aged from 8 to 23 years; however, these were prospective data on participants enrolled in the study during childhood.[14]

Results of individual studies

Seizures and epilepsy

Seizures and epilepsy in children with coeliac disease. The reported figures on the occurrence of febrile seizures in the context of coeliac disease display a wide range (0.3–3.6%).[14,15,24] There is no evident rationale, however, for including febrile seizures, a condition that is often monophasic, in the context of a gluten-derived disease.

Table II summarizes the paediatric studies on epilepsy in individuals with coeliac disease. In a large multicentre series of 3 969 children with the disease, the prevalence of epilepsy was as high as 1%, although this falls within the range reported for the prevalence of epilepsy in the general paediatric population (0.6–1.7%).[18] Subgroup analysis, however, revealed that the prevalence of epilepsy in classical coeliac disease was 0.79%. Among individuals with atypical coeliac disease, the prevalence was 1.6%, and among those with silent coeliac disease the prevalence was 3.5%, suggesting that the later the diagnosis of the disease is made, the longer the time of exposure to gluten and the higher the risk of developing epilepsy.[18]

In a recent population-based prospective study of 835 children with coeliac disease, only four participants (0.5%) had epilepsy, in agreement with the prevalence in the general paediatric population.[14] Similar findings were recorded by Cakir et al.,[24] who found no case of epilepsy among 27 children with coeliac disease, and by Kieslich et al.,[23] who reported one child (1.3%) with absence seizures among 75 children with the disease. Only Zelnick et al.[15] reported an increased prevalence of epilepsy in children with the coeliac disease (8/111; 7.2%) compared with healthy individuals (6/211; 2.8%). However, these authors reported the following: (1) the 'epileptic patients were not homogeneous'; (2) a 'strong association with coeliac disease probably existed' in only one 'patient with epilepsy and occipital calcifications'; and (3) the 'presence of epilepsy could be only an incidental finding'. Notably, this study included (among the 'epileptic' participants) benign febrile seizures (n=4) and a single unprovoked non-febrile seizure (n=1).

The overall calculated prevalence of non-febrile seizures in children with coeliac disease (i.e. 1%) is similar to that of the general population (i.e. 0.6–1.7%);[26] the meta-analysis shows that the RR of developing epilepsy among children with the disease is 2.1 (95% CI 1.5–2.8), the OR is 2.1 (95% CI 1.5–2.8), and the RD is 0.007 (95% CI −0.003 to 0.004; p<0.03, I^2 <33.2%).

Coeliac disease in children with seizures and epilepsy. Verd and Amat,[25] in a retrospective medical record review involving 56 participants with febrile seizures, identified five children (8.9%) who tested positive for coeliac disease autoantibodies and were confirmed as having the disease by biopsy analysis.

As summarized in Table III, several studies have evaluated the prevalence of coeliac disease in children with epilepsy. Both studies of Fois et al.[17] and Vascotto and Fois[18] found that the prevalence of the disease in children with epilepsy (0.8% and 1.1% respectively) was in agreement with the prevalence of the disease in the general population. Labate et al.[22] screened children with childhood partial epilepsy both with and without occipital paroxysms, and recorded a prevalence of the disease as high as 2.7% among those with occipital paroxysms (0% for those without occipital paroxysms). In a recent population-based prospective study[14] of children with neurological dysfunction of unknown cause (n=630) or known neurological syndromes (n=300), 6 out of 279 children with epilepsy also had coeliac disease (2.1%). Salur et al.[20] measured anti-gliadin antibody (AGA IgA and IgG) and anti-endomysial antibodies in children with epilepsy (n=69). None of the participants were positive for anti-endomysial antibodies and one participant who had villous atrophy compatible with coeliac disease was positive for AGA IgA and IgG (1.4%). Three recent prospective controlled studies have been conducted to further explore this issue; two studies[12,13] demonstrated an increased prevalence of coeliac disease among children with idiopathic epilepsy compared with healthy children (2.8% vs 0% and 0.8% vs 0%; p<0.05 respectively), and one study[11] failed to show any difference (0.8% vs 0.3%; p=0.5). Lahat et al.[21] examined the prevalence of coeliac disease in 167 children with various neurological disorders, including 36 children with epilepsy. Although they detected

Table I: Summary of included studies evaluating the neurology of coeliac disease (CD)

Source	Study design	Setting	Number of participants	Number of comparison individuals	Age	Inclusion criteria (*n*)	Outcome measures	Risk of bias[a]
Fois et al.[17]	O, CS	PNO	783	–	7y 6mo	Epilepsy	Prevalence of CD	Unclear
Vascotto and Fois[18]	O, CS	PGO	3969	–	15y 6mo	CD at diagnosis	Prevalence of epilepsy	Low
	O, CS	PNO	1210	–	9y 3.6mo	Epilepsy	Prevalence of CD	Low
Pavone et al.[19]	O, CS	PGO	120	20	9y 7.2mo	CD	Prevalence of autism	Unclear
	O, CS	PNO	11	11	6y 10.8mo	Autism	Prevalence of CD	Low
Salur et al.[20]	O, CS	PNO	206	–	8y 2.4mo	Epilepsy (69) Psychomotor delay (29) Cerebral palsy (23) Headache (21) Learning disabilities* (16) Other (48)	Prevalence of CD	Unclear
Lahat et al.[21]	O, CS	PNO	167	34	12y 6mo 9y 6mo 8y 6mo 2y 6mo	Epilepsy (36) Headache (41) Attention-deficit–hyperactivity disorder (39) Hypotonia (51)	Prevalence of CD	Low
Labate et al.[22]	O, CS	PNO	72	–	12y 7.2mo	Epilepsy	Prevalence of CD	Low
Kieslich et al.[23]	O, CS	PGO	75	–	10y 8.4mo	CD on GFD	Neurological involvement	Unclear
Pratesi et al.[11]	C, O, cohort	PNO	119	2034	7y 11.6mo	Epilepsy	Prevalence of CD	Low
Zelnik et al.[15]	C, O, case–control	PGO	111	211	20y 1.2mo	CD on GFD	Prevalence of epilepsy, ataxia, peripheral neuropathy, headache, tic, learning disabilities, hypotonia, and developmental delay	Unclear
Dalgiç et al.[12]	C, O, cohort	PNO	70	103	10y 7.2mo	Epilepsy	Prevalence of CD	Unclear
Mavroudi et al.[13]	C, O, cohort	PNO	255	280	7y 11.2mo	Epilepsy	Prevalence of CD	Low
Cakir et al.[24]	O, CS	PGO	27	–	11y 2.6mo	CD on GFD	Neurological abnormalities	Unclear
Ruggieri et al.[14]	C, O, cohort	PGO	835	300	7y 1mo	CD at diagnosis	Prevalence of:	Low
		PNO	930	300	6y 6mo	Epilepsy (180) Ataxia (10) Neuropathy (8) Headache (50) Mental retardation (100) Developmental delay (270) Neurological syndromes (300)	Epilepsy Ataxia Peripheral neuropathy Headache Prevalence of CD	Unclear
Verd and Amat[25]	O, CS	DP	56	–	1y 7.2mo	Febrile seizures	Prevalence of CD	Unclear
Lionetti et al.[16]	C, O, case–control	PGO	354	200	9y 4.8mo	CD on GFD	Prevalence of headache	Low
	C, O, cohort	PNO	79	–	9y 10.8mo	Headache	Prevalence of CD	Low

[a]Low, unclear or high risk of bias for one or more key domains. O, observational; CS, cross-sectional; PNO, paediatric neurology outpatient; PGO, paediatric gastroenterology outpatient; GFD, gluten-free diet; C, comparative; DP, Department of Paediatrics; –, data not available.
*North American usage: mental retardation.

Table II: Summary of paediatric studies on epilepsy in individuals with coeliac disease (CD)

Reference	No. of cases of CD	No. of cases of epilepsy (%)	Type of epilepsy
Vascotto and Fois[18]	3969	46 (1.1)	16 GTCS 10 CPS 8 SPS 2 CPS, SPS 5 CPS (started as GTCS) 2 absence seizures 1 SPS and myoclonic seizures 1 Hallucinatory seizures 1 Status epilepticus
Kieslich et al.[23]	75	1 (1.3)	1 Absence seizure
Zelnik et al.[15]	111	8 (7.2)	4 Febrile seizures 1 Unprovoked non-febrile seizure 3 CPS
Cakir et al.[24]	27	nil	–
Ruggieri et al.[14]	835	4 (0.5)	3 GTCS 1 Infantile spasm

GTCS, generalized tonic–clonic seizures; CPS, complex partial seizures; SPS, simple partial seizures; –, data not available.

AGA IgG in 22 of 167 children (13%) compared with 3 out of 32 children (9%) in the comparison group, no child was positive for AGA IgA or anti-endomysial antibodies, and therefore duodenal biopsies were not performed.

Overall, in children with epilepsy, the calculated prevalence of coeliac disease (i.e. 1.1%) is in agreement with that recorded in the general paediatric population (i.e. 0.4–1.3%).[2] The meta-analysis shows that the RR of the disease among children with epilepsy is 1.7 (95% CI 1.4–2.1), the OR is 2.4 (95% CI 1.8–3.2), and the RD is 0.007 (95% CI 0.004–0.01; $p<0.03$, $I^2<33.2\%$).

Based on a literature review and meta-analysis on coeliac disease we conclude that (1) most authors cluster all participants with epilepsy into one group as if epilepsy is a single disorder, despite the fact that epilepsy is widely recognized to be a heterogeneous entity with multiple underlying aetiologies; (2) despite the calculated twofold increased risk of individuals with coeliac disease developing epilepsy, and vice versa, the low RD figures indicate that is probably a chance association between two common disorders; and (3) in children with coeliac disease and epilepsy, the most frequently recorded types of seizures are in line with those reported in the general population.[26]

Coeliac disease, epilepsy and cerebral calcifications. We calculated that 7 (0.2%) of the 2893 children with epilepsy screened for coeliac disease in the studies reported so far presented with cerebral calcifications. Some authors have suggested that the well-known syndrome of coeliac disease, epilepsy, and cerebral calcifications might develop only later in life, and that early coeliac disease can manifest as epilepsy in the absence of calcifications – early identification and treatment of coeliac disease, therefore, could reverse the tendency to epilepsy and diminish the risk of developing cerebral calcifications.[12,22,27] There have been no prospective, controlled trials studying the effects of a GFD in participants with the disease who also have epilepsy.

Cerebellar ataxia ('gluten ataxia')

A few, mostly retrospective, studies have explored this issue in the paediatric age group (Table IV). Kieslich et al.[23] reported that two participants with coeliac disease on a GFD had 'mild ataxia' (2.7%), whereas Cakir et al.[24] recorded no children with the disease on a GFD with a clinical manifestation of ataxia. Zelnick et al.[15] found that six participants with ataxia also had coeliac disease (5.4%) but none of the 211 comparison individuals had ataxia. The clinical syndrome in this latter study[15] consisted of stance and gait ataxia in all participants, limb ataxia in four out of six participants, and nystagmus in three of six participants; in addition, four participants were hypotonic and two participants had sensory neuropathy. In

Table III: Summary of paediatric studies on screening for coeliac disease (CD) in individuals with epilepsy

Reference	No. of cases of epilepsy	No. of cases of CD (%)	AGA IgA+	AGA IgG+	EMA+	tTG+	Biopsy+	Type of epilepsy	Cerebral calcifications (%)
Fois et al.[17]	783	9 (1.1)	9	–	9	–	9	3 CPS 6 CPS (started as GTCS)	3 (0.4)
Vascotto and Fois[18]	1210	10 (0.8)	10	10	10	–	10	7 CPS 1 GTCS 2 CPS (started as GTCS)	3 (0.2)
Salur et al.[20]	69	1 (1.4)	1	4	Nil	–	1	Epilepsy	Nil
Lahat et al.[21]	36	Nil	Nil	7	Nil	–	Nil	–	Nil
Labate et al.[22]	72	2 (2.7)	2	–	2	–	2	2 CPEO	1 (1.4)
Pratesi et al.[11]	119	1 (0.8)	–	–	1	–	1	Lennox–Gastaut syndrome	Nil
Dalgiç et al.[12]	70	2 (2.8)	–	–	–	8	2	Epilepsy	Nil
Mavroudi et al.[13]	255	2 (0.8)	5	35	Nil	2	2	1 GTCS 1 SPS	Nil
Ruggieri et al.[14]	279	6 (2.1)	6	–	6	6	6	1 GTCS 3 CPS 2 Myoclonic seizures	Nil

AGA, anti-gliadin antibodies; IgA, immunoglobulin A; IgG, immunoglobulin G; EMA, anti-endomysial antibodies; tTG, anti-transglutaminase antibodies; CPS, complex partial seizures; GTCS, generalized tonic–clonic seizures; CPEO, idiopathic childhood partial epilepsy with occipital paroxysms; SPS, simple partial epilepsy; +, positive; –, data not available.

Table IV: Summary of paediatric studies on cerebellar ataxia in individuals with coeliac disease

Reference	No. of cases of coeliac disease	No. of cases of ataxia (%)
Kieslich et al.[23]	75	2 (2.7)
Zelnik et al.[15]	111	6 (5.4)
Cakir et al.[24]	27	Nil
Ruggieri et al.[14]	835	Nil

this study,[15] however, a mean age of 20 years 1 month (SD 8.9y) was reported, indicating that the onset of ataxia could have been in adulthood. No child exhibited cerebellar dysfunction in the prospective study of Ruggieri et al.,[14] and none of the children with ataxia of known or unknown origin screened for coeliac disease-associated antibodies had positive serology.

One possible explanation for the high prevalence of ataxia in adults with coeliac disease (i.e. 40%)[3] compared with low or null prevalence of cerebellar dysfunction in children with the disease could be its age-related effect on the nervous system, and specifically on the cerebellum. Another additional explanation could be the possible effects of the early GFD in preventing the development of ataxia. Nonetheless, it remains unclear whether coeliac disease antibodies directly contribute to the pathogenesis of the cerebellar disorder or whether they represent an epiphenomenon of another disease-causing process. Notably, there is also evidence of a higher prevalence of anti-gliadin positivity in genetic neurodegenerative disorders.[3]

Peripheral neuropathy

Very few studies have addressed the prevalence of peripheral neuropathy in childhood, and its potential association with coeliac disease (Table V). Cakir et al.[24] found that 7.4% of children with the disease on a GFD had peripheral polyneuropathy with mixed patterns of axonal motor and sensory polyneuropathy and pure sensory polyneuropathy (including children non-compliant with a GFD). Ruggieri et al.[14] reported the long-term follow-up of one female (out of 835 children with coeliac disease; 0.1%) affected by an acute, predominantly motor, demyelinating peripheral neuropathy (compared with no peripheral neuropathy in the healthy comparison group and no coeliac disease in the comparison group followed-up for peripheral neuropathy), who experienced relapses when gluten was accidentally reintroduced into her diet and whose condition remitted rapidly on institution of a GFD regimen.[28]

Brain white matter lesions

Kieslich et al.[23] used brain imaging to study individuals with coeliac disease, and they detected unilateral and bilateral focal T_2 hyperintense white matter lesions localized in the biparietal–occipital, uniparietal, frontal, and uniparieto-temporo-occipital areas in 20% of diet-treated participants with the disease. There was no correlation between the presence of the lesions and the dietary compliance or between the neurological or electroencephalographic abnormalities; however, the mean gluten exposure was slightly longer in these participants than in the magnetic resonance imaging-negative participants (not significant). These authors hypothesized that focal white matter lesions in the brain may be ischaemic in origin, either as a result of vasculitis or secondary to inflammatory demyelination. Periventricular white matter lesions were also recorded in 13.6% of children with coeliac disease with neurological dysfunction studied by Ruggieri et al.[14] (Figs S2 and S3; available online only); two were females with associated psychiatric disturbances and poor diet compliance: one presented with headache.

Focal white matter lesions in the brain may represent an extraintestinal manifestation of coeliac disease because these occur in other chronic, immune-mediated gastrointestinal diseases of childhood.[29]

Headache

In a recent series of children with coeliac disease, Lionetti et al.[16] found an increased prevalence of headaches at the time of diagnosis, a prevalence significantly higher than in comparison individuals (24.8% vs 8%; p=0.001). This figure is in agreement with the prevalence figures (i.e. 29.7%) reported by Zelnik et al.[15] in participants with the disease. Contradicting an alleged higher prevalence of headache in individuals coeliac disease are previous data[14] that report a frequency of headache among children with the disease of only 0.35%. These conflicting results may be because of different methodologies in data collection, including: (1) an earlier age at diagnosis of coeliac disease in children enrolled, who were probably unable to complain of headache; (2) different sources of information (questionnaires compared with general interview and neurological examination); and (3) multicentre hospital-based versus single centre population-based studies.

Notably, the meta-analysis applied to the available samples shows that the RR of participants with coeliac disease develop-

Table V: Summary of paediatric studies on peripheral neuropathy in individuals with coeliac disease

Reference	No. of cases of coeliac disease	No. of peripheral neuropathy cases (%)	Type of peripheral neuropathy
Cakir et al.[24]	27	2 (7.4)	Axonal sensory–motor Axonal pure sensory
Ruggieri et al.[14]	835	1 (0.1)	Demyelinating motor

ing headache is 3.2 (95% CI 2.2–4.7), the OR is 4.0 (95% CI 2.6–6.1; $p<0.001$, $I^2<27.6\%$), and the RD is 0.08 (95% CI 0.06–0.11; $p<0.001$, $I^2=99.7\%$), indicating that children with the disease may be at high risk of headache.

In the series of Lionetti et al.,[16] adherence to a GFD led to the amelioration of headache symptoms in 76.4% of children. Moreover, in the prospective part of the same study,[16] aimed at ascertaining the prevalence of coeliac disease in children with headache, it was observed that 5% of children referred to the outpatient neurological service for headaches had the disease; this prevalence was significantly higher than expected. This observed difference in prevalence corresponds to an estimated odds ratio of 7.9. Of note, Lahat et al.[21] found no participant with the disease among 41 children with headache.

Autism

The suggestion that coeliac disease might be involved in the pathogenesis of autism was based primarily on the observation of abnormal intestinal mucosa in children with autism, and this could have allowed abnormal absorption of molecules, thus provoking an immune reaction or affecting the nervous system directly.[3] Pavone et al.[19] assessed 20 healthy individuals and 120 participants with coeliac disease for behavioural problems and autistic features. The investigators also screened 11 participants with infantile autism and 11 age- and sex-matched comparison individuals. No cases of coeliac disease were detected among the group of participants with autism, and although two participants had slightly increased levels of AGA IgG and anti-endomysial antibodies, subsequent antibody determinations and jejunal biopsy specimens were normal. Moreover, none of the coeliac participants had a positive test for infantile autism (DSM-III-R).

These results appear to challenge an association between coeliac disease and autism. In addition, it must be noted that autism is a neurological disorder of early brain development, and thus a temporal correlation with gluten-derived damage is difficult to envisage.

CONCLUSIONS

A systematic survey of the literature indicates that individuals with coeliac disease have an increased risk of developing (at least some) neurological complications during childhood (e.g. headache, peripheral neuropathy, and white matter disease). The overall prevalence of neurological involvement in children is lower than in adults. Such a discrepancy may have different explanations: (1) the relatively short duration of illness in children might not be sufficient do determine nervous system involvement;[5] (2) early elimination of gluten from the diet may prevent the development of neurological manifestations; (3) strict adherence to a GFD may play a preventative role (dietary compliance is higher in childhood than in adolescence or adulthood); (4) the two populations may differ in susceptibility to immune-mediated disorders, for example children are more prone to natural autoimmune phenomena, and T cells in children with coeliac disease recognize a wider spectrum of gliadin and gluten peptides than in adults.

The main limitations of the present review are: (1) the paucity of available studies in the paediatric age group; (2) the fact that some studies labelled as purely paediatric or childhood studies analysed mixed (age) populations (e.g. extension of age limits towards adolescence and young adulthood); (3) clustering of all participants with neurological disorders into single studies; (4) clustering of heterogeneous conditions into one group as if they were single disorders (e.g. epilepsy in participants with coeliac disease); and (5) poorly defined clinical criteria for inclusion in specific neurological categories (e.g. ataxia, epilepsy, and headache).

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ONLINE MATERIAL

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