Is there a role for gluten in Multiple Sclerosis?

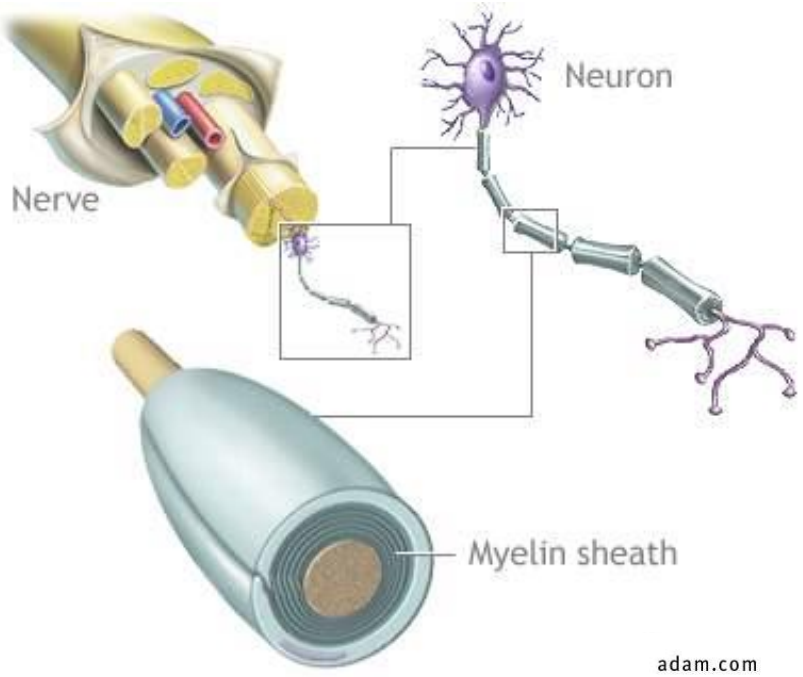
Lina Moschoula Passali

Agenda

- Introduction to Multiple Sclerosis
- The role of gluten in Multiple Sclerosis - A systematic Review
  - Background & Aim
  - Methodology
  - Results
  - Conclusions and Perspectives
- Our work with gluten-free dieting in Multiple Sclerosis
- Questions

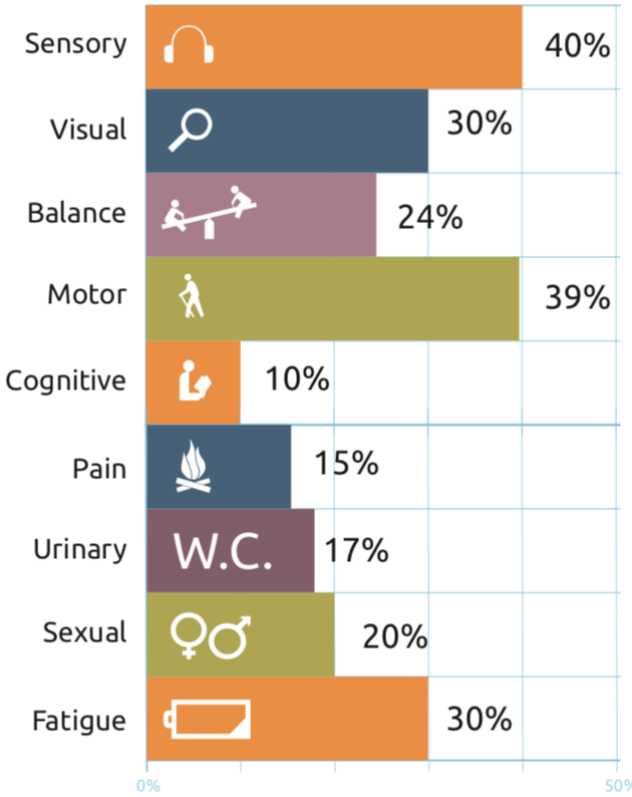
What is Multiple Sclerosis?

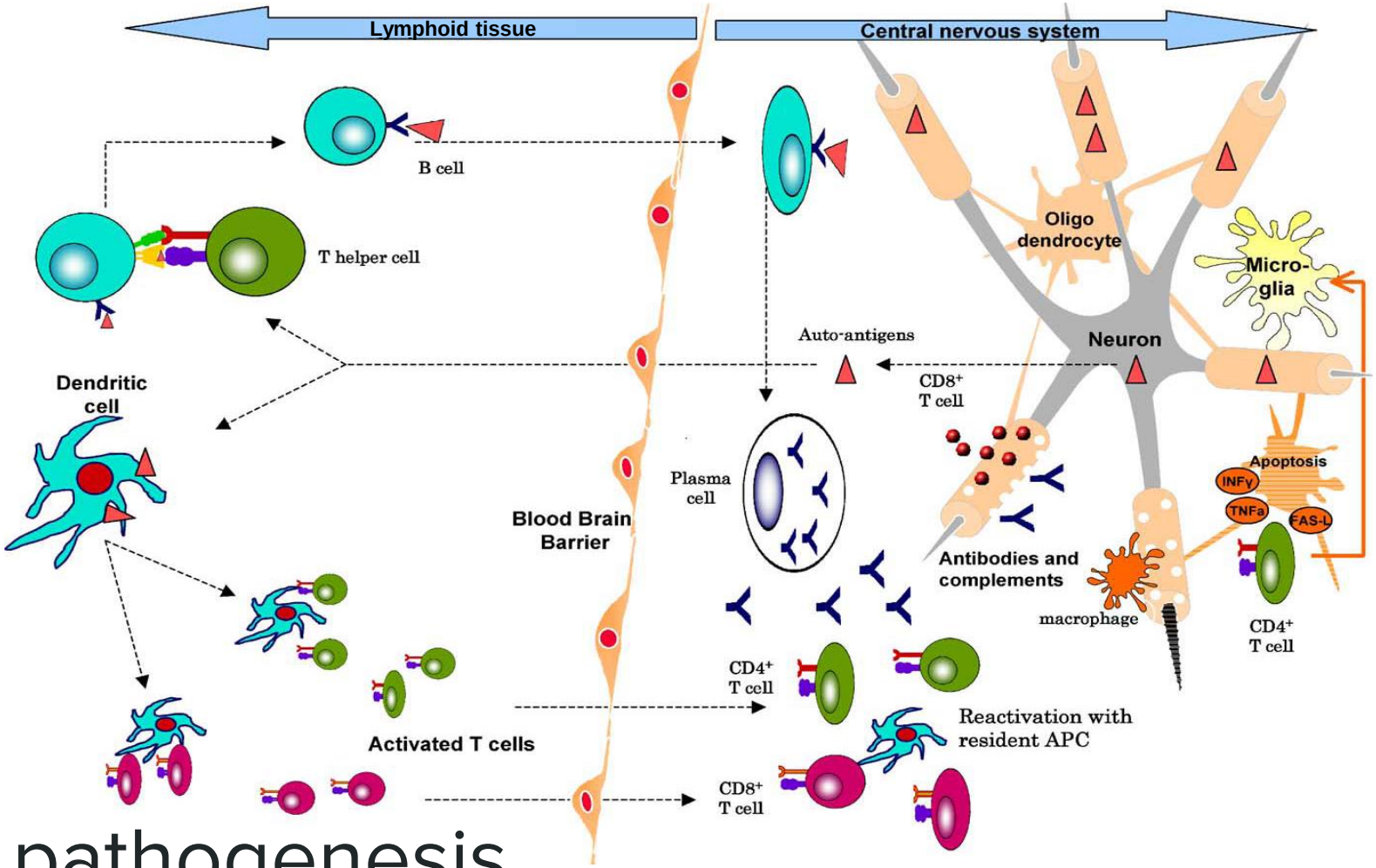
- Chronic, autoimmune disease affecting the central nervous system (CNS)
- Loss of tolerance towards myelin antigens
- CNS inflammation, lesion formation, demyelination, axonal loss, degeneration



Facts about MS

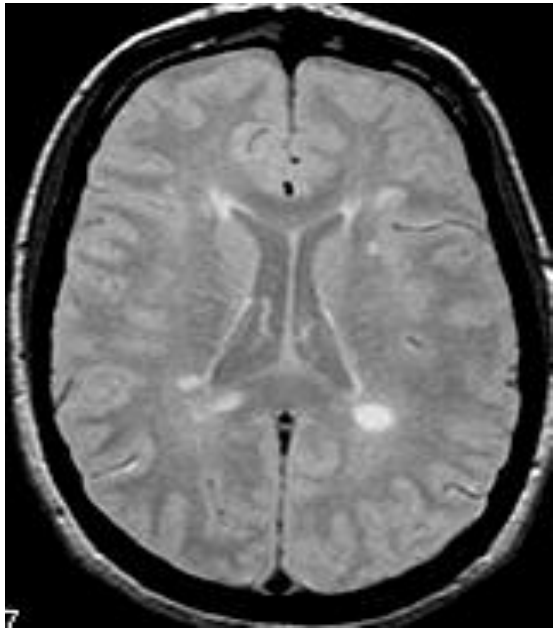
- Relapses (attacks) & remissions
- Symptoms vary depending on which part of the CNS is affected
- 2.5 million MS patients worldwide
- Female/ Male ratio ➞ 2:1
- Mean age of diagnosis ➞ 30 years
- Not curable, but treatable

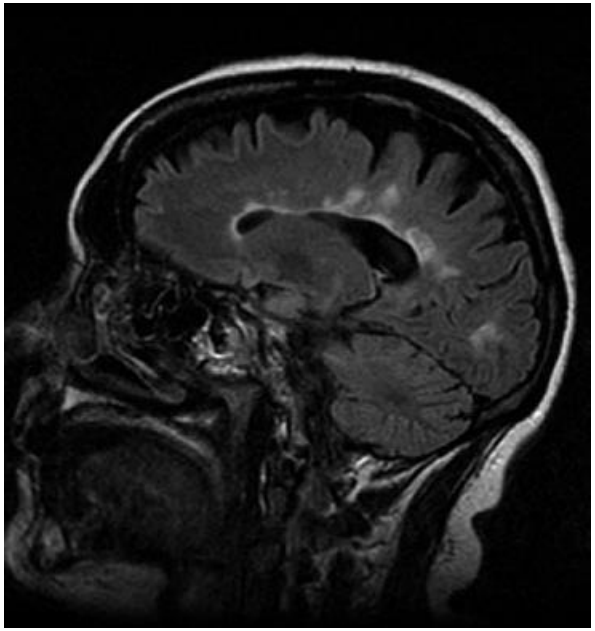




MS pathogenesis

Classical MS lesions





The 2017 Mc Donald Criteria

- If the 2017 McDonald Criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is **multiple sclerosis**.
- If multiple sclerosis is suspected by virtue of a clinically isolated syndrome but the 2017 McDonald Criteria are not completely met, the diagnosis is **possible multiple sclerosis**.
- If another diagnosis arises during the evaluation that better explains the clinical presentation, the diagnosis is **not multiple sclerosis**.

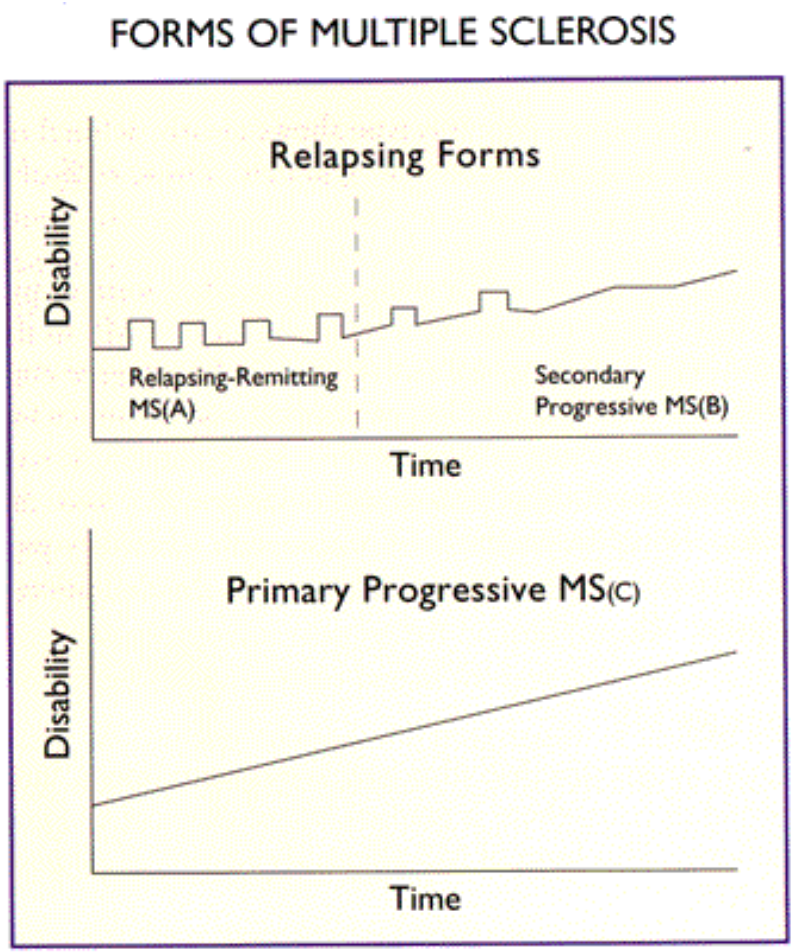
	Number of lesions with objective clinical evidence	Additional data needed for a diagnosis of multiple sclerosis
≥2 clinical attacks	≥2	None*
≥2 clinical attacks	1 (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location†)	None*
≥2 clinical attacks	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡
1 clinical attack	≥2	Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands¶
1 clinical attack	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡ AND Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands¶

Lancet Neurol 2018; 17: 162–73

Dissemination in Time & Space

Dissemination in space	Dissemination in time
One or more T2-hyperintense lesions* that are characteristic of multiple sclerosis in two or more of four areas of the CNS: • periventricular, • cortical or juxtacortical • infratentorial • spinal cord	• Simultaneous presence of gadolinium-enhancing and non-enhancing lesions* at any time **or** • A new T2-hyperintense or gadolinium-enhancing lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI

Lancet Neurol 2018; 17: 162–73



Expanded Disability Status Scale (EDSS):

- A scale from 0-10 used to quantify disability in MS
- 0 = no symptoms at all,
  10 = death from MS,
  ≥5 inability to walk without aids
- Scoring is based on neurological examination

Multiple Sclerosis and Related Disorders 27 (2019) 156–163

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Review article

The role of gluten in multiple sclerosis: A systematic review

Henriette Lynge Thomsen[a,1], Elise Barsøe Jessen[a,1], Moschoula Passali[a,1], Jette Lautrup Frederiksen[b,*]

[a] Department of Nutrition, Exercise and Sports, Faculty of Science, University of Copenhagen, Denmark and Bartholin Institute, Rigshospitalet
[b] Multiple Sclerosis Clinic, Department of Neurology, Rigshospitalet Glostrup and University of Copenhagen, Valdemar Hansens Vej 13, DK-2600 Denmark

ARTICLE INFO

Keywords:
Clinically isolated syndrome
Diet
Gliadin
Gluten
Multiple sclerosis

Abbreviations:
AGA
anti-gliadin antibodies
ARA
anti-reticulin antibodies
CNS
central nervous system
CSF
cerebrospinal fluid
EDSS
expanded disability status scale
EMA
endomysial antibodies

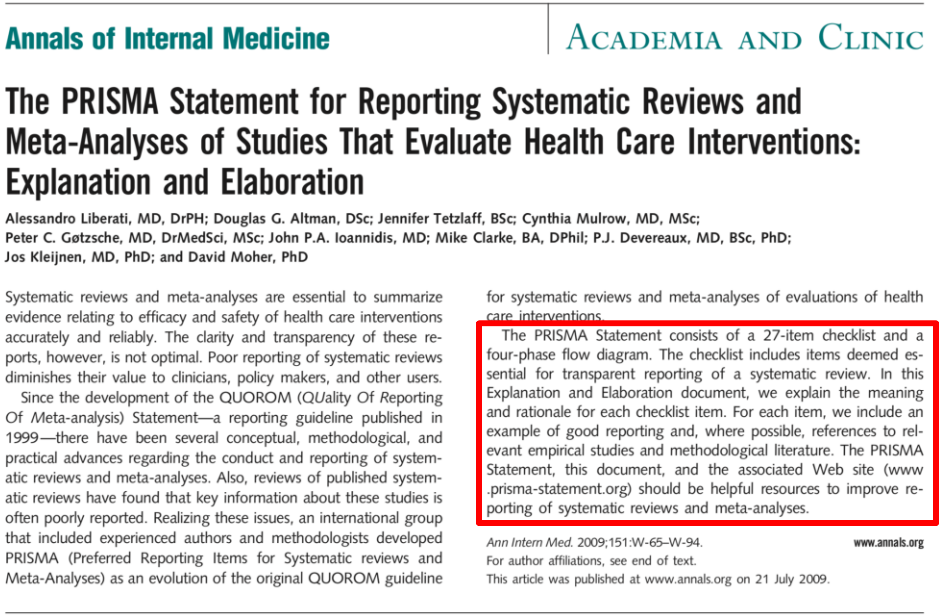
ABSTRACT

Background: There is an increasing interest in diet as a modifying factor in multiple sclerosis (MS), and gluten has been suggested to affect MS.
Objective: The aim of this systematic review is to qualitatively evaluate the evidence on the role of gluten in MS.
Methods: A review protocol was submitted to PROSPERO. A systematic literature search was conducted in PubMed, Web of Science, Scopus, Embase, Cab Abstracts, and Google Scholar. Studies on patients with MS, clinically isolated syndrome, or celiac disease presenting with MS-related markers were included, if they investigated effects of diets containing specified amounts of gluten or associations between gluten sensitivities and MS.
Results: Forty-nine publications presenting 50 studies/cases met the inclusion criteria. Study designs, methods, and outcomes varied broadly across studies. Two intervention studies found a positive effect of a gluten-free diet on disease-related markers in patients with MS. One prospective cohort study also found a positive effect of a gluten-free diet, while a survey found intake of cereal/bread to be protective against MS. Four observational studies did not find increased comorbidity of MS and celiac disease. Seventeen studies investigated the level of different gluten-sensitivity markers in patients with MS with inconsistent results. Finally, 12 cases and 13 posters/abstracts/master's theses contributed to shed light on the topic.
Conclusions: There is still not sufficient evidence to state whether gluten plays a role in MS, but limitations of current evidence have been identified and directions of future research have been suggested.

Aim – **Three Questions**

1. **Can patients with MS benefit from a GFD?**
    - Endpoints of interest: neurological symptoms, expanded disability scale score (EDSS), relapse rate, quality of life, biomarkers from cerebrospinal fluid, lesion activity, and other magnetic resonance imaging (MRI) measures
2. **Is there an increased prevalence of markers of gluten-reactivity in patients with MS compared to HC?**
    - Markers of interest: gastrointestinal symptoms, positivity for HLA-DQ2 & -DQ8 haplotypes, presence of antibodies (IgG and IgA antibodies against gliadin, other gluten fractions, transglutaminases, as well as anti-endomysial and anti-reticulin antibodies), increased gut permeability, abnormal gut histology as well as increased numbers of T cell infiltrates in the gut
3. **Is there an increased risk of MS among patients with CD or vice versa?**

Method



Annals of Internal Medicine | ACADEMIA AND CLINIC

The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration

Alessandro Liberati, MD, DrPH; Douglas G. Altman, DSc; Jennifer Tetzlaff, BSc; Cynthia Mulrow, MD, MSc; Peter C. Gøtzsche, MD, DrMedSci, MSc; John P.A. Ioannidis, MD; Mike Clarke, BA, DPhil; P.J. Devereaux, MD, BSc, PhD; Jos Kleijnen, MD, PhD; and David Moher, PhD

Systematic reviews and meta-analyses are essential to summarize evidence relating to efficacy and safety of health care interventions accurately and reliably. The clarity and transparency of these reports, however, is not optimal. Poor reporting of systematic reviews diminishes their value to clinicians, policy makers, and other users.

Since the development of the QUOROM (*QU*ality *O*f *R*eporting *O*f *M*eta-analysis) Statement—a reporting guideline published in 1999—there have been several conceptual, methodological, and practical advances regarding the conduct and reporting of systematic reviews and meta-analyses. Also, reviews of published systematic reviews have found that key information about these studies is often poorly reported. Realizing these issues, an international group that included experienced authors and methodologists developed PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) as an evolution of the original QUOROM guideline for systematic reviews and meta-analyses of evaluations of health care interventions.

The PRISMA Statement consists of a 27-item checklist and a four-phase flow diagram. The checklist includes items deemed essential for transparent reporting of a systematic review. In this Explanation and Elaboration document, we explain the meaning and rationale for each checklist item. For each item, we include an example of good reporting and, where possible, references to relevant empirical studies and methodological literature. The PRISMA Statement, this document, and the associated Web site (www.prisma-statement.org) should be helpful resources to improve reporting of systematic reviews and meta-analyses.

Ann Intern Med. 2009;151:W-65–W-94. www.annals.org
For author affiliations, see end of text.
This article was published at www.annals.org on 21 July 2009.

- **Protocol registration in PROSPERO**
- Search Strategy
  - Six Databases:
    Pubmed, Scopus, Web of Science, Embase, Cab Abstracts & Google Scholar
  - Keywords:
    Gluten, Gliadin, Cereal, Wheat, Rye Barley, Celiac, Coeliac AND
    Optic neuritis, Multiple sclerosis, Disseminated sclerosis, Clinically isolated syndrome

PROSPERO International prospective register of systematic reviews

NHS National Institute for Health Research

Print | PDF

The role of gluten in multiple sclerosis: a systematic review

Moschoula Passali, Henriette Lynge Thomsen, Elise Barsøe Jessen, Jette Lautrup Battistini Frederiksen

Citation

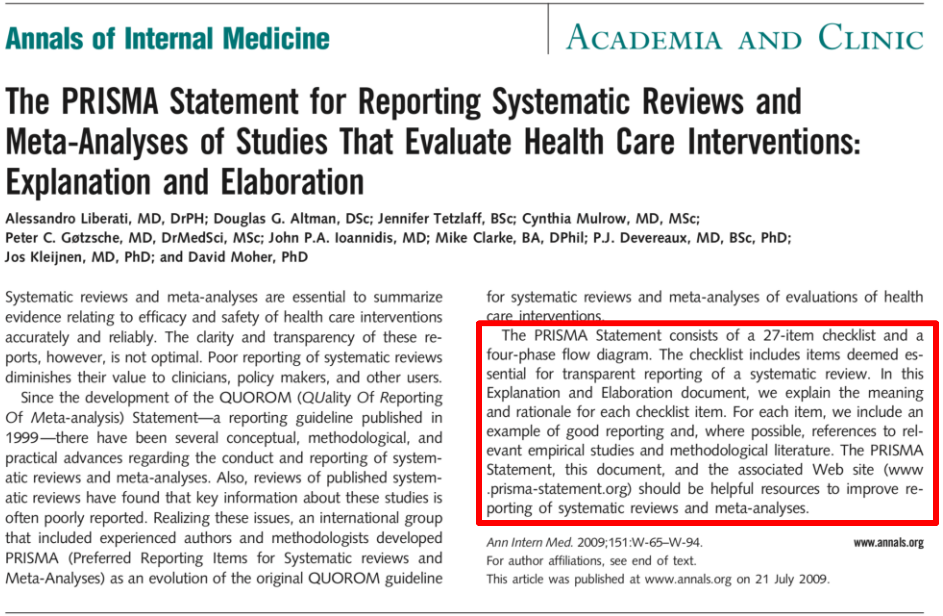
Moschoula Passali, Henriette Lynge Thomsen, Elise Barsøe Jessen, Jette Lautrup Battistini Frederiksen. The role of gluten in multiple sclerosis: a systematic review. PROSPERO 2018 CRD42018096246 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018096246

Review question

The objective of this systematic review is to collect all published studies investigating associations between gluten and multiple sclerosis (MS) as well as evidence supporting positive, negative or no effects of gluten-free diets (GFD) on patients with MS. This review aims to address the following questions:

1. When compared to MS patients following their usual diet, how do MS patients on GFD or low gluten diets do in regards to neurological symptoms, clinical scores such as EDSS, lesional activity, permeability of the blood-brain barrier, visual evoked potentials, relapsing rate, quality of life, CSF analysis including IgG index, leucocyte counts and oligoclonal bands or other disease markers?
2. Is there an increased prevalence of celiac disease (CD), non-celiac gluten sensitivity (NCGS) or CD-related

Method



Annals of Internal Medicine | ACADEMIA AND CLINIC

The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration

Alessandro Liberati, MD, DrPH; Douglas G. Altman, DSc; Jennifer Tetzlaff, BSc; Cynthia Mulrow, MD, MSc; Peter C. Gøtzsche, MD, DrMedSci, MSc; John P.A. Ioannidis, MD; Mike Clarke, BA, DPhil; P.J. Devereaux, MD, BSc, PhD; Jos Kleijnen, MD, PhD; and David Moher, PhD

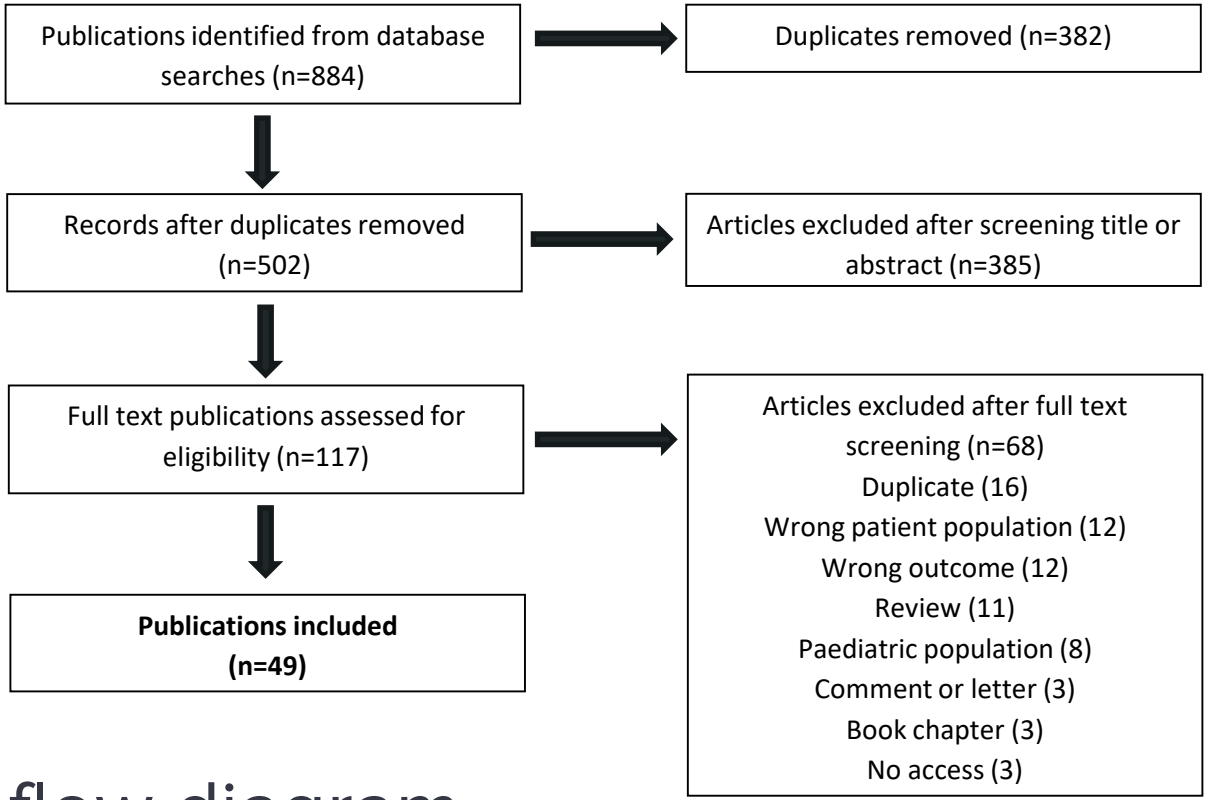
Systematic reviews and meta-analyses are essential to summarize evidence relating to efficacy and safety of health care interventions accurately and reliably. The clarity and transparency of these reports, however, is not optimal. Poor reporting of systematic reviews diminishes their value to clinicians, policy makers, and other users.

Since the development of the QUOROM (*QU*ality *O*f *R*eporting *O*f *M*eta-analysis) Statement—a reporting guideline published in 1999—there have been several conceptual, methodological, and practical advances regarding the conduct and reporting of systematic reviews and meta-analyses. Also, reviews of published systematic reviews have found that key information about these studies is often poorly reported. Realizing these issues, an international group that included experienced authors and methodologists developed PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) as an evolution of the original QUOROM guideline for systematic reviews and meta-analyses of evaluations of health care interventions.

The PRISMA Statement consists of a 27-item checklist and a four-phase flow diagram. The checklist includes items deemed essential for transparent reporting of a systematic review. In this Explanation and Elaboration document, we explain the meaning and rationale for each checklist item. For each item, we include an example of good reporting and, where possible, references to relevant empirical studies and methodological literature. The PRISMA Statement, this document, and the associated Web site (www.prisma-statement.org) should be helpful resources to improve reporting of systematic reviews and meta-analyses.

Ann Intern Med. 2009;151:W-65–W-94. www.annals.org
For author affiliations, see end of text.
This article was published at www.annals.org on 21 July 2009.

- Protocol registration in PROSPERO
- **Search Strategy**
  - **Six Databases**:
    Pubmed, Scopus, Web of Science, Embase, Cab Abstracts & Google Scholar
  - **Keywords**:
    Gluten, Gliadin, Cereal, Wheat, Rye Barley, Celiac, Coeliac **AND**
    Optic neuritis, Multiple sclerosis, Disseminated sclerosis, Clinically isolated syndrome



PRISMA flow diagram of study identification

Can patients with MS benefit from a GFD?

Table 1
Study characteristics and results in studies investigating the effect of GFD or gluten-containing diet on MS-related outcomes.

Reference	Study design	Participants total	F	M	Groups	Intervention/ exposure	Duration
Bisht et al. (2015)	Open-label, single-arm, prospective cohort study	20 MS (18 SPMS, 2 PPMS)	15	5	I: 20	Multimodal intervention incl. GFD	12 months
Ghadirian et al. (1998)	Survey	399 MS + HC	274	125	MS: 197 HC: 202	Nutritional factors incl. gluten-containing food items	–
Irish et al. (2017)	Randomized controlled intervention trial	17 RRMS	15	2	I: 8 C: 9	I: Modified Paleolithic diet incl. GF. C: RD	3 months
Rodrigo et al. (2014)	Controlled intervention trial	72 RRMS	60	12	I: 36 C: 36	I: GFD C: RD	54 months

Reference	Outcomes	Results
Bisht et al. (2015)	Perceived fatigue and health-related QoL	Perceived fatigue decreased ($p < 0.0005$) and health-related QoL increased ($p < 0.05$) throughout the study.
Ghadirian et al. (1998)	Risk of MS per unit intake of food items	Cereal/bread was borderline protective against MS (OR = 0.62, $p = 0.04$). Other gluten-containing food items NS
Irish et al. (2017)	Perceived fatigue, QoL	I vs. C: Perceived fatigue decreased ($p = 0.05$), QoL improved ($p = 0.02$).
Rodrigo et al. (2014)	Annual relapse rate, EDSS, lesion activity	I vs. C: EDSS and lesion activity improved ($p = 0.001$). Annual relapse rate NS

Table 4 Risk of multiple sclerosis per 100 grams of foods per day (log transformed), Montreal 1992–1995

Variable	All subjects (197 cases/202 controls)		Males (61 cases/64 controls)		Females (136 cases/138 controls)	
	Odds ratio[a] (CI)[b]	*P*	Odds ratio[a] (CI)[b]	*P*	Odds ratio[a] (CI)[b]	*P*
Milk	0.95 (0.87–1.05)		0.99 (0.84–1.18)		0.93 (0.83–1.05)	
Yogurt	0.96 (0.87–1.06)		0.97 (0.81–1.16)		0.95 (0.84–1.09)	
Coffee	1.07 (0.99–1.16)		1.08 (0.93–1.25)		1.07 (0.98–1.17)	
Juice	0.82 (0.74–0.92)	0.0006	0.70 (0.54–0.90)	0.006	0.87 (0.76–0.98)	0.02
Cheese	0.90 (0.74–1.08)		0.84 (0.59–1.19)		0.92 (0.74–1.16)	
Egg	0.85 (0.69–1.04)		0.94 (0.65–1.38)		0.81 (0.63–1.04)	
Pasta/pizza	1.03 (0.82–1.30)		0.99 (0.58–1.69)		1.05 (0.81–1.36)	
White root veg.	1.13 (0.88–1.44)		0.86 (0.55–1.33)		1.29 (0.95–1.77)	
Red root veg.	0.94 (0.78–1.13)		0.91 (0.66–1.26)		0.95 (0.76–1.19)	
Cruciferous veg.	0.94 (0.80–1.12)		1.04 (0.79–1.37)		0.89 (0.72–1.10)	
Peas	0.95 (0.80–1.13)		1.01 (0.76–1.35)		0.92 (0.75–1.14)	
Other veg.	0.95 (0.76–1.18)		1.10 (0.73–1.67)		0.90 (0.68–1.18)	
Butter	0.96 (0.82–1.12)		1.15 (0.89–1.49)		0.86 (0.71–1.06)	
Margarine	0.96 (0.82–1.12)		0.73 (0.55–0.96)	0.02	1.09 (0.90–1.33)	
Oils	0.89 (0.73–1.10)		1.49 (0.78–1.67)		0.80 (0.62–1.03)	
Beef	1.10 (0.88–1.36)		1.18 (0.81–1.73)		1.05 (0.80–1.37)	
Pork, hot dog, etc.	1.24 (1.02–1.51)	0.03	1.29 (0.93–1.80)		1.21 (0.94–1.55)	
Fish	0.91 (0.78–1.05)		1.08 (0.84–1.40)		0.83 (0.69–1.00)	0.05
Cereal/breads	0.62 (0.40–0.97)	0.04	0.26 (0.10–0.70)	0.008	0.86 (0.50–1.48)	
Cakes	0.88 (0.75–1.04)		0.77 (0.58–1.03)		0.95 (0.77–1.17)	
Fruits	0.97 (0.81–1.15)		0.85 (0.65–1.11)		1.08 (0.84–1.37)	
Sweets	1.12 (0.97–1.30)		0.83 (0.63–1.10)		1.29 (1.07–1.55)	0.007
Chicken	0.86 (0.67–1.10)		0.74 (0.44–1.23)		0.88 (0.67–1.16)	
Stew	0.96 (0.83–1.10)		1.02 (0.81–1.29)		0.92 (0.77–1.09)	

[a] Odds ratios for all foods are adjusted for total energy and body mass index.

[b] CI = 95% confidence intervals

Note: items underlined are statistically significant.

Ghadirinian *et al.* 1998

validated 164-item Food Frequency Questionnaire

International Journal of
Neurology and Neurotherapy

Rodrigo L et al. Int J Neurol Neurother 2014, 1:1
DOI: 10.23937/2378-3001/1/1/1012
Volume 1 | Issue 1

ISSN: 2378-3001

Original Article: Open Access

Randomised Clinical Trial Comparing the Efficacy of A Gluten-Free Diet Versus A Regular Diet in A Series of Relapsing-Remitting Multiple Sclerosis Patients

Rodrigo L[1]*, Hernández-Lahoz C[2], Fuentes D[1], Mauri G[2], Alvarez N[1], Vega J[2] and González S[3]

[1]*Gastroenterology, University Hospital Central of Asturias, University of Oviedo, Spain*

[2]*Neurology, University Hospital Central of Asturias, University of Oviedo, Spain*

[3]*Immunology Services, University Hospital Central of Asturias, University of Oviedo, Spain*

***Corresponding author:** *Luis Rodrigo, Gastroenterology Service, University Hospital Central of Asturias, c/ Celestino Villamil s.n, University of Oviedo, 33.006, Spain, Tel: 00-34-985-10-80-58, Fax: 00-34-985-10-81-15, E-mail: lrodrigosaez@gmail.com*

Abstract

Objectives: To analyse the clinical efficacy of a Gluten-Free Diet (GFD) compared with a Regular Diet (RD) in Relapsing-Remitting Multiple Sclerosis (RRMS) patients.

Methods: Seventy-two RRMS patients were included into a prospective study. Annual relapse rate (ARR), Expanded Disability Status Scale (EDSS) and lesional activity were compared. Patients were randomly separated according to diet: (GFD, n=36) and (RD, n=36). Follow-up study period was 5.3 ± 1.6 years (median 4.5 years).

Results: At the end of the study period, a clear improvement in the EDSS was observed in GFD (1.5 ± 1.4) compared with RD (2.1 ± 1.5) (p=0.001), and lesional activity (MRI) was found in 10 (28%) in GFD, compared to 24 (67%) in RD (p=0.001) [OR: 5.200; (CI-95%: 1.901- 14.220)]. Average ARR was lower in GFD (0.4 ± 0.6) compared to RD (0.6 ± 0.6) (NS).

Conclusions: A GFD has shown a neuro-protective effect in our RRMS patients.

Keywords

Randomised Clinical trial, Gluten-free diet, Regular diet, Relapsing-remitting, Multiple Sclerosis

of demyelination and gliosis areas in the CNS. MS affects about 0.1% of the population worldwide. The relapsing-remitting form of MS (RRMS) is the initial course of more than 80% of individuals with MS. The diagnosis of MS requires that the symptoms and signs of CNS white matter involvement are disseminated temporally and spatially, with supporting evidence from MRI findings and the presence of oligoclonal bands of immunoglobulin G in the cerebrospinal fluid (CSF) if needed [1,2].

Coeliac disease (CD) is a common condition that affects 1-2% of the population worldwide and is more prevalent in females than males by a ratio of 2:1. The atypical form, which is more frequent in adult individuals, refers to CD that presents not with prominent gastrointestinal symptoms but with extra-intestinal manifestations [3-5].

Autoimmune disorders (AIDs) occur approximately 10 times more frequently in CD patients than in the general population. The most predominant associated diseases are autoimmune thyroiditis, type 1 diabetes mellitus (T1DM), Sjögren´s syndrome (SS), Addison's disease (AD), autoimmune type 1 hepatitis (AIH), psoriasis and biliary cirrhosis primary (CBP), among others [6-12]. The association of AIDs with CD is considered to be mainly owing to a shared genetic tendency. CD is approximately 10 times more common than MS.

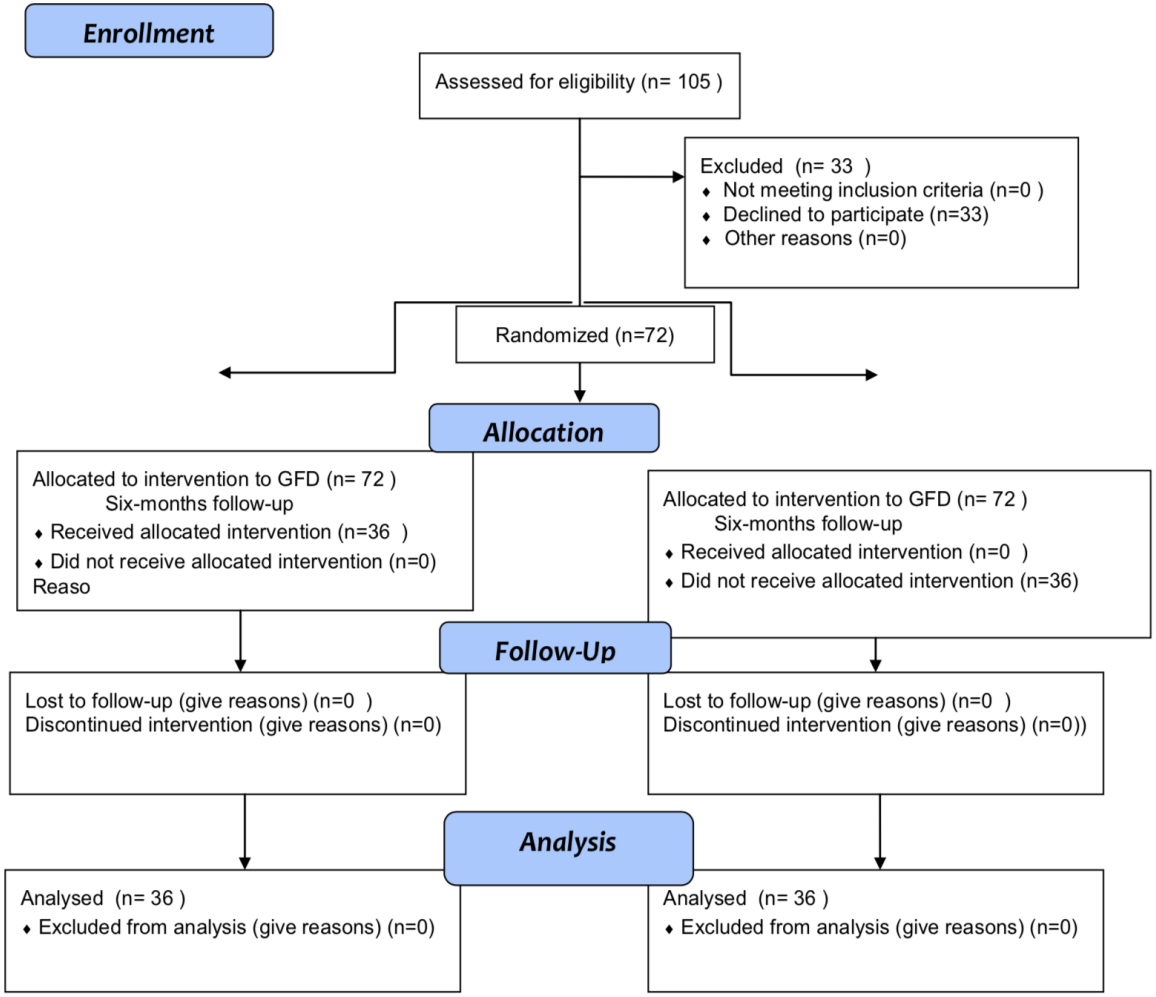


Figure 1: CONSORT 2008 flow diagram.

- All patients were offered a GFD. Only 36 (50%) strictly followed a GFD throughout the study. The remaining 36 (50%), who left the GFD or committed frequent irregularities during the 6 first months constituted the control group (regular diet).
- Adherence to the GFD was confirmed by specific questioning of patients and their families at each biannual visit.

International Journal of
Neurology and Neurotherapy
ISSN: 2378-3001
Rodrigo L et al. Int J Neurol Neurother 2014, 1:1
DOI: 10.23937/2378-3001/1/1/1012
Volume 1 | Issue 1
Original Article: Open Access

Randomised Clinical Trial Comparing the Efficacy of A Gluten-Free Diet Versus A Regular Diet in A Series of Relapsing-Remitting Multiple Sclerosis Patients

Rodrigo L[1], Hernández-Lahoz C[2], Fuentes D[1], Mauri G[2], Alvarez N[1], Vega J[2] and González S[3]*

	GFD (n = 36)	RD (n = 36)	p
Annual Relapse Rate, (SD)	0.4 ± 0.6	0.6 ± 0.6	NS
EDSS, mean ± SD, (median)	1.5 ± 1.4 (2)	2.1 ± 1.5 (3)	0.001
MRI activity, n (%)	10 (28)	24 (67)	0.001

GFD: Gluten-Free Diet; RD: Regular Diet; SD: Standard deviation; EDSS: Expanded Disability Status Scale; MRI: Magnetic Resonance Imaging

- Study period was 5.3 ± 1.6 years (median **4.5 years**).
- 8 patients had all of the histological criteria of CD. **All coeliac patients were in the GFD (22.2% vs 0%)**
- MRI activity = positive ➔ increased number of T2-weighted lesions or new contrast-enhanced T1-weighted lesions

*MRI was repeated once each year, and usually using contrast agent.

Is there an increased risk of MS among patients with CD or vice versa?

- No increased comorbidity of MS and celiac disease
- Good agreement among studies
- Problem with underdiagnosis of CD?

Table 2
Study characteristics and results in studies evaluating the co-occurrence of MS and CD.

Reference	Study design	Participants, total	F	M	Country	Outcomes	Results
Eaton et al. (2007)	Cross-sectional	5 472 032 people			Denmark	Co-occurrence of CD and MS	$1.09*10^{-6}$% of people had both CD and MS. 0.2% of CD patients had MS
Escudié et al. (2017)	Cross-sectional	741 CD			France	Co-occurrence of CD and MS	0.1% of CD patients had MS
Ludvigsson et al. (2007)	Case-control	14 371 CD, 70 096 HC	49 700	34 767	Sweden	Prevalence of MS among CD patients vs. MS among HC	NS
Volta et al. (2002)	Cross-sectional	160 CD	120	40	Italy	Co-occurrence of CD and MS	0.6% of CD patients had MS

CD = celiac disease, F = females, HC = healthy controls, M = males, MS = multiple sclerosis, NS = not significant.

Eaton *et al*. 2007

Table 2

Comorbidity of 31 Autoimmune Diseases in Denmark Numbers of Co-occurring Cases above the diagonal Pairwise Odds Ratios Below the Diagonal

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1	Thyrotoxicosis		293	1195	37	32	108	19	52	97	48	98	16	172	312	18	52
2	Thyroiditis	6.3		107	13	11	20	5	7	11	7	10		19	21	2	11
3	Type I Diabetes	2.3	2.4		90	108	179	33	82	147	183	249	24	217	435	47	118
4	Other Adrenal Gland	3.5	12.9	7.8		7	11		1	2	4	4		7	10	2	5
5	Celiac Disease	1.5	5.0	4.2	13.0		32	4	3	6	10	11		101	77	3	17
6	Pernicious Anemia	2.2	5.6	3.2	11.7	22.6		18	9	22	26	13	3	23	29	3	9
7	Acq. Hemolytic Anemia	1.9	5.8	2.6		8.3	16.9		41		4		5	8	23	3	6
8	Purpura	2.2	3.0	2.5	1.5	1.5	4.1	63.8		13	7	19		17	32	4	8
9	Multiple Sclerosis	0.9	1.0	1.2	0.8	1.0	3.6		2.2		165	81	3	36	74	2	8
10	Guillain Barre Syndrome	1.2	2.0	3.1	4.1	4.9	5.8	4.0	2.7	19.2		18	3	14	25	3	8
11	Iridocyclitis	1.3	1.5	2.4	2.1	2.7	1.8		3.6	4.2	2.2		14	77	112	3	15
12	Wegener's Granulomatosis	2.7		2.7			5.3	35.3		2.0	4.2	12.5		3	8		2
13	Crohn's Disease	1.8	2.0	1.7	2.7	16.7	3.3	3.7	2.0	1.2	1.4	3.5	2.1		2676	9	21
14	Ulcerative Colitis	1.8	1.2	1.8	2.1	7.4	2.0	5.8	2.4	1.4	1.3	2.9	2.9	67.4		22	57
15	Primary Biliary Cirrhosis*	1.5	1.7	4.6	8.8	6.8	3.2	14.6	9.0	0.9	3.7	2.0		5.2	6.6		95
16	Chronic Active Hepatitis	2.0	4.4	3.7	8.0	12.9	4.2	10.9	5.2	1.2	3.2	3.0	5.2	3.1	4.7	213.0	
17	Interstitial Cystitis	1.4	1.7	3.2	2.9	2.4	2.3	3.6	1.6	4.1	2.9	1.7	1.9	2.5	1.8	2.5	3.1
18	Endometriosis*	1.2	1.5	1.0	1.3	1.6	1.1	2.2	1.9	1.3	1.3	1.1	0.8	1.5	1.4	2.0	1.5
19	Pemphigoid	1.3	1.0	3.4		54.9	4.1	22.6	1.5	3.7	3.4	1.5		1.2	2.2	4.7	
20	Pempigus	0.8		4.0				15.5	6.5	5.9	3.7			2.3	2.3		
21	Psoriasis	1.7	2.2	3.2	2.0	2.3	2.2	0.9	3.2	1.4	2.0	2.1	3.6	3.3	2.3	6.9	4.1
22	Alopecia Areata	2.2	11.4	2.4	8.9	3.2	2.2		5.9	1.1	3.9	1.1	17.8	2.5	1.6	6.7	1.8
23	Vitiligo	3.4	7.9	4.5	23.8	2.4	21.0			2.0	2.4	2.1	5.6	0.7	2.0	4.2	2.2
24	Sero+ Rheum. Arthritis	1.7	2.0	1.9	2.5	1.7	2.5	5.4	3.9	0.8	2.0	6.2	6.4	2.8	2.5	2.3	4.8
25	Dermatomyositis	1.7	3.0	2.8	20.6	3.8	3.1		1.6	1.2	9.6	2.1	6.2	2.0	1.7	17.5	8.0
26	Myositis	1.5	1.8	2.3	1.7	2.6	2.3	2.0	1.8	2.5	3.3	1.7	0.7	2.7	1.7	2.2	2.7
27	Polymyalgia Rheumatica	1.7	2.1	2.0	3.5	2.3	2.3	1.4	1.6	2.0	2.8	2.4	5.6	2.8	2.5	2.7	2.0
28	Myasthenia Gravis	2.9	3.9	2.3			5.3		1.5	5.3	18.2	0.5	6.1	0.4	1.7	4.4	1.6
29	Scleroderma	1.7	4.5	2.1	8.2	3.7	2.4		6.0	3.1	7.0	2.0		3.5	2.7	23.1	7.6
30	Systematic Lupus Erythematosis	2.0	1.3	2.2	6.2	2.7	7.8	78.4	43.0	2.5	10.1	7.0	15.4	2.5	2.8	14.8	23.7
31	Sjogren's Syndrome	1.6	2.7	1.7	3.4	7.4	4.9	16.0	4.0	2.5	2.0	4.6	14.0	2.7	2.6	26.9	7.9

RESEARCH ARTICLE Open Access

Prevalence of celiac disease in multiple sclerosis

Luis Rodrigo[1*], Carlos Hernández-Lahoz[2], Dolores Fuentes[1], Noemí Alvarez[1], Antonio López-Vázquez[3], Segundo González[3]

Methods: We analyzed the prevalence of serological, histological and genetic CD markers in a series of 72 MS patients and in their 126 first-degree relatives, compared to 123 healthy controls.

Results: Tissue IgA-anti-transglutaminase-2 antibodies were positive in 7 MS patients (10%), compared to 3 healthy controls (2.4%) ($p < 0.05$). OR: 5.33 (CI-95%: 1.074-26.425). No differences were found in HLA-DQ2 markers between MS patients (29%) and controls (26%) (NS).

We detected mild or moderate villous atrophy (Marsh III type) in duodenal biopsies, in 8 MS patients (11.1%). We also found a high proportion of CD among first-degree relatives: 23/126 (32%). Several associated diseases were detected, mainly dermatitis 41 (57%) and iron deficiency anemia in 28 (39%) MS patients. We also found in them, an increased frequency of circulating auto-antibodies such as anti-TPO in 19 (26%), ANA in 11 (15%) and AMA in 2 (3%).

Conclusions: We have found an increased prevalence of CD in 8 of the 72 MS patients (11.1%) and also in their first-degree relatives (23/126 [32%]). Therefore, increased efforts aimed at the early detection and dietary treatment of CD, among antibody-positive MS patients, are advisable.

Rodrigo *et al. BMC Neurology* 2011, **11**:31
http://www.biomedcentral.com/1471-2377/11/31

RESEARCH ARTICLE Open Access

Prevalence of celiac disease in multiple sclerosis

Luis Rodrigo[1*], Carlos Hernández-Lahoz[2], Dolores Fuentes[1], Noemí Alvarez[1], Antonio López-Vázquez[3], Segundo González[3]

Table 4 Demographic, serological, genetic and histological characteristics of the eight patients exhibiting an associated CD

Patients	Sex	Age	Anti-tTG2 (U/ml)	HLA-DQ2	HLA-DQ8	Marsh[2]
1	F[1]	33	187	(+)	ND[3]	3b
2	F	28	10.3	(+)	ND	3a
3	F	25	8.5	(+)	ND	3a
4	F	27	4.2	(+)	ND	3a
5	F	26	9.4	(+)	ND	3b
6	F	29	2.8	(+)	ND	3a
7	F	23	3.6	(-)	(+)	3a
8	F	34	1.8	(+)	ND	3a

[1]F = Female; [2]Marsh = Histological classification of duodenal biopsies for CD; [3]ND = Not done.

As the determination of anti-TGt-2 antibodies became used more routinely, a marked decrease of sensitivity was found to exist when studying patients without villous atrophy (or with a mild degree, as normally happens in adults). Several published studies among large groups of celiac patients, have clearly demonstrated that a positive anti-TGt-2 antibody test, correlates linearly with the degree of severity of the histological duodenal lesions found. In patients presenting only lymphocytic enteritis (Marsh I), its sensitivity is very low, between 15-30% at best [26-28]. These findings have led to the application of new diagnostic strategies, such as the concurrent use of genetic testing, or the determination of anti-TGt-2 antibodies in duodenal aspirate in cases of negative serology. An alternative approach to increasing sensitivity relies on the use of a corrected threshold for positivity; its value has been recommended as 2 U/ml for adults [15,29]. This is the threshold that we have applied in the present study. We did not employ EMA antibodies, because they

A Genetic Study of Celiac Disease in Patients with Multiple Sclerosis in Comparison with Celiac Patients and Healthy Controls

Fateme Barazandeh Ahmadabadi [1], Bijan Shahbazkhani [2,*], Abbas Tafakhori [3], Asghar Khosravi [4], Marzie Maserat Mashhadi [5]

Table 2: The comparison of HLA DQ frequency in MS, CD, and control groups

HLA Classification	MS	Celiac	Control
DQ2 Positive	17 (28.3%)	66 (47.1%)	61 (40.4%)
DQ8 Positive	11 (18.3%)	24 (17.1%)	21 (13.9%)
DQ2/DQ8 Positive	6 (10%)	45 (32.1%)	8 (5.3%)
DQ2/DQ8 Negative	26 (43.3%)	5 (3.6%)	61 (40.4%)
Total	60	140	151

HLA: Human leukocyte antigen, MS: Multiple sclerosis, CD: Celiac disease

Table 3: Serological markers in MS group

Serologic Marker	Mean±SD
AGA IgA	2.50±1.30
AGA IgG	2.44±0.98
Anti tTG IgA	2.35±1.37
Anti tTG IgG	2.34±0.63
Anti EMA IgA	2.47±1.01
Anti EMA IgG	2.39±0.70

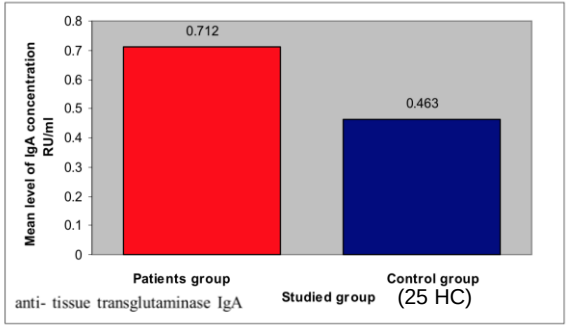
MS: Multiple sclerosis, SD: Standard deviation

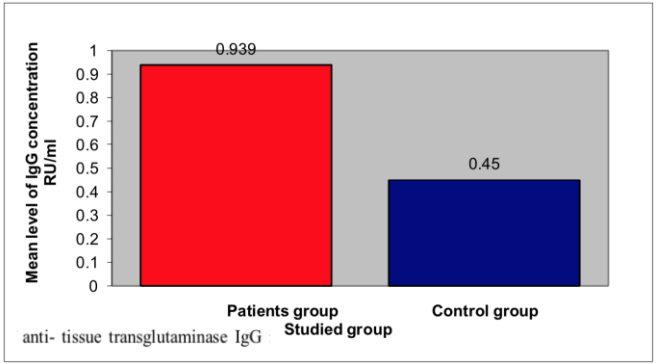
Iraqi Journal of Science

Detection of Human Leukocyte Antigen and Celiac Disease Auto Antibodies in serum of Patients with Multiple Sclerosis

Rana S. Aboud[1*], May K. Ismael[1], and Haider J.Mohammed[2]

4/ 30 (13.3%) MS patients were DQ8 positive





Studies finding no association between MS & CD

Study	Study Size	IgA-tTG	IgG-tTG	Other endpoints
Bodil Roth et al. 2008	85 MS/ 100 HC	0 MS/ 1HC	0 MS/ 1HC	-
De Oliveira et al. 2016	249 MS	2 MS	-	IgA-EMA (2 MS)
Khoshbaten et al. 2012	100 MS/ 121 HC	0 MS/ 0 HC	-	-
Nicoletti et al. 2008	217 MS/ 200 HC	0 MS/ 1 HC	-	IgA & IgG AGA, EMA, ARA (0 MS)
Salvatore et al. 2004	95 MS	0/ 95	-	-

Occurrence of IgA and IgG Autoantibodies to Calreticulin in Coeliac Disease and Various Autoimmune Diseases

D. Sánchez[1], L. Tučková[1], P. Šebo[1], M. Michalak[2], A. Whelan[3], I. Šterzl[4], L. Jelínková[1], E. Havrdová[5], M. Imramovská[5], Z. Beneš[6], S. Krupičková[1] and H. Tlaskalová-Hogenová[1]

Journal of Autoimmunity (2000) **15**, 441–449

Table 1. *Comparison of anti-CRT*, anti-tTG**, anti-gliadin and anti-enterocyte Abs levels in sera of adult patients with coeliac disease, and other diseases to healthy controls*** (Mann–Whitney test)*

Antibodies		Autoimmune diseases					
Against	Class	CD (n=75)	SLE (n=75)	IDDM (n=44)	MS (n=46)	AT (n=29)	IBD (n=34)
Calreticulin	IgA	$P<0.001$	NS	NS	$P<0.05$	NS	$P<0.01$
Calreticulin	IgG	$P<0.001$	$P<0.001$	$P<0.01$	$P<0.001$	$P<0.05$	NS
tTG	IgA	$P<0.001$	$P<0.05$	NS	NS	NS	NS
Gliadin	IgA	$P<0.001$	NS	NS	$P<0.05$	NS	NS
Enterocytes	IgA	$P<0.001$	$P<0.01$	NS	NS	$P<0.001$	$P<0.001$

*CRT (calreticulin), **tTG (tissue transglutaminase), ***59 adults.
n=number of patients.

Occurrence of IgA and IgG Autoantibodies to Calreticulin in Coeliac Disease and Various Autoimmune Diseases

D. Sánchez[1], L. Tučková[1], P. Šebo[1], M. Michalak[2], A. Whelan[3], I. Šterzl[4], L. Jelínková[1], E. Havrdová[5], M. Imramovská[5], Z. Beneš[6], S. Krupičková[1] and H. Tlaskalová-Hogenová[1]

Journal of Autoimmunity (2000) **15**, 441–449

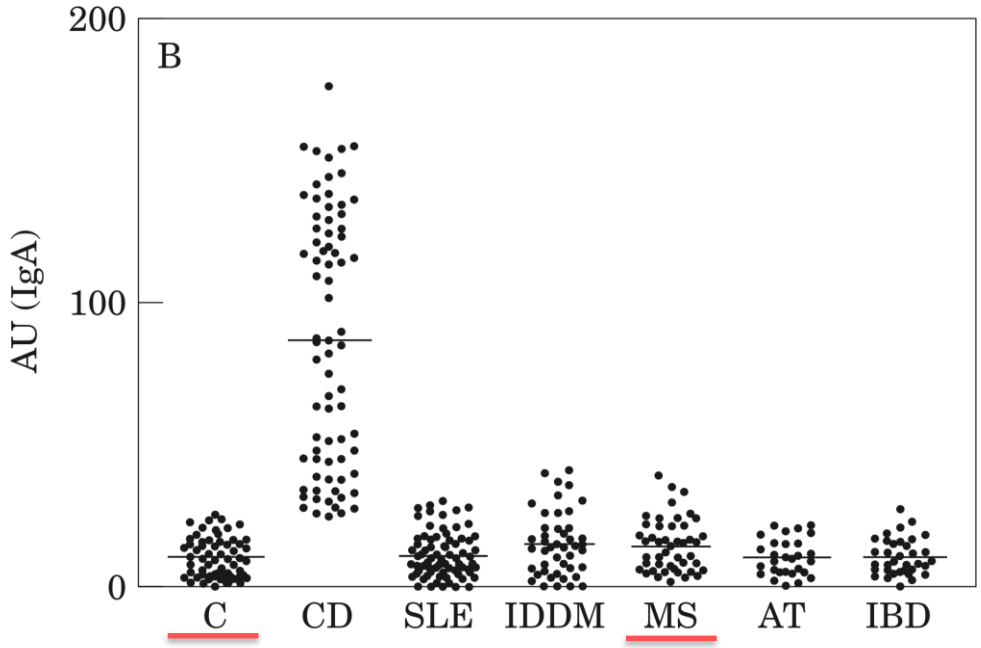


Figure 3. Distribution of IgA Abs to tissue transglutaminase (A), gliadin (B) and rat enterocytes (C) in sera from adult patients with coeliac disease (CD, n=75), systemic lupus erythematosus (SLE, n=75), insulin dependent diabetes mellitus (IDDM, n=44), multiple sclerosis (MS, n=46), autoimmune thyroiditis (AT, n=29), inflammatory bowel disease (IBD, n=34) and adult healthy controls (C, n=59). Values are expressed in AU. Solid lines represent the mean, and values above cut-off (which equals 25.3 AU for Abs to tTG, to gliadin 24.3 AU and to enterocytes 67.5 AU) are considered positive.

Multiple sclerosis and gluten sensitivity☆

Afshin Borhani Haghighi [a,*], Neda Ansari [b], Maral Mokhtari [b], Bita Geramizadeh [c], Kamran B. Lankarani [d]

Clinical Neurology and Neurosurgery 109 (2007) 651–653

Endpoint	MS (n=161)	HC (n=166)	
AGA IgG/ IgA positivity	6 (3.7%)*/ 5 (3.1%)*	5 (3%)/ 6 (3.6%)	*Biopsy & tTG negative for CD
Mean AGA IgG/ IgA	3.62 ± 2.75/ 2.13 ± 1.29	4.02 ± 2.38/ 2.09 ± 1.52	p=0.11 (IgG) p=0.26 (IgA)
95%-CI for AGA IgG/ IgA	3.62 ± 0.42/ 2.13 ± 0.199	4.02 ± 0.36/ 2.09 ± 0.23	

No significant difference in mean values of IgG and IgA AGA between different MS courses or involvement of different MS functional systems.

Reichelt K-L, Jensen D. IgA antibodies against gliadin and gluten in multiple sclerosis.

Acta Neurol Scand 2004: 110: 239–241.

Table 1 Serum IgA antibody levels in multiple sclerosis (MS) and controls

	Mean	Median	Number	95% CI	*P*-value
MS					
IgA gliadin	0.327	0.441	38	0.156–0.498	<0.001
IgA gluten	0.249	0.263	38	0.147–0.351	<0.001
IgA casein	0.103	0.159	38	0.041–0.165	0.035
Control					
IgA gliadin	0.061	0.067	27	0.035–0.088	
IgA gluten	0.056	0.051	27	0.035–0.076	
IgA casein	0.039	0.078	27	0.007–0.072	

P-values using Mann–Whitney *U*-test for patient data against controls. Six of 38 patients had IgA values against gliadin and gluten above the cutoff for celiac disease, while none of the controls showed such increases. Counting numbers with IgA antibody levels above the cutoff for celiac disease, we find chi-square values with $P < 0.01$.

Table 2 IgG antibodies against gluten and gliadin in MS

	Mean	Median	Number	95% CI	*P*-value
MS					
Gliadin	0.466	0.400	38	0.377–0.556	<0.001
Gluten	0.451	0.400	38	0.358–0.543	<0.001
Control					
Gliadin	0.154	0.100	24	0.073–0.236	
Gluten	0.158	0.100	24	0.066–0.251	

ELISA measured IgG antibodies are as described (6, 7). Although not very high, the level was very significant compared with controls run simultaneously.

Conclusions: The data presented indicate that there may be a possible moderately increased uptake of some specific proteins from the gut in MS compared with controls.

Gluten Sensitivity in Multiple Sclerosis

Experimental Myth or Clinical Truth?

Dana Ben-Ami Shor,[a] Ori Barzilai,[a] Maya Ram,[a] David Izhaky,[a] Bat Sheva Porat-Katz,[b] Joab Chapman,[c] Miri Blank,[a] Juan-Manuel Anaya,[d] and Yehuda Shoenfeld[a,e]

TABLE 1. IgG And IgA Antibodies against Gliadin and Tissue Transglutaminase in MS Expressed in Antibody Index (AI) Units

	Mean	Median	Number	Percentage
MS (n=98)				
IgA AGA	0.32	0.2	7	7.2%
IgA tTG	0.2	0.2	0	0
IgG AGA	0.52	0.2	7	7.1%*
IgG tTG	0.35	0.3	4	4.1%**
Control (n=140)				
IgA AGA	0.34	0.2	5	3.6%
IgA tTG	0.2	0.2	0	0
IgG AGA	0.25	0.2	2	1.4%
IgG tTG	0.33	0.3	0	0

AGA, antigliadin antibodies; tTG, anti-tissue transglutaminase antibodies.

*OR = 5.3; 95% CI: 1.08 to 26.13, $P = 0.03$.

**OR = 13.4; 95% CI: 0.71 to 251.62, $P = 0.028$.

Contemporary Challenges in Autoimmunity: Ann. N.Y. Acad. Sci. 1173: 343–349 (2009).

Our findings support the associations between antibodies against gliadin and tissue transglutaminase to multiple sclerosis. The specific role of these antibodies in the pathogenesis of multiple sclerosis remains uncertain and requires additional research. A gluten free diet should be considered in specific cases of patients who present with gluten antibodies.

Does cryptic gluten sensitivity play a part in neurological illness?

M Hadjivassiliou, A Gibson, G A B Davies-Jones, A J Lobo, T J Stephenson, A Milford-Ward

Summary

Background Antigliadin antibodies are a marker of untreated coeliac disease but can also be found in individuals with normal small-bowel mucosa. Because neurological dysfunction is a known complication of coeliac disease we have investigated the frequency of antigliadin antibodies, as a measure of cryptic gluten sensitivity, and coeliac disease in neurological patients.

patients from group 1 revealed histological evidence of coeliac disease in nine (35%), non-specific duodenitis in ten (38%), and no lesion in seven (26%) individuals.

Interpretation Our data suggest that gluten sensitivity is common in patients with neurological disease of unknown cause and may have aetiological significance.

Lancet 1996; **347:** 369–71

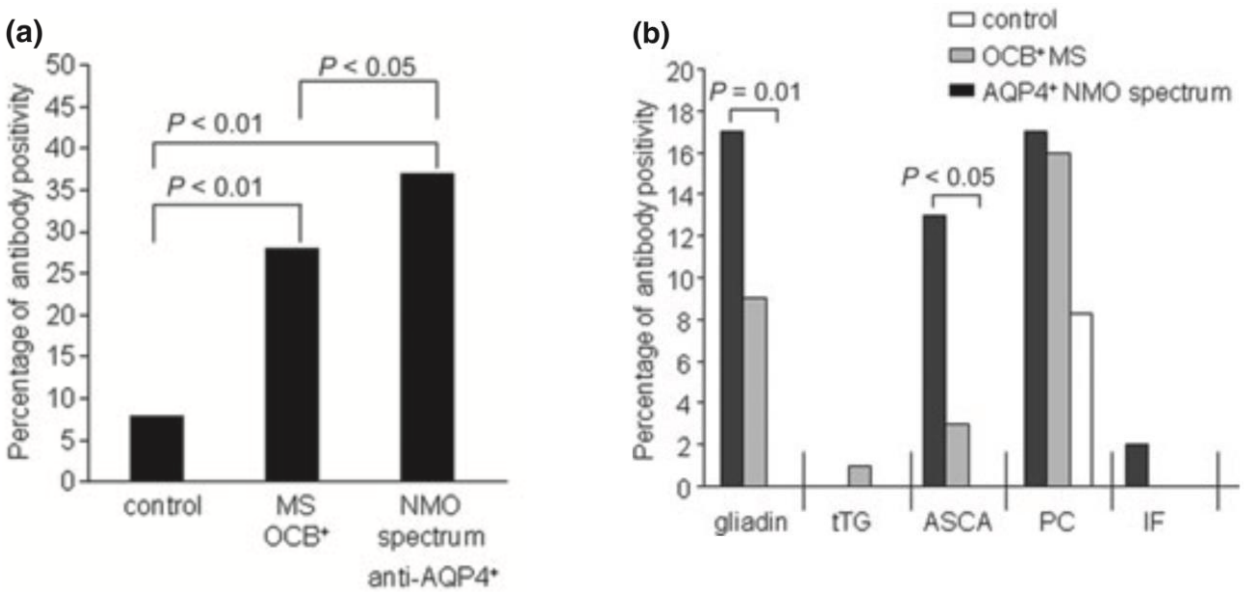


Table 1 The percentage of antibodies associated with gastrointestinal diseases in NMO, NMO spectrum disorders and MS compared to healthy controls

	Gliadin IgA	tTG IgA	tTG IgG	ASCA IgA	ASCA IgG	PC IgG	IF IgG	≥1 Ab
Controls $n = 48$	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (8.3)	0 (0)	4 (8.3)
Multiple sclerosis Patients $n = 85$	8 (9.4)	0 (0)	1 (1.2)	0 (0)	3 (3.5)	14 (16.5)	0 (0)	24 (28)**

NMO, neuromyelitis optica; NMO-SD, NMO spectrum disorders; RION, relapsing inflammatory or bilateral optic neuritis; LETM, longitudinally extensive transverse myelitis; tTG, tissue-transglutaminase; ASCA, anti-*Saccharomyces cerevisiae* antibodies; PC, parietal cell; IF, intrinsic factor; AQP4, aquaporin 4. Number (percentage) of gastrointestinal Ab-seropositive cases and results of Fisher's exact tests after Bonferroni's correction are indicated (*$P \leq 0.05$; **$P \leq 0.01$ compared to controls, respectively).

European Journal of Neurology 2013, 20: 1492–1495

Transglutaminase-6 is an autoantigen in progressive multiple sclerosis and is upregulated in reactive astrocytes

Multiple Sclerosis Journal
2017, Vol. 23(13) 1707–1715
DOI: 10.1177/1352458516684022

Massimiliano Cristofanilli, Daniel Gratch, Benjamin Pagano, Kelsey McDermott, Jessie Huang, Jeffrey Jian, Deneb Bates and Saud A Sadiq

Abstract

Background: Transglutaminase-6 (TGM6), a member of the transglutaminase enzyme family, is found predominantly in central nervous system (CNS) neurons under physiological conditions. It has been proposed as an autoimmune target in cerebral palsy, gluten-sensitive cerebellar ataxia, and schizophrenia.

Objective: To investigate TGM6 involvement in multiple sclerosis (MS).

Methods: Antibody levels against TGM6 (TGM6-IgG) were measured in the cerebrospinal fluid (CSF) of 62 primary progressive multiple sclerosis (PPMS), 85 secondary progressive multiple sclerosis (SPMS), and 50 relapsing-remitting multiple sclerosis (RRMS) patients and 51 controls. TGM6 protein expression was analyzed in MS brain autopsy, murine experimental autoimmune encephalomyelitis (EAE), and cultured astrocytes.

Results: CSF levels of TGM6-IgG were significantly higher in PPMS and SPMS compared to RRMS and controls. Notably, patients with clinically active disease had the highest TGM6-IgG levels. Additionally, brain pathology revealed strong TGM6 expression by reactive astrocytes within MS plaques. In EAE, TGM6 expression in the spinal cord correlated with disease course and localized in reactive astrocytes infiltrating white matter lesions. Finally, knocking down TGM6 expression in cultured reactive astrocytes reduced their glial fibrillary acidic protein (GFAP) expression.

Conclusion: TGM6-IgG may be a candidate CSF biomarker to predict and monitor disease activity in progressive MS patients. Furthermore, TGM6 expression by reactive astrocytes within both human and mouse lesions suggests its involvement in the mechanisms of glial scar formation.

Can we answer the three questions now?

1. **Can patients with MS benefit from a GFD?**
    - Endpoints of interest: neurological symptoms, expanded disability scale score (EDSS), relapse rate, quality of life, biomarkers from cerebrospinal fluid, lesion activity, and other magnetic resonance imaging (MRI) measures
2. **Is there an increased prevalence of markers of gluten-reactivity in patients with MS compared to HC?**
    - Markers of interest: gastrointestinal symptoms, positivity for HLA-DQ2 & -DQ8 haplotypes, presence of antibodies (IgG and IgA antibodies against gliadin, other gluten fractions, transglutaminases, as well as anti-endomysial and anti-reticulin antibodies), increased gut permeability, abnormal gut histology as well as increased numbers of T cell infiltrates in the gut
3. **Is there an increased risk of MS among patients with CD or vice versa?**

Next steps

- More clinical intervention trials with MS-specific endpoints
- Increase comparability & improve reporting of serology studies. Always include a group of HC and report the number and percentage of seropositive results as well as mean/median and measures of variance
- New markers to quantify adaptive and innate immune reactions to gluten
- Stay informed on the latest research and always be critical

My research

Gut-CNS interactions in early multiple sclerosis – is there a role for gluten?

- Patients with optic neuritis
- Six months on a GFD
- Blood-brain barrier permeability
- Intestinal permeability
- Flow cytometry
- Fecal microbiome

In collaboration with:

- Multiple Sclerosis Clinic/ Optic Neuritis Clinic, Department of Neurology, Rigshospitalet, Glostrup
- Functional Imaging Unit, Rigshospitalet, Glostrup
- Bartholin Institute, Rigshospitalet
- NEXS, University of Copenhagen
- FOOD, University of Copenhagen

Time for Questions