UNIVERSITE CADI AYYAD

FACULTE DE MEDECINE ET DE PHARMACIE

MARRAKECH

Year 2012 **Thesis N° 84**

Gluten sensitivity and neuropathies
A Moroccan case-control study

THESIS

Presented to The Medicine Faculty on ……,2012

BY

Mr. Bouroumane Mohamed Réda

Born on March 22nd, 1985 in Marrakesh

IN PARTIAL FULFILLEMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF MEDECINE

Key words:

Gluten sensitivity, neuropathies, antigliadin antibodies, prevalence.

JURY

M.	A. Alaoui Yazidi Professor of Pneumology and Phthisiology Director of PCIM research laboratory	CHAIRMAN
M.	B. Admou Aggregate Professor of immunology Member of PCIM research laboratory	ADVISOR
M.	N. Kissani Professor of Neurology	JUDGES
M.	M. Bourrous Aggregate Professor of Neuro-Paediatrics	
M.	L. Chabaa Professor of Biochemistry	
M.	M. Amine Aggregate Professor of Epidemiology Member of PCIM research laboratory	

PCIM **Research Laboratory**

The Prophet Mohamed (PBUH) said,
"There is no disease that Allah has created except that He also has created its treatment, apart from aging»

At the time of being admitted as a member of the medical profession:
I solemnly pledge myself to consecrate my life to the service of humanity;
I will give to my teachers the respect and gratitude which is their due;
I will practice my profession with conscience and dignity; the health of my patient will be my first consideration;
I will maintain by all the means in my power, the honor and the noble traditions of the medical profession; my colleagues will be my brothers;
I will not permit considerations of religion, nationality, race, party politics or social standing to intervene between my duty and my patient;
I will maintain the utmost respect for human life from the time of conception, even under threat;

I will not use my medical knowledge contrary to the laws of humanity;
I make these promises solemnly, freely and upon my honour.

Geneva Declaration 1948

LIST OF PROFESSORS AT THE MEDICINE FACULTY OF MARRAKESH - CADI AYYAD

UNIVERSITE CADI AYYAD
FACULTE DE MEDECINE ET DE PHARMACIE
MARRAKECH

Doyen Honoraire : Pr. Badie-Azzamann MEHADJI

ADMINISTRATION

Doyen : Pr. Abdelhaq ALAOUI YAZIDI

Vice doyen à la recherche : Pr. Badia BELAABIDIA

Vice doyen aux affaires pédagogiques : Pr. Ag Zakaria DAHAMI

Secrétaire Général : Mr. Azzeddine EL HOUDAIGUI

PROFESSEURS D'ENSEIGNEMENT SUPERIEUR

ABOUSSAD	Abdelmounaim	Néonatologie
AMAL	Said	Dermatologie
ASMOUKI	Hamid	Gynécologie – Obstétrique A
ASRI	Fatima	Psychiatrie
AIT BENALI	Said	Neurochirurgie
ALAOUI YAZIDI	Abdelhaq	Pneumo-phtisiologie
BENELKHAIAT BENOMAR	Ridouan	Chirurgie – Générale
BELAABIDIA	Badia	Anatomie-Pathologique
BOUMZEBRA	Drissi	Chirurgie Cardiovasculaire
BOUSKRAOUI	Mohammed	Pédiatrie A

CHABAA	Laila	Biochimie
CHOULLI	Mohamed Khaled	Neuropharmacologie
ESSAADOUNI	Lamiaa	Médecine Interne
FIKRY	Tarik	Traumatologie- Orthopédie A
FINECH	Benasser	Chirurgie – Générale
KISSANI	Najib	Neurologie
KRATI	Khadija	Gastro-Entérologie
LATIFI	Mohamed	Traumato – Orthopédie B
MOUDOUNI	Said mohammed	Urologie
MOUTAOUAKIL	Abdeljalil	Ophtalmologie
RAJI	Abdelaziz	Oto-Rhino-Laryngologie
SARF	Ismail	Urologie
SBIHI	Mohamed	Pédiatrie B
SOUMMANI	Abderraouf	Gynécologie-Obstétrique A

PROFESSEURS AGREGES

ABOULFALAH	Abderrahim	Gynécologie – Obstétrique B
ADERDOUR	Lahcen	Oto-Rhino-Laryngologie
AMINE	Mohamed	Epidémiologie - Clinique
AIT SAB	Imane	Pédiatrie B
AKHDARI	Nadia	Dermatologie
BOURROUS	Monir	Pédiatrie A
CHELLAK	Saliha	Biochimie-chimie (Militaire)
DAHAMI	Zakaria	Urologie
EL ADIB	Ahmed rhassane	Anesthésie-Réanimation
EL FEZZAZI	Redouane	Chirurgie Pédiatrique
EL HATTAOUI	Mustapha	Cardiologie
ELFIKRI	Abdelghani	Radiologie (Militaire)
ETTALBI	Saloua	Chirurgie – Réparatrice et plastique
GHANNANE	Houssine	Neurochirurgie
LMEJJATI	Mohamed	Neurochirurgie
LOUZI	Abdelouahed	Chirurgie générale

LRHEZZIOUI	Jawad	Neurochirurgie(Militaire)
MAHMAL	Lahoucine	Hématologie clinique
MANOUDI	Fatiha	Psychiatrie
MANSOURI	Nadia	Chirurgie maxillo-faciale Et stomatologie
NAJEB	Youssef	Traumato - Orthopédie B
NEJMI	Hicham	Anesthésie - Réanimation
OULAD SAIAD	Mohamed	Chirurgie pédiatrique
SAIDI	Halim	Traumato - Orthopédie A
SAMKAOUI	Mohamed Abdenasser	Anesthésie- Réanimation
TAHRI JOUTEI HASSANI	Ali	Radiothérapie
TASSI	Noura	Maladies Infectieuses
YOUNOUS	Saïd	Anesthésie-Réanimation

PROFESSEURS ASSISTANTS

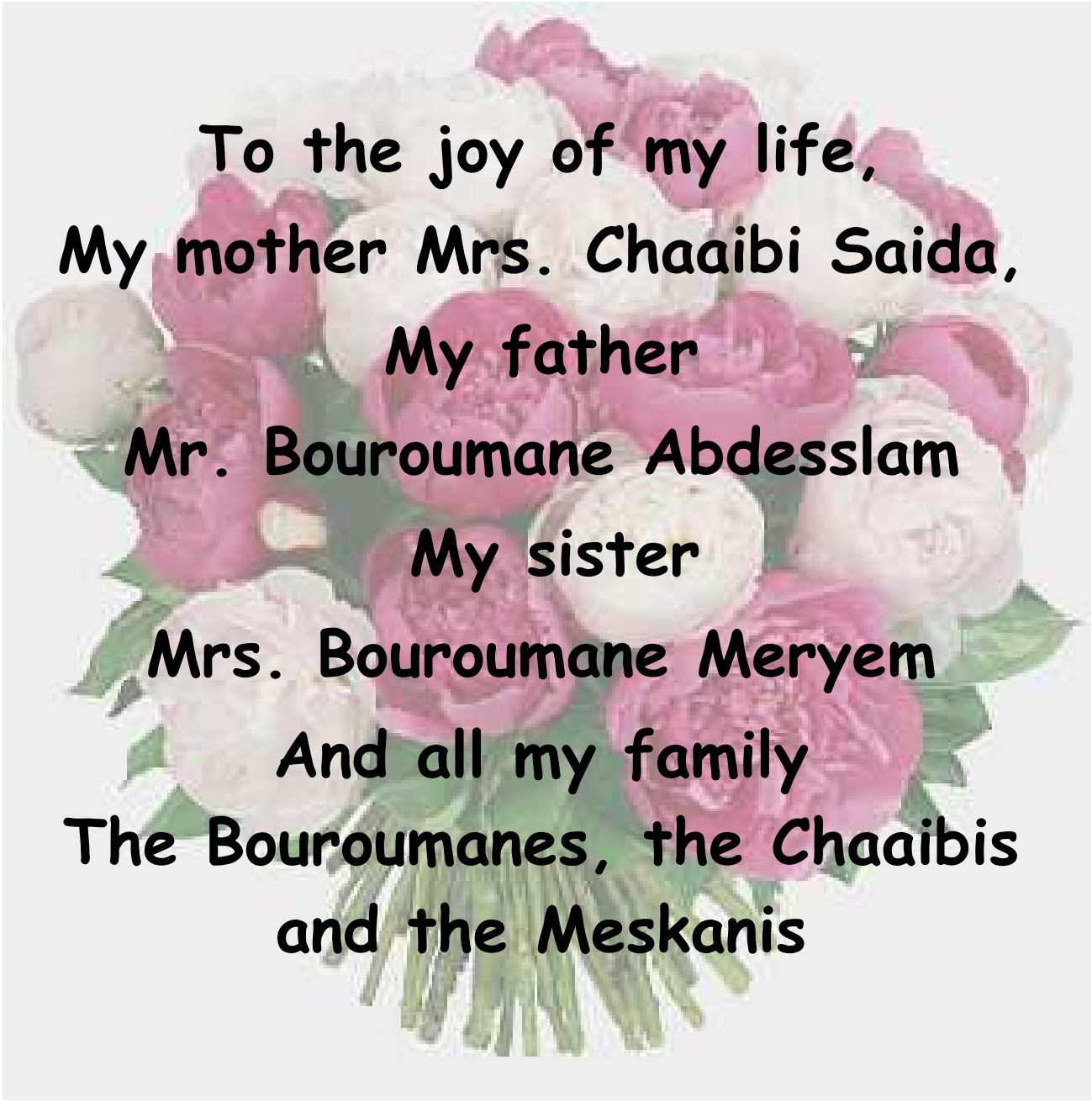
ABKARI	Imad	Traumatologie-orthopédie B
ABOU EL HASSAN	Taoufik	Anesthésie - réanimation
ABOUSSAIR	Nisrine	Génétique
ADALI	Imane	Psychiatrie
ADALI	Nawal	Neurologie
ADMOU	Brahim	Immunologie
AGHOUTANE	El Mouhtadi	Chirurgie – pédiatrique
AISSAOUI	Younes	Anésthésie Reanimation (Militaire)
AIT BENKADDOUR	Yassir	Gynécologie – Obstétrique A
AIT ESSI	Fouad	Traumatologie-orthopédie B
ALAOUI	Mustapha	Chirurgie Vasculaire périphérique (Militaire)
ALJ	Soumaya	Radiologie
AMRO	Lamyae	Pneumo - phtisiologie
ANIBA	Khalid	Neurochirurgie
ARSALANE	Lamiae	Microbiologie- Virologie (Militaire)
BAHA ALI	Tarik	Ophtalmologie
BAIZRI	Hicham	Endocrinologie et maladies métaboliques (Militaire)

BASRAOUI	Dounia	Radiologie
BASSIR	Ahlam	Gynécologie – Obstétrique B
BELBARAKA	Rhizlane	Oncologie Médicale
BELKHOU	Ahlam	Rhumatologie
BEN DRISS	Laila	Cardiologie (Militaire)
BENCHAMKHA	Yassine	Chirurgie réparatrice et plastique
BENHADDOU	Rajaa	Ophtalmologie
BENHIMA	Mohamed Amine	Traumatologie-orthopédie B
BENJILALI	Laila	Médecine interne
BENZAROUEL	Dounia	Cardiologie
BOUCHENTOUF	Rachid	Pneumo-phtisiologie (Militaire)
BOUKHANNI	Lahcen	Gynécologie – Obstétrique B
BOURRAHOUAT	Aicha	Pédiatrie
BSSIS	Mohammed Aziz	Biophysique
CHAFIK	Aziz	Chirurgie Thoracique (Militaire)
CHAFIK	Rachid	Traumatologie-orthopédie A
CHERIF IDRISSI EL GANOUNI	Najat	Radiologie
DAROUASSI	Youssef	Oto-Rhino – Laryngologie (Militaire)
DIFFAA	Azeddine	Gastro - entérologie
DRAISS	Ghizlane	Pédiatrie A
EL AMRANI	Moulay Driss	Anatomie
EL ANSARI	Nawal	Endocrinologie et maladies métaboliques
EL BARNI	Rachid	Chirurgie Générale (Militaire)
EL BOUCHTI	Imane	Rhumatologie
EL BOUIHI	Mohamed	Stomatologie et chirurgie maxillo faciale
EL HAOUATI	Rachid	Chirurgie Cardio Vasculaire
EL HAOURY	Hanane	Traumatologie-orthopédie A
EL HOUDZI	Jamila	Pédiatrie B
EL IDRISSI SLITINE	Nadia	Pédiatrie (Néonatologie)
EL KARIMI	Saloua	Cardiologie
EL KHADER	Ahmed	Chirurgie Générale (Militaire)
EL KHAYARI	Mina	Réanimation médicale
EL MANSOURI	Fadoua	Anatomie – pathologique (Militaire)
EL MEHDI	Atmane	Radiologie

EL MGHARI TABIB	Ghizlane	Endocrinologie et maladies métaboliques
EL OMRANI	Abdelhamid	Radiothérapie
FADILI	Wafaa	Néphrologie
FAKHIR	Bouchra	Gynécologie – Obstétrique B
FAKHIR	Anass	Histologie -embyologie cytogénétique
FICHTALI	Karima	Gynécologie – Obstétrique B
HACHIMI	Abdelhamid	Réanimation médicale
HAJJI	Ibtissam	Ophtalmologie
HAOUACH	Khalil	Hématologie biologique
HAROU	Karam	Gynécologie – Obstétrique A
HOCAR	Ouafa	Dermatologie
JALAL	Hicham	Radiologie
KADDOURI	Said	Médecine interne (Militaire)
KAMILI	El ouafi el aouni	Chirurgie – pédiatrique générale
KHALLOUKI	Mohammed	Anesthésie-Réanimation
KHOUCHANI	Mouna	Radiothérapie
KHOULALI IDRISSI	Khalid	Traumatologie-orthopédie (Militaire)
LAGHMARI	Mehdi	Neurochirurgie
LAKMICHI	Mohamed Amine	Urologie
LAKOUICHMI	Mohammed	Chirurgie maxillo faciale et Stomatologie (Militaire)
LAOUAD	Inas	Néphrologie
LOUHAB	Nissrine	Neurologie
MADHAR	Si Mohamed	Traumatologie-orthopédie A
MAOULAININE	Fadlmrabihrabou	Pédiatrie (Néonatologie)
MARGAD	Omar	Traumatologie – Orthopédie B
MATRANE	Aboubakr	Médecine Nucléaire
MOUAFFAK	Youssef	Anesthésie - Réanimation
MOUFID	Kamal	Urologie (Militaire)
MSOUGGAR	Yassine	Chirurgie Thoracique
NARJIS	Youssef	Chirurgie générale
NOURI	Hassan	Oto-Rhino-Laryngologie
OUALI IDRISSI	Mariem	Radiologie
OUBAHA	Sofia	Physiologie
OUERIAGLI NABIH	Fadoua	Psychiatrie (Militaire)

QACIF	Hassan	Médecine Interne (Militaire)
QAMOUSS	Youssef	Anesthésie - Réanimation (Militaire)
RABBANI	Khalid	Chirurgie générale
RADA	Noureddine	Pédiatrie
RAIS	Hanane	Anatomie-Pathologique
ROCHDI	Youssef	Oto-Rhino-Laryngologie
SAMLANI	Zouhour	Gastro - entérologie
SORAA	Nabila	Microbiologie virologie
TAZI	Mohamed Illias	Hématologie clinique
ZAHLANE	Mouna	Médecine interne
ZAHLANE	Kawtar	Microbiologie virologie
ZAOUI	Sanaa	Pharmacologie
ZIADI	Amra	Anesthésie - Réanimation
ZOUGAGHI	Laila	Parasitologie –Mycologie


DEDICATIONS



To the joy of my life,
My mother Mrs. Chaaibi Saida,
My father
Mr. Bouroumane Abdesslam
My sister
Mrs. Bouroumane Meryem
And all my family
The Bouroumanes, the Chaaibis
and the Meskanis

ACKNOWLEDGEMENTS

I am grateful to several people for the role they have played to enable me undertake and accomplish my studies and dissertation.

In particular, I extend my deepest appreciation to my Thesis Advisor Prof. Admou Ibrahim, for his unwavering support and enthusiasm during the entire research period, which enabled me to carry out and complete this project. I enjoyed his guidance, his modesty and positive criticisms at every stage of the project. His availability for consultation at any time, weekdays and weekends, day and night ensured the smooth completion of my project, and confirmed that I was not working alone.

I am grateful to my University supervisors,

Prof. Najib Kissani, Head of Neurology Department at the University Hospital of Marrakesh who granted me the permission to work on the patients hospitalized in the Department and was always ready for help and support.

Prof. Mohamed Amine, Head of Epidemiology Laboratory at the Medicine Faculty of Marrakesh and Prof. Laila Chabaa, Head of Bio-Chemistry Laboratory at the University Hospital of Marrakesh also deserve my sincerest thanks. Their friendship and professional assistance has meant more to me than I could ever express which helped me overcome the various challenges of the research project.

I am also very grateful to Prof. Mounir Bourouss, Professor of Neuro-Paediatrics at the University Hospital of Marrakesh for his invaluable friendly assistance and support throughout my studies and doctorial process.

This work would not have been possible without the dedicated efforts by Pr. Janati Idrissi, Director of Ibn-Sina Military Hospital of Marrakesh, Morocco, and Dr. Othmani, the head of Transfusion Center in the same hospital, for allowing me to include blood donors from the Transfusion Center of Ibn-Sina Military Hospital. Besides, I am grateful to its entire staff for their technical help and assistance.

The staff members of the Neurology Department and Bio-Chemistry Laboratory were also very helpful, because I often consulted for their technical advice for the patients' selection and the immunological screening process. Hence, special thanks goes to Prof. Nissrine louhab, Dr. Chraa Mohamed, Dr. Yassine Mebrouk and Dr. Safaa Zahlane, Mrs. Badia Bouzari, Mrs. Saida Hilm, Mrs. Siham sati and Mrs. Nadia Khalil. Also, I am grateful for the contribution and support of Dr. Benhiba Imane, Mr. Moumen and Mr. Sakoura.

Many thanks also go to Mr. Mohamed Lahjouji, Director of Morocco Diagnostic System Company and member of Orgentec Diagnostika GmbH (Germany), for sponsoring this project.

Finally, I wish to also acknowledge Prof. Sidihida Abderrahman (English Teacher at the American Language Center of Marrakesh) for the literary revision and assistance, and Ms. Rabiaa Goughri for checking up on the design of this document with creativity and enthusiasm.

ABBREVIATIONS

AGA	:	Antigliadin antibodies
AHD	:	Anterior horn disease
ALS	:	Amyotrophic lateral sclerosis
CD	:	Celiac disease
CSF	:	Cerebro-spinal fluid
CPK	:	Creatine Phospho-kinase
DGP	:	deamidated gliadin peptides
DM	:	Dermato-myositis
EMA	:	Anti-endomysium antibodies
EMG	:	Electro-myography
Gamma GT	:	Gamma glutamyl transferase
GFD	:	Gluten free diet
GS	:	Gluten sensitivity
HLA	:	Human leukocyte Antigen
IELs	:	Intra-epithelial lymphocytes
IFN	:	Interferon
IgA	:	Immunoglobulin A
IgG	:	Immunoglobulin G
IIM	:	Inflammatory idiopathic myopathy
IL-15	:	interleukine-15
M/F	:	Male to female
MICA	:	non-classical MHC molecules
MRI	:	Magnetic resonance imaging
MS	:	Multiple sclerosis
MSA	:	Multiple system atrophy
NKG2D	:	Natural killer receptor
NP	:	Not provided
PM	:	polymyositis
PN	:	Peripheral neuropathy
PNKD		paroxysmal non-kinesigenic dystonia

PT	:	Prothrombin time
Sd	:	Syndrome
s-IBM	:	Sporadic inclusion body myositis
SIgAD	:	Selective IgA deficiency
SR	:	Sedimentation rate
TCR	:	T cell receptor
tTGA	:	tissue transglutaminase antibodies
WBC	:	White blood cells

SUMMARY

INTRODUCTION

Introduction

I. Definitions

Gluten sensitivity (GS) is a systemic autoimmune disease with diverse manifestations. This disorder is characterized by a heightened immunological responsiveness to ingested gluten in genetically susceptible individuals[2].

It represents a spectrum of diverse manifestations, one of which is gluten-sensitive enteropathy (or celiac disease), dermatopathy (dermatitis herpetiformis) and neurological disorders (such as gluten ataxia and neuropathy)[2].

The term celiac disease (CD) should now be restricted to describe gluten-sensitive enteropathy (including the triad of villous atrophy, crypt hyperplasia and increased intraepithelial lymphocytes on histological examination of the small-bowel mucosa).

Although neurological manifestations in patients with established CD have been reported since 1966, it was not until 30 years later that, in some individuals, GS was shown to manifest exclusively with neurological dysfunction. Furthermore, the concept of extra-intestinal presentations without enteropathy has only recently become accepted[2].

Hadjivassiliou reports in a prospective study on 145 cases of idiopathic axonal neuropathies a prevalence of 34% of gluten sensitivity. Also, in a study realized on 71 celiac patients, 22,5% developed neurologic disorders[3]. In addition, other studies showed unusual frequency of

CD's immunologic markers in the idiopathic cerebellar ataxia and peripheral neuropathies with undetermined etiology[4, 5]. Besides, the prevalence of IgG anti-gliadin antibodies is found to be 57% in idiopathic neuropathies versus 5% in the neuropathies with known aetiology and 12% in the healthy controls[6].

Otherwise, many researchers shed the light on the efficacy of gluten free diet (GFD) as a potential treatment for gluten sensitivity linked pathologies[7].

The high frequency of the GS within the population, the impact on the treatment and the absence of any research about the relation between GS and neuropathies in Morocco motivated us to carry out this study.

We take the celiac disease as a prototype of the GS in order to describe the physiopathology, and immunology and pathology and diagnostic tools.

II. Gluten sensitive enteropathy

1. Historical review:

The gluten sensitive enteropathy was first described by Samuel Gee in 1888, a similar description of malabsorption syndrome by Arateus and Cappadocie (turkey) has been performed since the 2nd century AD.

The etiology was unknown until a Netherland's pediatrician,Willem K.Dicke, showed a relation between the consummation of bread and cereals and chronic diarrhea.

This observation was reinforced during the World War II, when doctors witnessed the improvement of patients when bread was excluded from soldiers' food[6].

Dick and Van de Kamer made series of experiments, exposing celiac children to diets with a follow-up of the faeces' weight and faecal fats in order to measure the malabsorption.

Wheat, rye, barley and oats caused a malabsorption syndrome that could be inversed after exclusion of these "toxic" cereals. Short after this observation, the role of gluten as a trigger of this toxicity has been confirmed[8].

The lesion on the proximal duodenum was first described in 1954; the first descriptions were a mucosa inflammation, cryptic hyperplasia and villous flattening[9]. The first duodenal biopsy was performed on a child in 1957[10].

The antibodies against transglutaminase II were identified 10 years ago.

The toxic sequences of gluten were also deciphered 10 years ago, (more than 100 different peptides)

2. Physiopathology:

Celiac disease is an inflammatory multifactor disorder of the small intestine caused by an immune response to ingested wheat gluten and similar proteins of rye and barley.

Data accumulated since the discovery of gluten specific T cells in the intestine of celiac disease patients the early 1990s have allowed the deciphering of the interplay between the triggering environmental factor, gluten, the main genetic risk factor, the HLA-DQ2/8 haplotypes and the auto-antigen: the enzyme tissue transglutaminase (tTG).

More recent work points to an important contribution of innate immunity triggered by a distinct gluten peptide and driven by the pro-inflammatory cytokine Interleukine-5 (IL-15)[11].

2.1 Genetic aspects:

A high prevalence (10%) among first-degree relatives of CD patients indicates that susceptibility to develop CD is strongly influenced by inherited factors[12]. Familial clustering is stronger in CD than in most other chronic inflammatory diseases with a multi-factorial etiology. The strong genetic influence in CD is further supported by a high concordance rate (75%) in monozygotic twins[13].

Both HLA and non-HLA genes contribute to the genetic predisposition. The presence of certain HLA genes appears to be necessary but sufficient for CD development. The characteristic of the HLA association suggest that the HLA genes are involved in a process that controls CD development[14].

For HLA genes, most CD patients carry the DR3-DQ2 haplotype (the DRB1*0301-DQA1*0501-DQB1*0201 haplotype), or are DR5-DQ7/DR7-DQ2 heterozygotes. Available genetic and functional data favor DQ8 as the major susceptibility determinant in these patients[15].

Otherwise, much less is known about non-HLA genes in this disorder. There are several reports that imply involvement of the gene for the negative co-stimulatory molecule CTLA4 (cytotoxic T lymphocyte associated-4), or a neighbouring gene (such as those encoding CD28 or ICOS); however, the overall effect of this gene is small[16].

The region that has most consistently been linked to CD is on the long arm of chromosome 5 (5q31-33)[17, 18]; also, there is accumulating evidence for a susceptibility factor on chromosome 11q32 and on chromosome 19p13 [18].

2.2 Toxic fractions of gluten:

Wheat gluten is a complex mixture of at least 100 related proteins. The major components of gluten are the gliadins and glutenins which can both be subdivided into distinct protein families [14]. The gliadin is composed of monomeric proteines, subdivided into 4 groups (α, β, γ and ω). The Gliadin A (N-terminal region of fraction α) is suspected to be the toxic molecule resulting in the majority of the troubles linked to the CD.

As wheat is used in many food products, exposure to relatively large amounts of gluten starts very early. Usually gluten is introduced into the diet at the age of 6 months and a child of 12 months age eats between 6 and 9 g gluten daily[19].

2.3 The immunologic response in CD:

a. The role of the enzyme tissue transglutaminase

The enzyme tissue transglutaminase (tTG), or transglutaminase 2, is expressed by almost all cell types and is usually retained intra-cellularly in an enzymatically inactive form. It can be released to the extracellular space to become associated with the extracellular matrix[20, 21] and this release is increased when cells are under mechanical or inflammatory stress.

The tTG belongs to a family of at least eight calcium-dependent transamidating enzymes that catalyze the covalent and irreversible cross-linking of a protein with a glutamine residue (glutamine donor) to a second protein with a lysine residue (glutamine acceptor), resulting in the formation of a 3-(gamma-glutamyl)-lysine isopeptide bond[22].

The tTG is only active in the presence of high calcium concentrations, as are found in the

extracellular space, where it contributes to the stabilization of the extracellular matrix[23]. However, intracellular activation and subsequent cross- linking can also occur when cellular integrity is lost and extracellular calcium floods the cell, as found in apoptosis.

Under certain conditions, when no primary lysines are available as glutamine acceptors or at low pH, as can prevail in intestinal inflammation, tTG merely deamidates a target glutamine in the substrate protein, transforming the neutral glutamine to a negatively charged glutamic acid residue[19].

b. The Gluten specific T-Cell response

The DQ2 and DQ8 molecules predispose to CD by preferential presentation of gluten peptides to CD-4 T-cells in the lamina propria. HLA-DQ2 and HLA-DQ8 preferentially bind peptides that contain amino acids with a negative charge, whereas such peptides are not found in the gluten molecules. It was found that the enzyme tissue transglutaminase (tTG), the target of the autoantibodies in CD, can modify gluten peptides, which introduces the negative charges required for binding to HLA-DQ-molecules[24, 25].

Thus, ingested gluten molecules are degraded to peptides by gastrointestinal enzymes, modified by tTG, bind to HLA-DQ2 or HLA-DQ8, and trigger an inflammatory T cell response.

This inflammatory reaction stimulates the production of antigliadin antibodies (AGA) and anti TG antibodies IgA and IgG.

In 1998, the identity of the first gluten peptides that were recognised by such T cells was reported[26](Table I). The now known source proteins for these T cell stimulatory peptides are the a-gliadins, g-gliadins and the low and high molecular weight glutenins[27, 28].

Table I: Amino acid sequence of typical immune stimulating gluten peptides.	
a-gliadin	PQPQLPYPQ and PFPQPQLPY
g-gliadin	FPQQPQQPF and PQQSFPQQQ
Low molecular weight glutenin	FSQQQQSPF
High molecular weight glutenin	QGYYPTSPQ

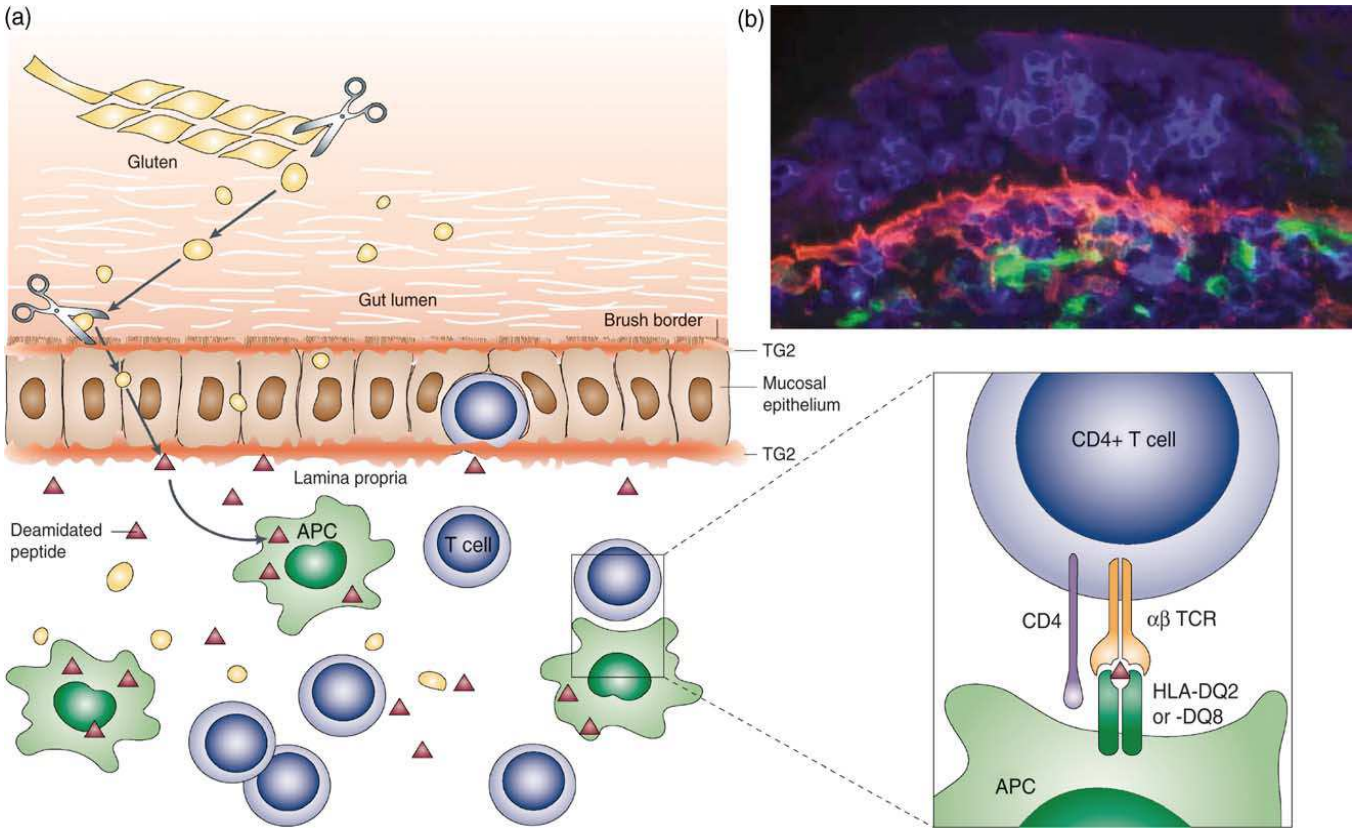


Figure I: *Depiction of the intestinal mucosa with emphasis on the factors taking part in the development and control of celiac disease.*

(a) The parts of gluten which are resistant to luminal and brush border enzymes will survive digestion, and can be transported across the epithelial barrier as polypeptides.

- Gluten peptides are deamidated by tissue transglutaminase (tTG or TG2), which, in the intestinal mucosa, is mainly located extra-cellularly in the sub-epithelial region, but is also found in the brush border.
- CD4C T-cells in the lamina propria recognize predominantly deamidated gluten peptides, presented by HLA-DQ2 or -DQ8 molecules on the cell surface of antigen presenting cells (APC).
- The activation of the CD4 T-cells triggers an inflammatory T cell response.

(b) Immunofluorescence staining of TG2 (red), HLA-DQ (green) and T cells (CD3; blue) in the small Intestinal mucosa of an untreated celiac disease patient.
(Immunofluorescent image courtesy of H. Scott, Riksh

C. *The role of IL-15 in gluten sensitivity pathogenesis*

The massive increase in IEL is considered a diagnostic criterion of GSE, and is not a usual feature of inflammatory conditions in the small intestine.

The Gliadin-Peptides 31-49, common to the N-termini of a-gliadins, induce the production of the cytokine IL-15 in epithelial cells and macrophages via -as yet unknown- relays[29].

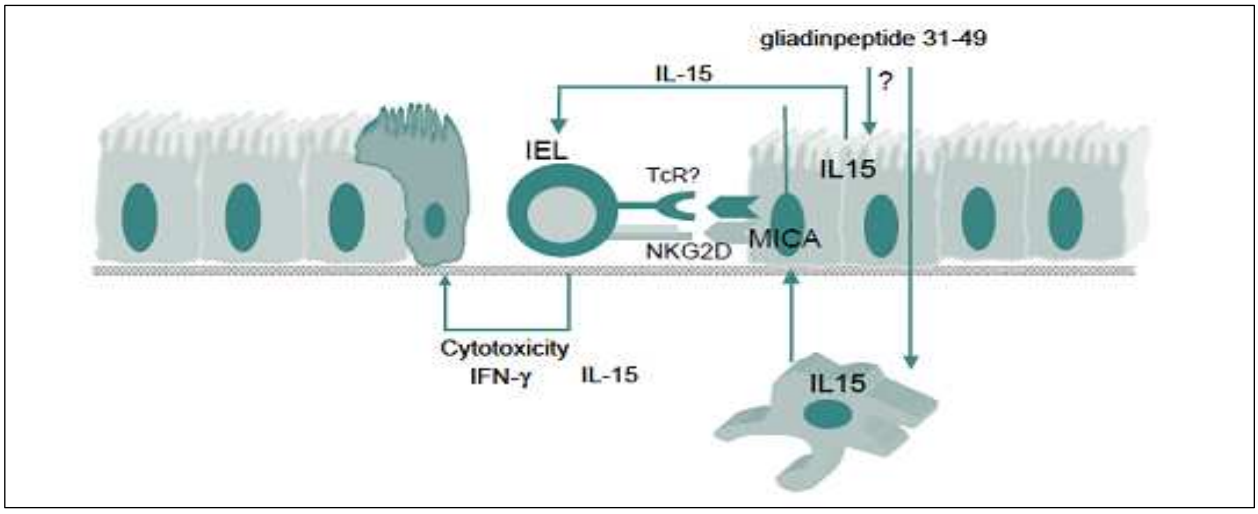


Figure II : ***Mechanisms leading to the activation of IEL by IL-15 in celiac disease***.
NKG2D: natural killer receptor
MICA : non-classical MHC molecules
IL-15 : interleukine-15
TCR : T-Cell receptor
IFN : Interferon
IEL : Intra-epithelial lymphocytes

In turn, IL-15 arms IEL by stimulating their cytotoxic properties and their expression of the innate immune receptor NKG2D (the activating natural killer NK receptor also expressed by intraepithelial T- cells)[30]. Furthermore, IL-15 induces the expression of MICA (non-classical MHC molecules), the epithelial ligand of NKG2D. Binding of NKG2D to MIC can then trigger the cytotoxicity of IEL against epithelial cells.[29, 30] .

3. Epidemiology

3.1. The prevalence of GSE

The prevalence rate of GSE in the population generally depends on the forms of the disease.

Actually, the estimate frequency of combined undiagnosed (or silent form) and diagnosed (active form) GSE was remarkably similar, between 0.7%–2% in most of the populations, including the United States [31]. The prevalence of childhood GSE has been reported to be between 1:285 and 1:77 in Sweden, 1:99 and 1:67 in Finland, 1:230 and 1:106 in Italian schoolchildren. Generally, similar rates have been reported for non-European white populations, such as New Zealand and Australia[31].

In US adults, the prevalence varied from 1:1750 (clinically diagnosed GSE, including dermatitis herpetiformis) to 1:105 (presence of IgA endomysial antibodies) [31].

GSE is virtually unknown in East Asian populations who also lack this HLA haplotype; however, rates close to those in Europe have been reported from the Middle East and India. Although the disease is believed to be rare in Africa (and in Afro-Americans), a highest prevalence (5,6%) has been reported for Saharaouii in North Africa [31-34]; thus, the estimates were 1 :187 in Egypt [35] and 1 :157 in Tunisia [36].

The estimates based on sero-epidemiologic studies suggest that for each diagnosed case of GSE, there may be many undiagnosed cases [37] and that 1%–3% of the general population in Europe and the United States becomes affected at some point in life. [31]

The prevalence was found to be higher among type 1 diabetics and patients with immunologic

pathologies, Down syndrome, Turner syndrome…etc [33, 38, 39].

The contrast between the high rate of the GSE and increased number of undiagnosed cases could be explained by the frequency of asymptomatic forms and also by the fact that physicians don't usually think about this condition.

To sum up, GSE is a systemic disease affecting almost 1% of the general population.

3.2. The incidence of CD

Population-based estimates of the incidence of small bowel biopsy (SBB)- confirmed GSE in adults vary from 2–13/100,000 per year [40, 41]. Those rates have to be interpreted with caution because many patients diagnosed as adults likely have had 20–60 years of untreated GSE, thus hardly represent truly incident new cases of disease.

The recent raise in the incidence rates is likely due to increasing use of serologic screening leading to diagnosis in milder cases. However, there is a paucity of incidence data that would represent the full spectrum of disease, including silent and latent cases.[31]

The variation of nutrition regimens in early childhood and infants among populations and differences in the prevalence of susceptible HLA alleles may explain inter-population variation in the incidence of GSE[31].

The effects of nutritional practices on the risk and severity of GSE may also account for geographic and temporal variation in the incidence and be of great public health importance. [31]

3.3. The Progression

Over time, individuals progress from latent to silent or active disease and can reverse to the

latent subclinical state on a strict GFD [31].

The higher frequencies are registered in two periods of age :

-The first one is ranging between 1 and 5 years old, maximum at 2 years old.[42]

-The second one in adulthood, with a slight sex difference: between the 3rd and 5th decade for females, and later for males [42].

3.4. Gender

Most studies report the female predominance in childhood. The male to female sex ratio ranges between 1/1 and ½; however, the complications are more likely to happen with males[42]. In the region of Marrakesh, series of studied patients showed that 58,62% of GSE patients were females [33].

4. Diagnosis

The presumption of GSE is mainly clinical; however, the high rate of atypical or asymptomatic forms pushes to consider serologic and histologic parameters to establish the diagnosis.

4.1 Clinical description[43]

GSE is diagnosed typically in early childhood around the age of 2 years and a second peak is found around age of 40 years [43]

The clinical manifestations differ greatly, depending on each case and ranging from asymptomatic to full blown CD. The severity of symptoms is not necessarily proportional to the severity of the mucosal lesions and patients with total atrophy can be asymptomatic or present with subclinical symptoms such as iron deficiency or muscle cramps. Recently, more subjects present with asymptomatic or mild GSE than with the classical symptoms of severe malabsorption[43] .

Different forms of GSE are listed below (table II).

Table II : Definition states of GSE.

States of GSE	Definition
Clinically overt GSE	Typical gastrointestinal symptoms and signs of malabsorption. Histological changes with villous atrophy and hypertrophic crypts.
Silent GSE	Asymptomatic patients with typical histological changes
Asymptomatic GSE	Same findings as in silent GSE.
Atypical GSE	Extra-intestinal findings such as IgA-nephropathy symptoms. Typical histological symptoms.
Latent GSE/ Potential GSE	Subjects with genetic predisposition who have initially a normal histology with no atrophy or crypt hyperplasia. Immunological abnormalities such as increased count of IELs and positive EMA or tTG-antibody tests are sometimes present. These subjects may develop clinically overt GSE later in life.
Refractory GSE	Patients who do not respond to gluten-free diet or who previously responded but later become non-responsive to a gluten-free diet. Intestinal lymphoma may have developed.

Symptoms begin at various times after the ingestion of gluten. Patients generally present with various presentations (see below). Beside the typical symptoms mainly occurring in infants and young children GSE may manifest at any age :

a. ***Typical presentation***: [44]

- Chronic diarrhea
- Anorexia
- Abdominal distension
- Abdominal pain
- Poor weight gain
- Weight loss
- Vomiting
- Severe malnutrition can occur if the diagnosis is delayed
- Behavioral changes are common and include irritability and an introverted attitude

Rarely, severely affected infants present with a celiac crisis, which is characterized by explosive watery diarrhea, marked abdominal distension, dehydration, hypotension, and lethargy, often with profound electrolyte abnormalities, including severe hypokalemia.

The variability in the age of symptom onset possibly depends on the amount of gluten in the diet and other environmental factors, such as duration of breast feeding.

o ***Extra-intestinal symptoms secondary to malabsorption***: [43]

- Peripheral neuropathy (vitamin B12 and B1 deficiency)
- Anemia (iron, vitamin B12 and folate deficiency)
- Growth failure in children
- Bone pain (osteoporosis and osteopenia, vitamin D and calcium deficiency)
- Muscle cramps (magnesium and calcium deficiency)
- Night blindness (vitamin A deficiency)

- Weight loss (impaired absorption of most nutrients)
- Edema (Protein and albumin loss)
- Weakness (hypokalemia and electrolyte depletion)
- Bleeding and hematoma (vitamin K deficiency)

b. Atypical manifestations

- Neurological disorders such as peripheral neuropathies, ataxia, epilepsy.
- Dermatitis herpetoformis.
- Elevetad liver enzymes, liver failure.
- Infertility
- Stomatitis
- Myocarditis
- IgA nephritis
- Idiopathic pulmonary hemosiderosis
- Arthritis

c. Conditions associated with GSE

- Autoimmune diseases such such as type 1 diabetes, sjorgen syndrome, thyroid dieases (Hashimoto's thyroiditis and Graves's disease), autoimmune and primary biliary cirrhosis.
- Selective IgA deficiency
- Turner's syndrome
- Down's syndrome

4.2 Serology Testing

The widespread availability of serologic tests has permitted disease to be considered and tested for by any physician.

Serologic testing is recommended in different clinical situations showed in table (III)

Table III: Clinical indications for serologic testing

Unexplained, chronic diarrhea with and without malabsorption.
Unexplained weight loss.
Iron deficiency anemia
Folate deficiency
Vitamin E or K deficiency
Osteoporosis
Hypocalcaemia or vitamin D deficiency, secondary hyperparathyroidism
Unexplained elevation of transminases
First degree relatives of celiac patients
Associated autoimmune diseases: Type 1 diabetes, Sjorgen's syndrome primary billiary cirrhosis
Down and Turner syndromes
Neurologic disorders: Unexplained peripheral neuropathy, epilepsy and ataxia.

Serologic tests allowed to diagnose both classical and atypical forms of GSE and to specify patients whom jejunal biopsy is required, to screen patients likely to develop GSE and evaluate observance to GFD. The most sensitive tests are based on the use of IgA isotypes.

The available tests include antigliadin antibodies and anti-endomysial and/or tissue transglutaminase antibodies).

The gold standard in celiac serologies remains the IgA endomysial antibody (EMA) with high specificity for celiac disease that approaches 100%.

The endomysium is a protein located within the collagene of the human connective tissue and monkey esophagus. The titer of EMA correlates with the degree of mucosal damage. Accordingly,

the sensitivity declines when greater number of patients with less degrees of villous flattening are included in the studies[5]

The EMA is an observer-dependent immunoflourescence test that requires expertise in reading it and the use of either primate esophagus or human umbilical cord as tissue substrate.

The IgA and IgG antigliadin and tTG antibodies are produced against deamidated gliadin peptids.[45]

The use of an antigliadin IgA with a biopsy increases the rate of diagnosis of coeliac disease by up to 20% [46]

The recognition of the tissue transglutaminase (tTG), an ubiquitary intracellular enzyme, as the autoantigen for the EMA allowed development of an enzyme-linked immunoassay (ELISA) [47]. Initially the antigen in the assay was tTG derived from guinea pig liver (GP-tTG): subsequently human tTG (H-tTG), either recombinant or derived from human red cells has replaced the assays using GP-tTG.

Overall, the sensitivity of both the EMA and tTG is greater than 90%[48]. While the specificity of the EMA is considered to be virtually 100%, the tTG test does not achieve that degree of specificity.

There are numerous reports of positive tTG results in the absense of GSE. They may be seen in Type 1 diabetes, chronic liver disease, psoriatic or rheumatoid arthritis and heart failure, though biopsy has not been performed in most of these studies.[49-52]

a. Selective Iga deficiency

Selective IgA deficiency (SIgAD) occurs more commonly in patients with GSE than the general population. As a result, patients with CD lack IgA-EMA, IgA-tTG and IgA-antigliadin

antibodies. In order to detect GSE in those with SIgAD, a total IgA level should be incorporated into the testing for CD, as well as an IgG antibody-based test, either IgG-antigliadin or IgG-tTG.[53, 54]

b. Seronegative celiac disease

Several studies have demonstrated that serologic studies may lack sensitivity when used in the practice setting. Reliance on EMA as a single test has, in fact, underestimated the prevalence of GSE by at least 20–25%. This is mainly due to the inclusion of patients with mild mucosal changes, a situation when patients may not express an EMA. A similar situation occurs with tissue transglutaminase, with titers decreasing as the mucosal lesion becomes less marked. [55, 56]

c. ***Role of HLA DQ2/DQ8 assessment***

The HLA DQ2 is found in up to 90–95% of patients with GSE, while most of the remaining patients are HLA DQ8. However, these HLA alleles are found in up to 40% of the general population. They appear to be a necessary, but not sufficient, factor in the pathogenesis of coeliac disease. The role of determining whether an individual carries HLA DQ2 or DQ8 in the assessment of coeliac disease lies in their high negative predictive value.

The main roles are in determining whether family members require screening for coeliac disease, in excluding coeliac disease when patients are already on a gluten-free diet and in the situation, where the diagnosis of coeliac disease is unclear.[57-59].

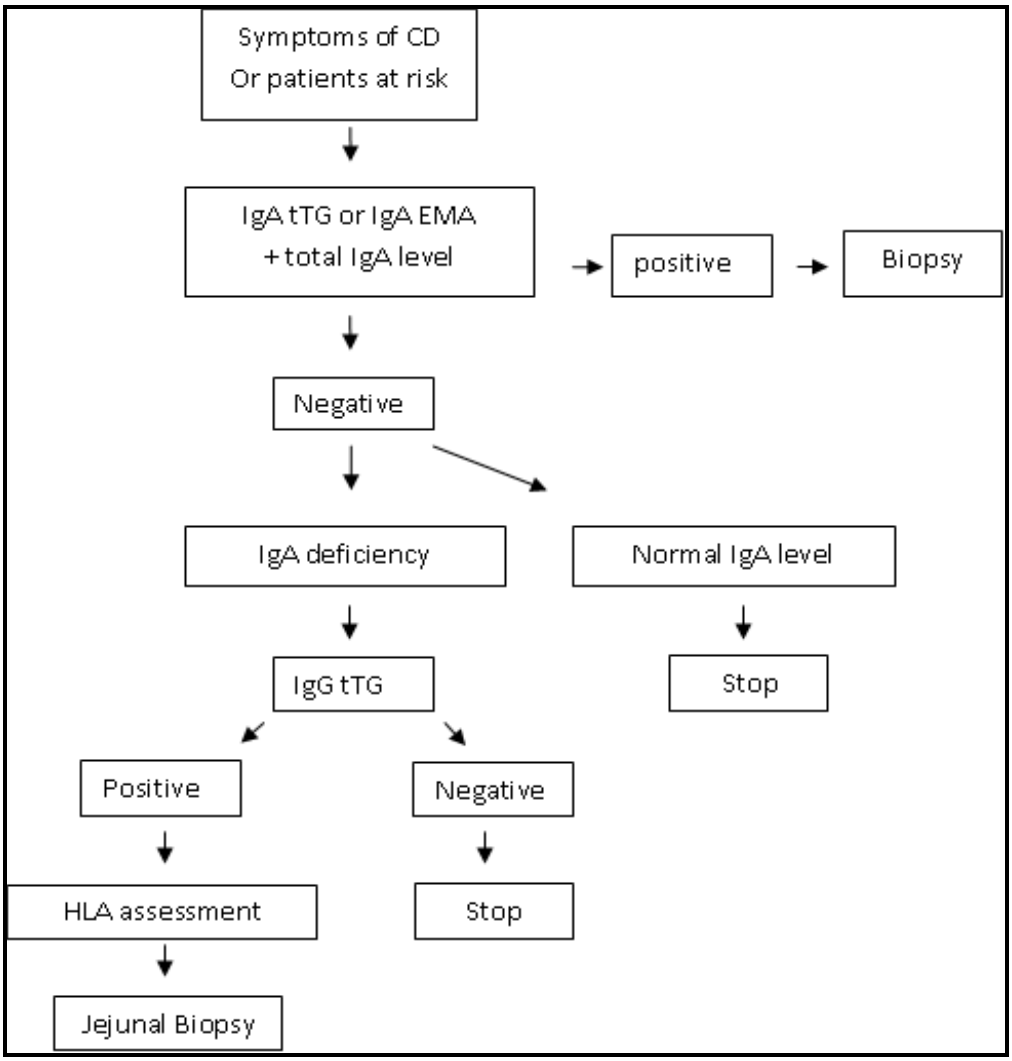


Figure III : *Diagnosis of GSE using serology testing antibodies*.[1]

Table IV : sensitivity and specificity of serology tests in children

Test performance (%)	IgA-EMA	IgA-tTGA	IgA-AGA
Sensitivity	90	93	83
Specificity	99	95	82
Reproducibility	93	83	62

4.3 Biopsy and histology

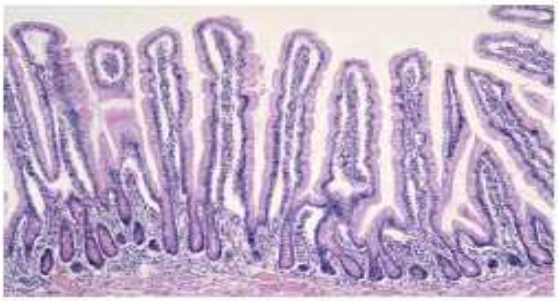
Biopsy of the small intestine remains the gold standard in the diagnosis of GSE (Figure III). Biopsies of the descending duodenum, rather than the more distal intestine seem sufficient for the diagnosis of GSE [60, 61]. Also, duodenal biopsies are more reproducible in angle of Treitz.

Due to the patchy nature of villous changes in GSE, multiple biopsies are necessary (at least six) as well as standard sized forceps [61].

The recognition of the spectrum of histological changes in GSE, as classified by Marsh (figure IV), have provided a major advance in the diagnosis of GSE.

These histological criteria are used for establishing the diagnosis [62] :

- Villous atrophy.
- Intraepithelial lymphocytosis.
- Crypt hypertrophy.
- Stromal hyper-cellularity

Marsh 1	normal villous architecture with an intraepithelial lymphocytosis (>30 lymphocytes per 100 enterocytes)	 Marsh I: lymphocytic enteritis

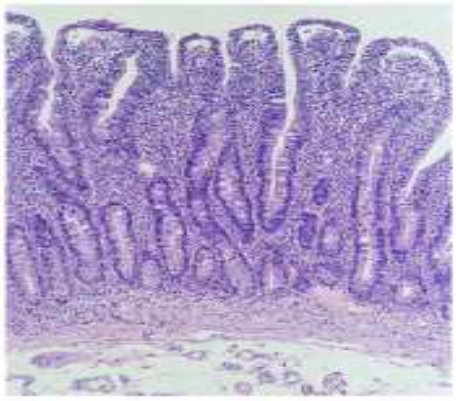
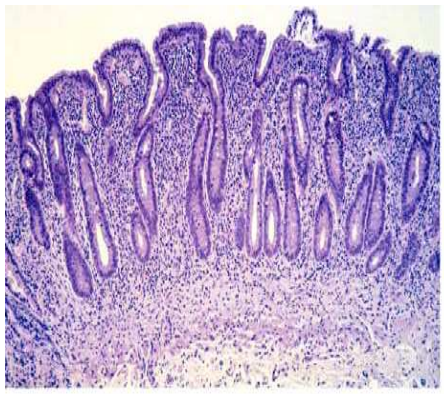
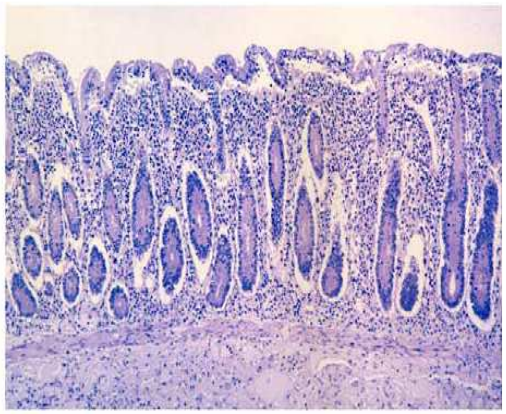
<table>
<tr><td>Marsh 2</td><td>intraepithelial lymphocytosis is accompanied by crypt hypertrophy</td><td> 
Marsh II: lymphocytic enteritis with crypthyperplasia</td></tr>
<tr><td>Marsh 3</td><td colspan="2">Moderate to very severe reduction in villous height.
The majority of patients diagnosed with GSE (50-60%) fall into this category
 
Marsh III A: partial villous atrophy
 
Marsh III B: subtotal villous atrophy
 
Marsh III C: total villous atrophy</td></tr>
</table>

Figure IV: Histo-pathological classification of GSE according to Marsh criteria.

II. Gluten sensitive neuropathies

Gluten sensitivity is associated with multiple neurological abnormalities including gluten ataxia, peripheral neuropathy, and ischemic stroke [63].

1. Epidemiologic data

There are no accurate estimates of the prevalence of the neurological expressions of GS in the general population.[64]. Otherwise, the reported frequency of neurological abnormalities among patients with established GSE varies between 10% to 22,5% [65, 66].

A japanese research showed that patients with cerebellar ataxia have significantly higher rates of AGA positivity than patients without cerebellar ataxia or normal controls, which suggests that ataxic patients are more likely to have gluten sensitivity [63].

In another study in Sheffield Hospital, UK, series of 500 patients with progressive ataxia were evaluated over a period of 13 years and showed that 46,97 % (101/215) of patients with idiopathic sporadic ataxia had serological evidence of gluten sensitivity [67]. The prevalence of gluten ataxia was 20% among all patients with ataxias, 25% among patients with sporadic ataxias, and 45% among those with idiopathic sporadic ataxias [67, 68].

Otherwise, peripheral neuropathy was found in up to 23% of patients with established GSE on a gluten-free diet [69]. Also, in a large population-based study (84.000 participants) in Sweden that examined the risk of neurological disease in patients with GSE, polyneuropathy was significantly associated with GSE (odds ratio 5,4; 95% CI 3,6-8,2) [70]. Besides, a UK-based study showed that 47 of 140 (34%) patients with idiopathic sporadic axonal neuropathy had circulating AGA [71]. In an Italian study, a greater proportion of patients with various types of

neuropathies were positive for IgA anti-TG2 (68 of 330 ;21%) compared with controls (1of 68; 1,5 %; $p<0\cdot0001$)[72]. Further more, a retrospective evaluation of 400 patients with neuropathy showed the prevalence of GSE to be between 2,5% and 8% (compared with 1% in the healthy population) [73].

Finally, rare cases of ischemic stroke occurring in young adults have lead to the diagnosis of GSE [74, 75].

2. Physiology of neural damage

The search for causes of neurological dysfunction in GS has largely ignored the immunological aspect, and has concentrated on vitamin deficiencies (B12, E, D, folic acid, pyridoxine) as a result of malabsorption [76]. Vitamin replacement rarely improves the neurological deficit [76, 77].

Alternative hypotheses are that antigliadin antibodies are more directly involved in the neuropathological process, or are markers of autoimmune activity with an unidentified neurotoxic antibody[76].

If these antibodies are directly or indirectly neurotoxic, why do patients with neurological dysfunction and on gluten-free diet not always improve? One possibility is that damaged neural tissue (e.g. cerebellar Purkinje cells) does not regenerate[76]; the second is that patients may not strictly adhere to their gluten-free diet or that the diet may be insufficient to suppress the immunological process completely, especially since patients without gastrointestinal symptoms are unlikely to adhere to a gluten-free diet [76, 78].

Evidence suggests there might be antibody cross-reactivity between antigenic epitopes on Purkinje cells and gluten proteins. Serum from patients with gluten ataxia and from patients with

CD without neurological symptoms showed cross-reactivity with epitopes on Purkinje cells of both human and rat cerebellum[2, 79].

When using sera from patients with gluten ataxia, there is evidence of additional antibodies targeting Purkinje cell epitopes, because elimination of AGA alone is not sufficient to remove such reactivity. Additional antibodies might be causing this reactivity, such as antibodies against one or more transglutaminase isozymes. Furthermore, shared epitopes between TG2 and deamidated gliadin peptides (DGPs) could provide a link between these seemingly unrelated immunological targets. In the case of gluten neuropathy there is evidence of antibody cross-reactivity with the neuronal protein synapsin I [2, 80]. Additionally, gliadin can bind to GM1 gangliosides that are known to be associated with autoimmune peripheral neuropathies[2, 81].

Finally, sera from patients with celiac disease and neurological manifestations also evoke a mitochondrial-dependent apoptosis in vitro, suggesting that neurotoxic antibodies might be present[64, 82]. However, the nature of these antibodies and their role in vivo neurotoxicity remains to be shown[83].

3. Pathology of neural damage

Post-mortem examination from patients with gluten ataxia showed irregular loss of Purkinje cells throughout the cerebellar cortex, which is common in many end-stage diseases of the cerebellum (figure 5D)[84, 85] . However, additional findings supporting an immune-mediated pathogenesis include diffuse infiltration mainly of T-lymphocytes within the cerebellar white matter as well as marked peri-vascular cuffing with inflammatory cells (figure 5A) [2].

The peripheral nervous system also showed sparse lymphocytic infiltrates with perivascular

cuffing in sural nerve biopsy samples of patients with gluten neuropathy[71] and in dorsal root ganglia in patients with sensory neuronopathy and myopathy caused by gluten sensitivity [86]. Similar findings have been described in patients with established celiac disease who then developed neurological dysfunction[83, 84].

4. Neurologic categories

Although neurological manifestations in patients with established GSE have been reported since 1966, it was not until 30 years later that, in some individuals, gluten sensitivity was shown to manifest only with neurological dysfunction[2] .

Gluten Sensitive Neuropathies (GSN) can present with different symptoms, thus many categories of GSN are known nowadays:

4.1. Gluten ataxia

Cerebellar ataxia is one of the two most common neurological manifestations of gluten sensitivity. Gluten ataxia was defined in 1996 as apparently sporadic ataxia with positive serological markers for gluten sensitivity; this definition was based on the serological tests available at the time (AGA)[2]

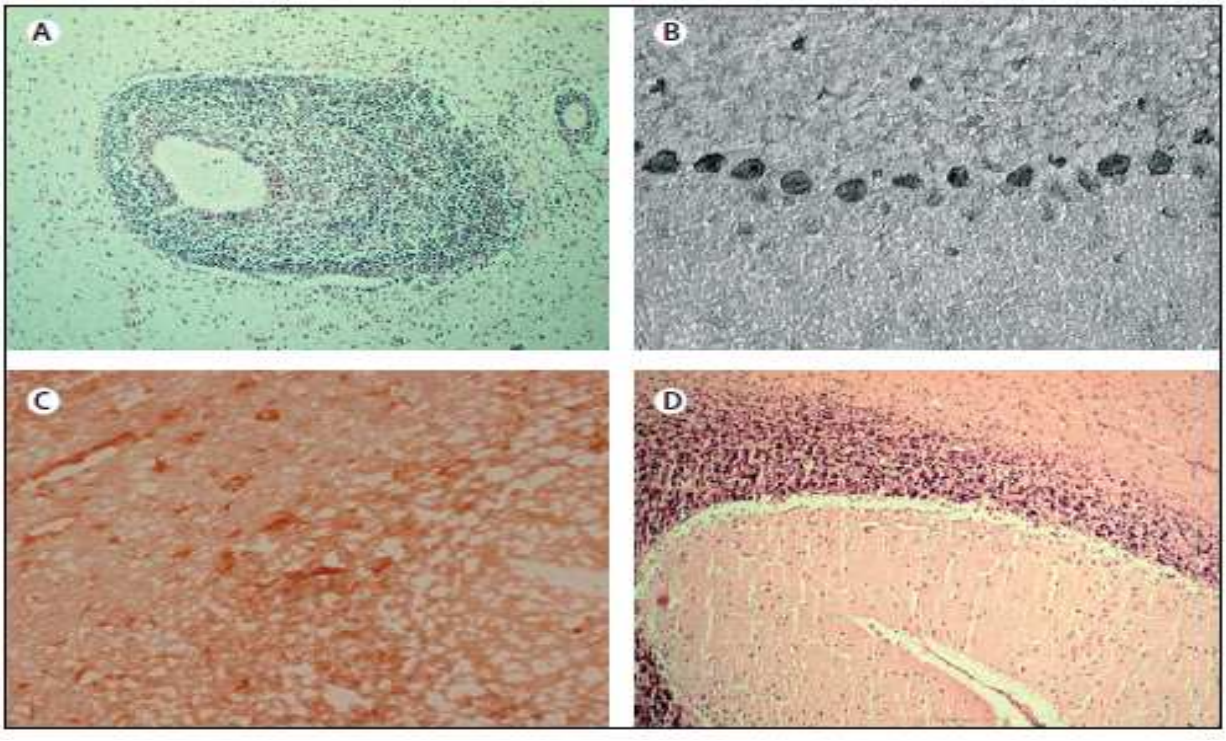


Figure 5: The immuno-pathology of gluten ataxia
A: Cerebellar tissue from a patient with gluten ataxia.
B: This perivascular inflammatory infiltrate is a characteristic finding in patients with neurological manifestations of gluten sensitivity and might contribute to the loss of the integrity of the blood–brain barrier, enabling circulating antibodies to enter the CNS. Serum from patients with gluten ataxia reacts with Purkinje cell epitopes.
C: Perivascular TG6 deposits are present in the cerebellum of a patient with gluten ataxia.
D: Cerebellar section from a patient with gluten ataxia showing profound loss of Purkinje cells.

a. History snapshot:

Elders first reported the association between sprue and ataxia in 1925 [85]. However, before the introduction of biopsies on the small bowel in 1953, the causes of steatorrhoea could not be verified, and neurological details were sparse. Cooke and colleagues reported in 1966 the first detailed study of patients with severe GSE and neurological complications [84]; all 16 patients in the study showed gait ataxia.

Since then many case reports of ataxia with or without myoclonus and GSE have been published [87]; most describe patients with established GSE and prominent gastrointestinal

symptoms who then develop ataxia. Some have shown improvement of ataxia [87] and peripheral neuropathy [88] on a gluten-free diet.

b. Clinical manifestations:

Table V : Clinical, radiological and neurophysiological characteristics of 68 patients with gluten ataxia (54 patients from North Trent plus 14 from The Institute of Neurology, London) [89]

Characteristics of the patients	Results
Male to female ratio	35 : 33
Mean age at onset of ataxia (range)	48 years (14±78 years)
Mean duration of ataxia (range)	9.7 years (1±40 years)
Occular signs	84%
Dysarthria	66%
Upper limb ataxia	75%
Lower limb ataxia	90%
Gait ataxia	100%
Gastrointestinal symptoms	13%
Cerebellar atrophy on MRI	79%
White matter hyperintensities on MRI	19%
Sensorimotor axonal neuropathy on neurophysiology	45%
Gluten-sensitive enteropathy on biopsy	24%
HLA DQ2	72%

Gluten ataxia usually presents with pure cerebellar ataxia or, rarely, ataxia in combination with myoclonus (see above), palatal tremor,[90] opsoclonus, or chorea [91].

Gluten ataxia usually has an insidious onset with a mean age at onset of 53 years. Rarely, the ataxia can be rapidly progressive, mimicking paraneoplastic cerebellar degeneration[92]. Gaze-evoked nystagmus and other ocular signs of cerebellar dysfunction are seen in up to 80% of cases [93]. All patients have gait ataxia and most have limb ataxia. Less than 10% of patients

with gluten ataxia will have any gastrointestinal symptoms but a third will have evidence of enteropathy on biopsy [90].

Up to 60% of patients have neurophysiological evidence of sensorimotor, length-dependent axonal neuropathy [90]; this neuropathy is usually mild and does not contribute to the ataxia.

c. Genetic findings:

The HLA type DQ2 is found in 70% of patients with ataxia who are positive for AGA (present in 90% of patients with GSE and in 36% of healthy controls); the remaining 30% carry the HLA DQ8 (10%) and HLA DQ1 (20%) variants [2]. These reported occurrences are consistent with strict association with the HLA risk genotype of GSE [2].

d. Radiological findings:

Up to 60% of patients with gluten ataxia have evidence of cerebellar atrophy on MRI[94]. The investigation of the metabolic status of the cerebellum in 15 patients with gluten ataxia and 10 controls by use of proton magnetic resonance spectroscopy showed significant differences in mean N-acetyl concentrations at short echo-time and in N-acetyl aspartate to choline ratios at long echo-time between patients with gluten ataxia and healthy controls, *suggesting that cerebellar neuronal physiology is abnormal* [95]. Even in patients without cerebellar atrophy, proton magnetic resonance spectroscopy of the cerebellum was abnormal[95].

4.2. Gluten neuropathy

Peripheral neuropathy is the other most common manifestation of gluten sensitivity. It is defined as apparently sporadic idiopathic neuropathy in the absence of an alternative etiology and in the presence of serological evidence of gluten sensitivity[2, 71].

a. Clinical characteristics

Gluten neuropathy is a slowly progressive disease with a mean age at onset of 55 years (range 24–77) and a mean duration of neuropathy to diagnosis of gluten sensitivity of 9 years (range 1–33) [71].

Sensory ganglionopathies can also be a manifestation of gluten sensitivity and might require immunosuppressive medication in addition to a strict gluten-free diet to achieve stabilization [86].

Chronic distal, symmetric, predominantly sensory neuropathy is described most commonly in patients with GSE; however, pure motor neuropathy, mononeuritis multiplex, Guillain–Barré–like syndrome and autonomic neuropathy also have been reported [84, 96].

b. Electrophysiological findings

The most common type is symmetrical sensorimotor axonal peripheral neuropathy [2], but other types of neuropathies have also been reported (asymmetrical neuropathy [97], sensory ganglionopathy [86], small fiber neuropathy [98], and, rarely, pure motor neuropathy or autonomic neuropathy [99]).

However, electrophysiologic studies can be normal or mildly abnormal in many GS patients with neuropathy [96].

c. Pathology:

A third of patients have evidence of enteropathy on biopsy[2]. The few data on pathology available from post mortems and nerve biopsy samples are consistent with an inflammatory etiology (perivascular lymphocytic infiltration) [71].

d. Follow-up

The capacity for recovery of the peripheral nerves might be reduced when the neuropathy is severe or that more time might be needed for such recovery to manifest [2, 71].

As there was a correlation between disease severity and longer disease duration, gluten neuropathy could be considered as a progressive disease if untreated[2].

4.3. Ischemic stroke

a. Pathogenesis:

Hyperhomocysteinemia, cerebral arterial vasculopathy and antiphospholipid syndrome are thought to be involved in the pathogenesis of stroke during GSE [74, 75]. Also, studies both *in vitro* and *in vivo* point to several possible mechanisms of vascular damage mediated by high homocysteine levels[100]. These include endothelial dysfunction, activation of factor V and tissue-type plasminogen activator, enhanced platelet aggregation, and inhibition of protein C[100].

In fact, recent data indicate that an elevated plasma level of the thiol-containing amino acid homocysteine is a common, independent, easily modifiable and possibly causal risk factor for atherosclerosis, which may be no less important than hypertension, hypercholesterolemia or smoking[101].

The tTG in the cerebral tissue has a key role in the integrity of the endothelium and the metabolism of neuronal cells [79]. The auto-antibodies anti-tTG IgA against the endothelial tTG may cause a cerebral vasculopathy that weakens the hematomeningial barrier and therefore expose the central nervous system to the circulating AGA.[102]

Also, the enterocyts apoptosis expose the cardiolipins on the cell's membrane in the digestive

mucosa, these are thought to be involved in the production of IgA anticardiolipins antibodies [75]. Otherwise, the children who have GSE are thought to develop an auto-immune angiopathy that may cause stroke [103].

In addition to the neurotoxic effects of gluten [89], authors suggested that the mechanism might be arythmogenic or thromboembolic regarding the high prevalence of GSE in idiopathic cardiomyopathy [104].

b. Clinical characteristics:

The GSE is suspected when the patient is young, with no vascular risk factors or cardiac cause identified [74]. However in some observations, the thrombotic manifestations during GSE are referred to an antiphospholipid syndrom [74, 105].

5. Serology testing

In a genetically predisposed individual, the consumption of gluten exposes the bowel to immuno-reactive epitopes that initiate a mal-adaptive immune response [106]. In patients with biopsy confirmed GSE, IgA antigliadin antibodies (AGA) have a sensitivity of (81%-83%)7 and a specificity of (82%-89%)7 where as the sensitivity of IgG AGA is (82-99%)[107] and the specificity is (76%-92%)[107]. It has been proposed that AGA testing, a marker of gluten sensitivity, is an essential investigation for patients with sporadic ataxia [89, 108] and that AGA of the IgG type is the best marker for neurological manifestations of gluten sensitivity[89].

Antiendomysium antibodies are detectable in only 22% of patients [90]. By use of ELISA, anti-TG2 IgA antibodies are present in up to 38% of patients with gluten ataxia, but often at lower titres than patients with GSE; however, unlike in GSE, IgG class antibodies to TG2 in patients with

gluten ataxia are more common than IgA.

This finding is in line with data that have provided evidence for intra-thecal antibody production against tTG in patients with neurological diseases; that is because the high prevalence of IgG class antibodies to tTG2 and TG6 is consistent with an immune response in the CNS[109].

Antibodies against either TG2 or TG6, or both, can be found in 85% of patients with ataxia and AGA antibodies [110].

In reverse, antibodies to TG2 and TG6 can also be detected in patients with idiopathic sporadic ataxia who are negative for AGA, although at much lower frequency compared with patients with circulating antigliadin antibodies [92].

Some patients also are positive for anti-TG3 antibodies, although the frequency of such antibodies is low when compared with patients with dermatitis herpetiformis, and no patients tested positive for such antibodies in isolation [2].

Whether combined detection of TG2 and TG6 IgA/IgG can identify all patients with gluten sensitivity remains unclear; however, detection of anti-DGP (deamidated gliadin peptides) antibodies did not identify any additional patients[92].

The discrepancy between antitransglutaminase antibody and AGA detection is in agreement with the expected rate of false-positive results (about 12%) and with the sensitivity reported for GSE [111].

For ischemic stroke, the screening of classic immunological disorders (anti-nuclear antibodies, anti-DNA antibodies) is negative[112] . In a recent study, there was no important difference in the prevalence of anti-cardiolipin and and B-2GPI antibodies; however, the anticardiolipin IgA antibodies were more frequent during GSE [112].

PATIENTS AND METHODS

Patients and Methods

1. Patients' selection

We performed a prospective study about 60 patients with different categories of idiopathic neuropathies and 57 controls. The patients were recruited at the department of neurology in the University Hospital of Marrakesh over a period of one year (from June 2010 to June 2011). Patients with known CD undergoing gluten free diet and those with etiological established diagnosis of their neuropathy were excluded from the study.

The control individuals were selected from blood transfusion center affiliated to Ibn-Sina Military Hospital of Marrakesh.

2. Clinical examination and investigations

Using a preset questionnaire, the clinical data of the population were picked up, including:

- Socio-demographic characteristics : sex, age, origin, education level and occupation;
- Medical history: diabetes, HBP, smoking, alcohol intake, nutrition deficiency, known GSE, gluten introduction age, digestive symptoms, tuberculosis, and the type of onset and progression;
- Clinical examination: all the patients had neurological and general physical examination, letting to characterize the type of the neurological disorder.
- Investigations: according to the neuropathy's aetiology categories, patients underwent different investigations, which are cerebral and/or medullar neuro-imaging (scanner,

magnetic resonance imaging), chest radiograph and echocardiography and vascular echo-Doppler. The electromyography testing was performed in cases of peripheral neuropathy; and the electro-encephalogram in patients presenting with epilepsy. In myopathy suspicious cases, muscular biopsy was performed. In addition, depending on the clinical context, a complementary laboratory investigations have been indicated, including blood cell count, inflammatory markers, syphilis and HIV serology, urea and electrolytes, liver and thyroid function tests, glycaemia, lipid profile, and proteins electrophoresis. Additional investigations were carried out if clinically indicated, and included vitamin B12, serum folate, antinuclear antibodies, hepatitis B and C serology, complement levels, serum homocystein, vitamin E.

3. Immunologic testing

All the patients and controls were screened for both IgG and IgA antigliadin antibodies, using an immuno-enzymological method (ELISA IgG-Gliadin, IgA-Gliadin, Diagnostic System, Germany, threshold: 12 IU/ml), followed by the anti-IgA tissue transglutaminase antibodies using the ELISA system (tGT IgA, DRG instruments, GmbH, Germany, threshold 10 IU/mL).

4. Statistical analysis

All statistical analysis was performed in the laboratory of Epidemiology, Faculty of Medicine of Marrakesh, using Epi Info™ version 6.0 and SPSS program.

RESULTS

Results

I. Global data

1.1 Socio-demographic characteristics

The study included 60 patients. The median of age was 43 years (+/- 13,91years) ranging between 13 and 76 years, with a female predominance (36 females versus 24 males, sex-ratio M/F = 0.66).

The standard of living was medium for 55 % (n=33) of patients, low for 36,66% (n=22) , and high for 3,33% (n=2), and not defined for 3 other patients.

About half of patients (n=29, 48,33%) had primary school level, 26,66% (n=16) of them were illiterate, 15% (n=9) had high school level, while only one patient (1,6%) had university status of education.

Regarding the social status of patients, 77,77% (n=28) of females were housewives, 11,6% (n=7) were labourers, 8,33% (n= 5) were employees, 8,33% (n= 5) were traders, 6,6% (n= 4) were students; the five other occupations corresponded to 1 imam, 2 hairdressers, 1 sailor and 1 cook, however 5 patients didn't precise their job. The level of education was primary school for 29 patients (48,33%), high school for 9 patients (15%), and only one patient (1,6%) had an university status, while 16 patients (26,66%) were illiterate. (Table VI)

Table VI: socio-demographic characteristics of the patients

Characteristics	Number	%
Standard of living		
- Medium	32	53,3
- Low	22	36,6
- High	2	3,3
- Not defined	4	6,6
Level of education		
- Primary school	29	48,3
- Illiteracy	16	26,6
- High school	9	15
- University	1	1,6
Jobs % (total)		
- Housewives	28	46,6
- Labourers	7	11,6
- Employees	5	8,3
- Trader	5	8,3
- Students	4	6,6
- Hairdresser	2	3,3
- Imam	1	1,6
- Sailor	1	1,6
- Cook	1	1,6
- Not defined	5	8,3

1.2 Clinical data

Among our patients, 8 had gluten sensitivity risk factors, corresponding to 1 case of confirmed celiac disease, 2 cases of consanguinity status, 4 cases of type 2 diabetes and 3 had autoimmune conditions: rheumatoid polyarthritis, livedo and Raynaud disease.

Digestive symptoms were reported by 10% of patients (n=6) that were chronic diarrhea and dyspepsia (Table X) and one patient had nutrition deficiency.

Cardiovascular risk factors were found in 8 patients: high blood pressure, type 2 diabetes, heart disabilities (one case of valvulopathy and another with cardiac insufficiency) while tobacco

addiction was found in11 patients (18,3%); besides, 3 patients had miscarriage.

The gluten introduction age ranged between 5 to 9 months with a median of 6,25 months. For 28,3% of the patients (n=17), which represent the majority, gluten has been introduced in the 6th month.

The onset mode of the clinical symptoms was acute in 51,66% (n=31 patients), and progressive in 48,33 % (29 patients); furthermore, the progression was chronic in 48,33% (29 patients), remittent in 31,66% (16 patients) and one episode in 25% of cases (n=15 patients).

The global clinical data of the patients corresponded to 18 stroke cases (28,33%), 16 cases of peripheral neuropathy (26,66%), 7 cases of epilepsy (11,66%), 7 cases of cerebellar ataxia (11,66%), 3 cases of myopathy (6,66%) and 9 other cases (15%) corresponding to 2 patients with myelopathy, 2 patients with anterior horn disease, 1 with Parkinson disease,1 with lymphocytic meningitis,1 with multiple sclerosis, 1 with thrombophlebitis, and 1 with dystonia and (figure 6).

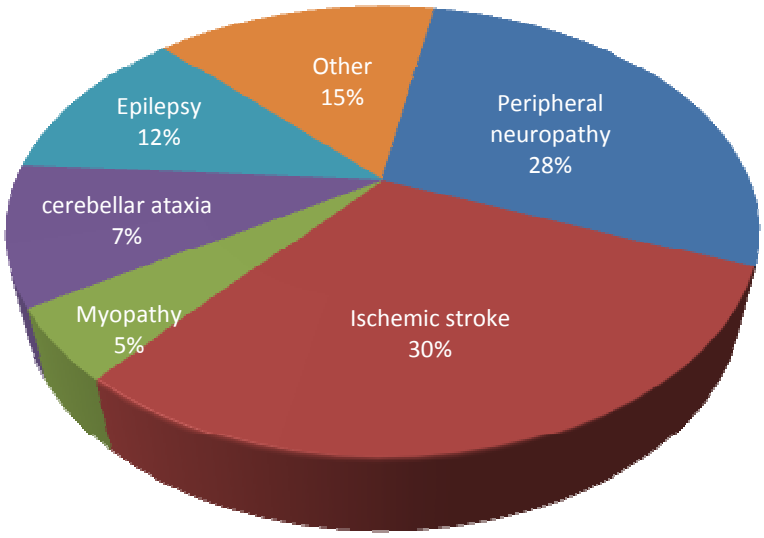


Figure 6: Distribution of the studied neurologic diseases

Table VII: General Clinical data of the patients

Characteristics	Number	%
Known GSE	1	1,6
GI symptoms	6	10
Onset:		
Acute	31	51,66
Progressive	29	48,3
Progression: - Remittent	16	26,7
- One episode	15	25
- Chronic	29	48,3

1.3 Biological investigations

The biologic investigations showed an hypochromic microcytic anaemia in 32 patients (53,33%) corresponding to 12 (37,5%) and 7 and 4 and 2 and 1 that are respectively stroke, peripheral neuropathy, myopathy, ataxia and epileptic cases.

An inflammatory syndrome, (increased CRP with or without sedimentation rate levels) was detected in 23 patients (28,3%) including 12 cases (52,17%) of peripheral neuropathies, 4 cases of strokes and 2 cases for each of the following, epilepsy, ataxia and myopathy.

Total Hypo-cholesterolemia was found in 10 patients (16,66%) which were 4 cases of stroke , 3 peripheral neuropathies and 2 epileptic patients.

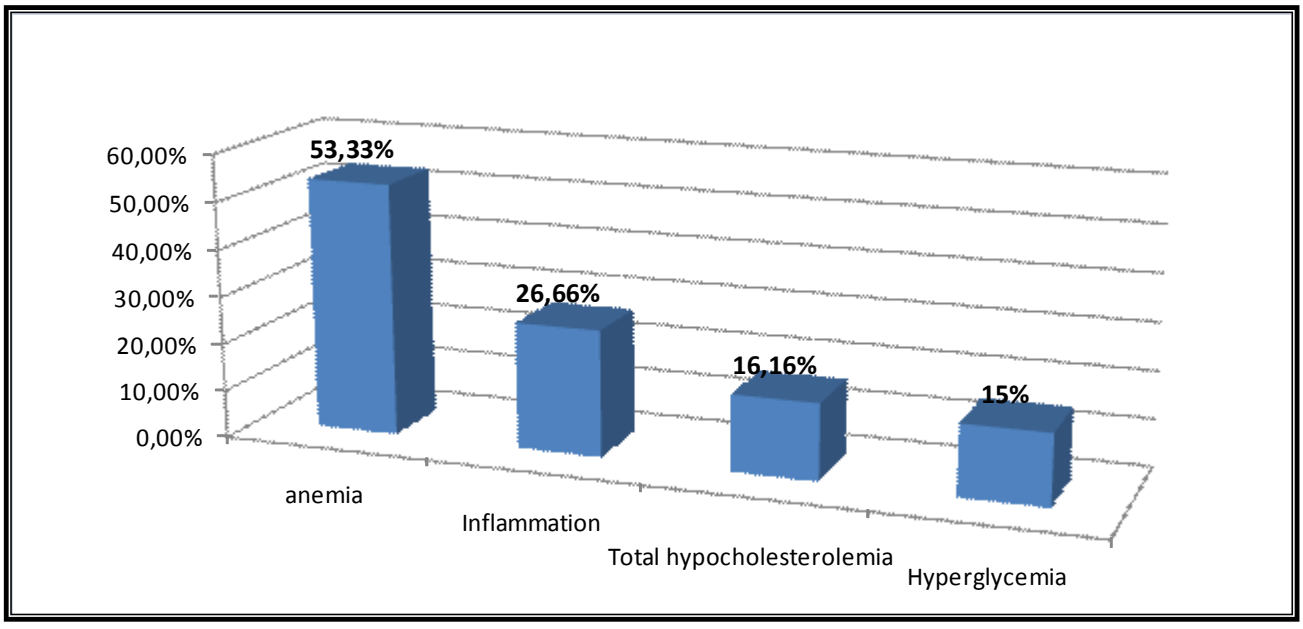


Figure 7: Major biological features of the patients

Diabetes was detected in 10 patients (16,7%); 6 of them had stroke, 1 had cerebellar ataxia and 2 had epilepsy.

The other biologic parameters including renal function, lipid profile and haemostasis testing were normal. The screening for HIV and syphilis infections was negative for all patients.

1.4 Immunologic findings

The testing of AGA was positive for 26,7% (n=16) of all the patients, including 16,6% (n=10) who had only IgA antigliadin Abs, and 10% (n=6) who were positive for IgG isotype (table XVIII). Only one patient was positive for both IgA and IgG AGAs (table XVIII). The antibodies titers varied between 14,18 u/l to more than 200 u/l for IgA AGA , between 14,4 u/l to more than 100 u/l for IgG AGA (table IX).

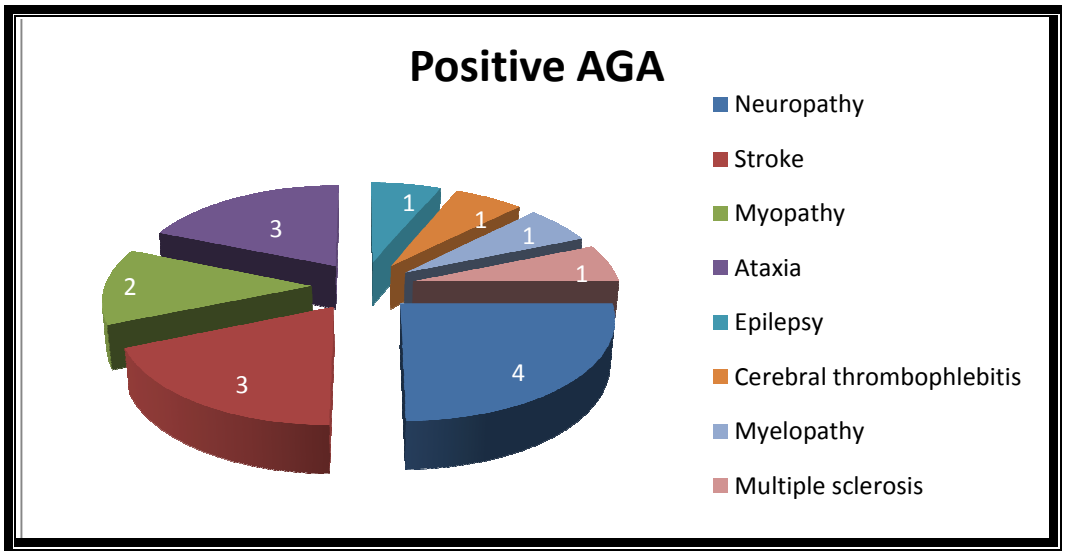


Figure 8: Distribution of positive AGA cases according to neuropathy categories

Among the positive IgA-AGA, 4 patients had peripheral neuropathy, one had stroke, 3 had cerebellar ataxias, one had epilepsy, and 1 patient had thrombophlebitis (figure 9).

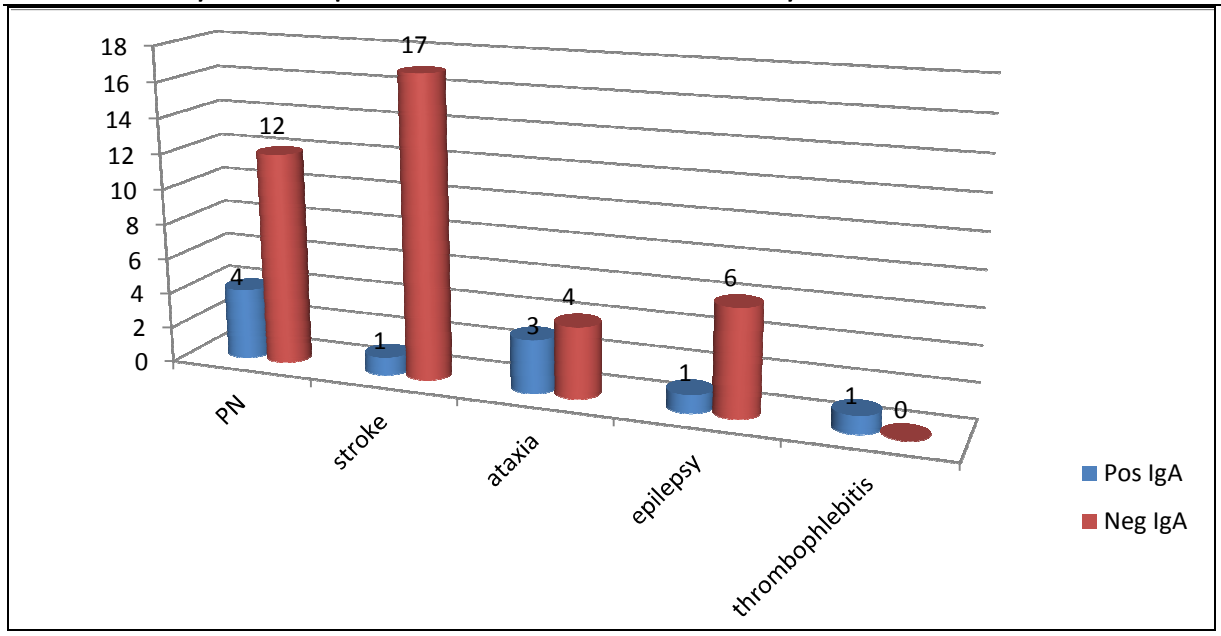


Figure 9: Results of IgA antigliadin antibodies according to different forms of neuropathies

Pos iga: positive IgA antigliadins; neg iga: negative IgA antigliadins; PN: peripheral neuropathy

Among the positive IgG-AGA patients, we found 2 cases of stroke, 2 cases of myopathy, one case of myelopathy and one case of multiple sclerosis (figure 10).

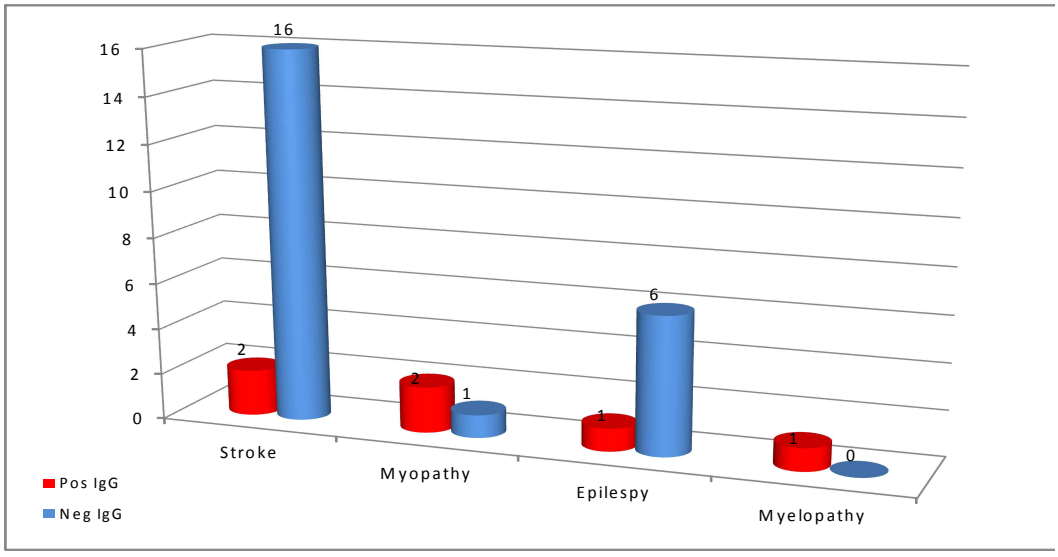


Figure 10: Results of IgG antigliadin antibodies according to different forms of neuropathies

Pos IgG: positive IgG antigliadins; neg IgG: negative IgG antigliadins

Only one patient who had cerebellar ataxia showed positivity for both IgA and IgG AGA.

Anti-IgA-tTG was negative for all the patients(table XVIII).

IgG AGA was negative for 54 patients (90%), and IgA AGA testing was negative for 50 patients (83,33%), and 44 patients (73,33%) were negative for both IgA and IgG AGA; None of neuropathic, nor ataxic nor epileptic patients had IgG AGA.

Table VIII: AGA and tTG testing results for the patients and healthy donors

Neuropathy categories	AGA IgG		AGA IgA		Combined IgA & IgG AGA	tTG-IgA		Total
	Pos n (%)	Neg n (%)	Pos n (%)	Neg n (%)		Pos n (%)	Neg n (%)	
Peripheral neuropathy	0	16 (100)	4 (25)	12 (75)	0	0	16(100)	16
Stroke	2(11)	16(88,8)	1(5,5)	17(94,4)	0	0	18(100)	18
Myopathy	2	1	0	3	0	0	3	3
Ataxia	1	6	3	6	1	0	7	7
Epilepsy	0	7	1	6	0	0	7	7
Myelopathy	1	1	0	2	0	0	2	2
Multiple sclerosis	1	1	1	0	0	0	1	1
Anterior horn sd	0	2	0	2	0	0	2	2
Thrombophlebitis	0	1	1	0	0	0	1	1
dystonia	0	1	0	1	0	0	1	1
Parkinson sd	0	1	0	1	0	0	1	1
Lymphocytic Meningitis	0	1	0	1	0	0	1	1
Total of Patients	6(10)	54(90)	9(15)	51(85)	1(1,7)	0	60 (100)	*60*
Healthy donors	4(7)	53 (93)	7(12,3)	50(87,7)	1(1,7)	1(1,7)	56(98,2)	*57*

Table IX: The immunologic profile of patients with positive serology testing

Neuropathy categories	Patients	IgG AGA* result	IgA AGA** result	IgA tTG*** result
Peripheral neuropathy	n°1	neg	18,25 UI/mL	neg
	n°2	neg	24,24 UI/mL	neg
	n°3	neg	16,56 UI/mL	Neg
	n°4	neg	20,39 UI/mL	Neg
Stroke	n°5	22,49 UI/mL	neg	Neg
	n°6	Neg	23,33 UI/mL	neg
	n°7	> 100 UI/mL	neg	Neg
Ataxia	n°8	> 200 UI/mL	> 200 UI/mL	Neg
	n°9	neg	14,18 UI/mL	Neg
	n°10	Neg	22,24 UI/mL	neg
Epilepsy	n°11	neg	16,25 UI/mL	Neg
Myopathy	n°12	27,41 UI/mL	Neg	Neg
	n°13	14,4 UI/mL	neg	Neg
Myeolpathy	n°14	34,25 UI/mL	neg	Neg
Cerebral Thrombophlebitis	n°15	neg	14,32 UI/mL	neg
multiple sclerosis	n°16	97 UI/mL	neg	neg

*threshold>12 IU/mL ** threshold >12 IU/mL *** threshold >12 IU/mL

Among the 57 healthy donors tested for IgG and IgA AGA and tTG, 9 (15,7%) were positive for AGA; 6 of them were positive for IgA-AGA and 3 were positive for IgG-AGA while one patient was positive for both AGA and tTG (Table X).

Besides, other immunologic features were found. In fact, 2 patients had positive ANAs and the anti DNA antibodies testing were negative for all.

Table X: The immunologic profile of healthy donors with positive serology testing

List of Control group	IgG- AGA result	IgA-AGA result	IgA- tTG result
C1	39 IU/mL	> 200 IU/mL	Neg
C2	31,25 IU/mL	neg	neg
C3	More than 200	neg	neg
C4	neg	36,10 IU/mL	neg
C5	neg	30,38 IU/mL	neg
C6	26,14 IU/mL	69,78 IU/mL	> 200 IU/mL
C7	neg	> 200 IU/mL	neg
C8	neg	> 200 IU/mL	neg
C9	neg	42,12 IU/mL	neg

Table XI: Comparison of the serology testing results in patients and controls

	Positive subjects	Total	p- value
Patients with neuropathies	16	60	*0,151*
Control group	9	57	

1.4 Imaging data:

36 patients (60% of the patients) included in the study had MRI and/or TDM imaging.

It showed Cerebral and/or cerebellar atrophy in 6 patients (Total: 6 patients).

Table XII: Biology and imaging findings.

Biological data	n (%)
Hypochrome microcytic anemia	32 (53,33)
Biological Inflammation	28 (26,66%)
Hyperglycemia	9 (15%)
Medical Imaging	
Cerebral and/or cerebellar atrophy	6 (10%)

2. Ischemic stroke

The clinical and investigations data of 18 patients having stroke are described below:

2.1. Clinical features

The median of age at onset was 40 years ranging between 25 and 76 years. The sex ratio was 0,5 (6 males vs12 females).

The medical history showed 3 cases of miscarriage, 2 cases of smoking, 3 patients had high blood pressure (HBP), and 4 patients were diabetics. Chronic diarrhoea was reported by 2 patients. No patient had a family history of consanguinity (table XIII).

A total of 17 patients had hemipyramidal syndrome (94,11%), affecting the right side in 9 patients and the left side in 7 patients; for the majority, it was pure in 12 cases (66,66%) and proportional hemi pyramidal syndrome in 13 cases (72,22%). Eight patients had aphasia and 17 had normal sensitivity (table XIII).

Table XIII: Clinical characteristics of patients with Brain ischemic stroke

Clinical data	Number	%
Hemipyramidal syndrome	17	94,44
pure	12	66,6
Proportional	13	72,2
aphasia	8	44,4
Tactile hypoesthesia	1	5,5
Total of patients	18	18

2.2. Imaging results

The medical imaging showed hypo-densities on the Scanner and hypo-intensities on MRI, mostly in the MCA areas (82%). Also, cortical and sub-cortical atrophy was observed in only two patients (table XIV).

Table XIV: The results of medical imaging of ischemic stroke patients

Medical Imaging (TDM & MRI)	Number (%)
Type of lesions	
Heterogeneous Lesions	1
Hypodensities	18 (100)
Topography :	
Left MCA area	5
Superficial area of the right ACA and MCA	2
Profound area of the right MCA	2
Profound and superficial area of right MCA	3
left ICA	1
Associated Lesions:	
corticale and sub-corticale atrophy	2
sequellae lesions	2
demyelinating white matter	1

2.3 Biological data

The immunologic testing detected 3 positive cases of AGA, in which 1 had elevated IgA AGA (23,33 UI/mL) and 2 had elevated IgG AGA titers, superior to 100 UI/ml in one case, and equal to 22,49 UI/mL.

The biological testing showed 6 cases of hypochromic microcytic anaemia and 6 cases of inflammatory syndrome, also, 5 patients had diabetes and 4 had hypocholesterolemia.

Hemostasis testing (prothrombin time, S and C proteins, factor V mutation, antithrombin III) was normal. One patient had an intermediate rate of Homocysteine (1,37 mg/l) (tables XV and XVI).

Table XV: Immunological and biological results in patients with ischemic stroke

Immunologic markers	number
AGA IgA	1
AGA IgG	2
Total	3
Biologic tests	
Intermediate rate of Homocystein (1.37 mg/l)	1
Hypochromic microcytic anemia	6
Inflammatory syndrome	6
Hyperglycemia	5
Hypertriglyceridemia	2
Decreased PT	0
Decreased Prot S	0
Elevated AT III	0
Factor V mutation	0

3. Peripheral neuropathy

The analysis of all clinical and imaging and biological data of the 16 patients presenting peripheral neuropathies is detailed as follows:

3.1. Clinical findings

These cases include 8 males and 8 females (sex-ratio =1), and the median of age was 44 years ranging between 18 and 63 years. There was neither history of consanguinity nor diabetes nor alcoholism nor thyroid disorders nor chronic nephropathies.

However, two patients had HBP, 3 others had recurrent miscarriage and three were chronic smokers. One patient had nutrition deficiency (diagnosis made according to diminished values of mid-arm muscle circumference and hypo-protidemia).

Among these patients, only 1 had evidence of GSE including chronic diarrhoea, loose stools,

weight loss and anaemia, associated to neurologic symptoms.

The onset was acute for 3 patients and progressive for the others and progression was chronic in 15 cases and remittent in one.

Weakness and sensitivity impairment such as paresthesias and dysesthesias were reported by 15 patients (93,75%). They were distal for 12 patients, proximal and distal in 2 patients and proximal in 1 patient. Those symptoms corresponded to burning, tingling, numb and "pins and needles" sensations.

On neurological examination, 10 patients had sensory abnormalities with predominant tactile hypoesthesia, associated to thermo-algic hypoesthesia in 2 cases. Meanwhile, no patient had muscular atrophy (Table XVII).

3.2. Electromyography results

The electro-diagnostic testing showed combined motor and sensitive, motor, and sensitive neuropathies in respectively 7, 2, and 2 cases.

Ten (58,8%) patients had polyneuropathy, 3 patients had mononeuropathy multiplex and 2 others had polyradiculoneuropathy (Table XVII).

Besides, 4 patients had the demyelinating form and 5 patients had the axonal form.

3.3. Neuro-imaging

The MRI was performed in only 3 patients and showed a discal protrusion L3-L4 in 1 of them.

3.5. Immunology testing

The AGA Abs were detected in 4 patients, all of them had an IgA isotype. Their titers varied between 16, 25, 18,25, 20,35 and 24,24 UI/l. None of them had IgG isotype or the tTG (Table

XVII).

Among the negative AGA antibodies (IgA and IgG) patients, one of them had villous atrophy marsh III grade.

3.6. Other biological results

Anaemia was found in 8 patients and the inflammation markers were positive in 9 patients (Table XVII).

Table XVI: Summary of the peripheral neuropathies related data

Patients' Data	Results
Male to female sex Ratio	1:1
Median of age (range)	44 years (18 and 63 years)
Distal extremities impairment (weakness, dysethesias and paresthesias)	12 (75%)
polyneuropathy	10 (58,8%)
Mononeuropathy multiplex	3(18,7)
polyradiculoneuropathy	2(12,5)
Motor and sensitive neuropathy	7(43,7)
Sensitive neuropathy	2(12,5)
Motor neuropathy	2(12,5)
Positive AGA	4(25%)
IgA-AGA	4(25%)
IgG-AGA	0
Anti-tTG abs	0
Hypochromic microcytic anemia	8(50%)
Inflammation markers	9(56,2%)

4. Ataxia

In our series, 7 patients had ataxia.

4.1 Clinical data

The Age ranged between 13 and 69 years and the median was 43 years. The female patients

were predominant (sex-ratio=0,16)

The onset of ataxia symptoms was progressive for all the patients, and the evolution was chronic for 6 of them and remittent for 1 patient.

Five cases of gait and limb cerebellar ataxia were found on the clinical examination as well as 2 cases of sensory ataxia.

One patient had a history of tuberculosis and another one had HBP and type 2 diabetes.

Digestive symptoms were reported by one subject who had chronic diarrhoea and moderate dyspepsia.

4.2. Immunological testing

Three patients had high titers of AGA antibodies which represent 42,85% of included ataxic patients.

Positive IgA AGA were found in two patients with the following titers: 14,18 UI/L and 22,24 UI/L.

Additionally, one patient had both IgA (more than 200 UI/L) and IgG (more than 200 UI/L) AGA antibodies.

4.3. Other biological features

Anaemia was present in 5 patients and inflammation in 4 patients.

In addition, we found hypocholesterolemia and hyperglycemia in one case.

4.4. Neuro-imaging

MRI revealed global cerebellar atrophy in 4 patients.

Table XVII: Summary of clinical, biological, immunological and imaging investigations on ataxic patients.

Patient's data	Results
Median of age (range)	43 years (13 and 69 years)
Male to female sex ratio	2:5
Cerebellar ataxia	5 patients
Sensory ataxia	2 patients
Associated digestive symptoms	1 patients
Positive AGA Abs	3 patients
IgA AGA Abs	2 patients
Both IgG and IgA AGA Abs	1 patients
Hypochromic microcytic anaemia	5 patients
Inflammation markers	4 patients
Global atrophy (cerebral and cerebellar atrophy)	4 patients

5. Epilepsy

Our study included 7 patients with epilepsy, with the following characteristics:

5.1. Clinical data

All the patients reported an acute onset with a remittent evolution of their condition.

Two patients were type 2 diabetics.

The patients had neither history of GSE nor digestive symptoms suggesting this disease.

On the clinical description, 5 patients had the generalized tonico-clonic form followed by confusion, 2 had partial seizures and one of them had partial status epilepticus.

Six patients were under a treatment based on sodium valproates, with a bad outcome while one patient was under Phenobarbital.

5.2. Electro-encephalogram results

Six patients had spikes and waves at the EEG investigation; they were generalized in 4 cases and localized to the left parietal lobe in 2 other cases, while the EEG was normal in one case.

5.3. Immunologic testing

One patient had positive IgA AGA with 16,25 IU/ml as a titre.

All the patients were negative for both IgG-AGA and IgA-tTG.

5.4. Biologic results

Three patients had microcytic hypochromic anaemia, while 4 patients had increased inflammation markers.

5.5. Neuro-imaging data

MRI and scanner imaging were normal for all epileptic patients. They showed neither atrophy nor focal lesions that may explain the seizures.

Table XVIII: Characteristics of the epileptic patients

Patient's data	Result
Median of age (range)	45 years +/- 16,31
Sex ratio (M/F)	0,75
generalized tonico-clonic form	5
Partial epilepsy	2
Status epilepticus	1
Generalized spikes and waves	4
partial spikes and waves	2
Normal EEG	1
Neuro-imaging data (MRI and TDM)	Normal
positive IgA AGA Abs	1

6. Myopathy

Our series included 3 patients with myopathy; their clinical and immunological and biological data are described below:

6.1. Clinical findings

The median of age was 45 years (range: 25-55 years), with 2 females and one male (sex ratio M/F =0,5). These patients had neither digestive symptoms, nor HBP, nor diabetes, nor nutrition deficiency nor cardiopathies.

For all the patients, the disease's symptoms were progressive and chronic.

On neurologic examination, all the patients had bilateral and symmetric myogenic syndrome, associated to muscular atrophy in one case. Besides, one of them had total muscular deficit and therefore confined to wheelchair. Cutaneous signs were found in one patient who had vasculitis of the hands with manicure sign and Gottron papules suggesting dermato-myositis (Table XX).

6.2. Immunological results

Two patients were positive for AGA and both of them had the IgG isotype. The titres were respectively 27,41 IU/ml and 14,4 IU/ml (Table XX). All of them were negative for IgA-tTG.

6.3. Biology results

Two patients had hypochromic microcytic anaemia and increased inflammation markers.

The patients had neither hyperglycemia nor hypocholesterolemia.

Two patients had increased CPK titers with respectively 1067 and 5213 U/L (Table XX).

6.4. Pathology

Two patients underwent muscular biopsy. One patient had mitochondriopathy with no expression of dystrophine or alpha sarcoglycan while the other one had chronic myositis with vasculitis lesions (Table XIX).

Table XIX: Characteristics of the patients with myopathy.

Patient's data	Results
Median of age (range)	45 (25 to 55 years)
Sex-ratio	1:2
Onset	Progressive
Progression	Chronic
Bilateral and symmetric myogenic Sd	3
Muscular atrophy	1
Dermato-myositis	1
Increased CPK titers	2
IgG AGA Abs	2

7. Myelopathy

Two cases of myelopathy are included in the study.

The first one is about a masculine patient aged 48 years old and having a HBP; otherwise, his medical record showed neither diabetes nor auto-immune conditions nor cancer nor GSE's evoking symptoms.

The symptoms (weakness and paresthesias of the lower limbs) were progressive and neurological examination found a medullar syndrome; also, the MRI and CSF analysis were normal.

The immunological testing showed a positive IgG-AGA with 34,25 IU/ml, but was negative for both IgA AGA and IgA-tTG.

The second case corresponds to a 67 years old man, with normal medical history, who presented progressively a weakness with proximal and distal paresthesias and pain affecting both of the lower limbs. Neurological examination found a tetra-pyramidal syndrome. The scanner showed a tight lumbar canal and normal cervical medulla, however, MRI results were not provided. The electro-diagnosis exploration revealed a myelopathy evoking aspect with an impairment of the S1 sensitive root.

The patient was offered an immunological analysis (for both IgA and IgG AGAs and ant-tTG) that was negative.

8. Cerebral thrombophlebitis

One patient included in the study was diagnosed as cerebral thrombophlebitis. This female patient was 38 years old; she had neither history of GSE nor digestive symptoms.

Also, the patient didn't have a history of surgery, or immobilization; there were neither obstetrical conditions (pregnancy, delivery and abortion) nor medications (such as anticoagulants, contraception). She had intracranial hypertension syndrome on physical examination.

The MRI was normal without any atrophy of the cerebral parenchyma, however, scanner imaging showed a thrombophlebitis evoking aspect without parenchyma lesions.

The IgA AGA Abs were positive (14,32 IU/mL), and both IgG AGA and tTG were negative.

9. Multiple sclerosis

A 44 years old man, with no previous medical conditions presented an acute episode of

headache, dizziness, nausea and gait impairment that progressed in a remittent way.

Neurological examination showed tetra-pyramidal syndrome.

There was hyper-gammaglobulinemia on serum proteins' electrophoresis without oligoclonal aspect in the CSF. Brain and cervical spine MRI showed peri-ventricular, bilateral and asymmetric hyposignal in T1 sequence and hypersignal in T2 and Flair mode. According to McDonald's criteria, the diagnosis of MS was made.

The patient was positive for IgG AGA Abs with 97 IU/mL, however, he was negative for IgA-AGA and IgA-tTG.

10. Others neurological conditions

The 3 others cases of this study corresponded to anterior horn disease, dystonia, Parkinson disease associated to global atrophy and demyelinating lesions of white matter on MRI, and lymphocytic meningitis (CSF analysis showing increased levels of lymphocytes, normal glycorachy and proteinorachy and negative bacteriology testing) with respectively 2 cases, 1 case, 1 case, 1 case. The immunologic testing of all these patients was negative.

DISCUSSION

Discussion

In our study, we screened for GS among patients with idiopathic neurologic disorders. IgG and IgA AGA were first tested in patients and controls. To rule out an authentic celiac disease (GSE) in our patients, we performed an anti-tTG testing for both positive and negative AGA patients, and also in the controls.

I. Relevance of the immunological testing

The AGA testing is used by a large number of researchers in patients presenting neurologic diseases to check out GS[2, 113, 114] . Even if they lack sensitivity and specificity for the diagnosis [106, 107], they might be useful for detection of GS in unexplained neurological diseases[2].

It has been suggested that AGA testing remains an essential investigation in patients with sporadic idiopathic ataxia [89, 108] and IgG-AGA isotype is the best marker of GS in neurological disorders[2, 89]

Meanwhile, tTG and/or EMA testing are principally used to diagnose CD, regarding their high sensitivity and specificity [2, 48, 113, 115, 116].

II. Socio-demographic characteristics of the positive cases

The male to female ratio among our AGA positive individuals is 1,6 which differs from the sex ratio of the whole group of patients, and the median of age was 45,5 +/- 11,9 years old.

As shown in table XXI, demographic data of other series, patients with gluten sensitive

neuropathies are mostly males and youth.

Table XX: Summary of demographic characteristics of patients with GS neuropathies

	M/F sex ratio	Mean age (range)
Hadjivassiliou and al, 1996 [117]	2	NP*
Hadjivassiliou and al, 1998[85]	3	61 years (21-79)
Ihara and al, 2006, [118]	1,5	69 years (53-88 years)
Hadjivassiliou and al, 2010[119]	0,4	67 years (47-58 years)
Chin and al, 2003 [120]	1,5	53 years (31-79 years)
Our study, 2011	1,6	45,8 years (13-69 years)

*Not provided

By contrast, In one of the studies led by Hadjivassiliou *et al,* the male to female ratio among AGA positive patients was 0,4 which means that females were prominent (Table XX).

III. Epidemiological analysis

Our study found a high prevalence (26.7%) of antigliadin antibodies in patients with neuropathies of unknown cause versus 15.7% In the control group. Even if the association of neuropathies and GS in our series is not significant (*p=0,151*), these findings support the fact that GS may represent a potential aetiology of idiopathic neuropathies in our patients.

In fact, the studies that assessed the prevalence of AGA abs in idiopathic neuropathies showed different results (table XXI). Our prevalence is among the highest ones published by authors, such us Hadjivassiliou *et al* who found respectively 34%, 41% and 57% in his series [71, 89, 117]. Meanwhile, our results surpassed other published ones, such us Pellecchia *et al*, Burk *et al* and Abele *et al* who found respectively 13%, 12% and 13% of AGA positive patients[108, 121, 122].

Table XXI: Prevalence of AGA abs in idiopathic neuropathies

	Idiopathic neuropathies with positive AGA abs	Healthy controls %	P Value	References
Hadjivassiliou, 2006 (n=140)	34%	12%	<0,001	[71]
Ihara, 2006, (n=14)	36%	2%	<0,001	[118]
Pellecchia, 1999, (n=24)	13%	NP	<0,05	[108]
Hadjivassiliou, 2003, (n =53)	57 %	12%	<0,0001	[89]
Wong (n=56)	11%	8%	0,68	[123]
Our study (n=60)	16 (26,7%)	9/57 (15,75%)	0.151	-

NP=Not provided

The positive GS cases of our series (n=16) correspond to peripheral neuropathies (n=4), followed by ataxia (n=3), ischemic stroke (n=3), myopathy (n=2) and 1 case for each of the following diseases: epilepsy, cerebral thrombo-phlebitis, myelopathy and multiple sclerosis.

Our results are supporting those of previous studies (table XXII) where peripheral neuropathy and ataxia are found to be the most common neurological manifestations of GS. We found that ischemic stroke was highly prevalent (18,75%) among positive AGA patients; it wasn't mentioned in the large based studies listed in the comparative table (table XXII),however, there are case-reports describing the association between stroke and GS and will be detailed in the next chapter (Clinical and investigation data) [74, 75].

Table XXII: Categories of gluten sensitivity neuropathies in different studies

Neurological manifestations	Hadjivassiliou [2] n (%)	Hadjivassiliou [117] n (%)	Bùrk [124] n (%)	Our study n (%)
Ataxia	184 (43,4)	17/53 (32,07)	27 (37,5)	3/16 (18,75)
Peripheral neuropathy	174 (41,03)	28/53 (52,8)	10 (14)	4/16 (25)
Ischemic stroke	NP*	NP	NP	3/16 (18,75)
Encephalopathy	62 (14,62)	NP	NP	NP
Myopathy	18 (4,2)	4/53 (7,5)	NP	2/16 (12,5)
Venous thrombosis	NP	NP	NP	1/16 (6,25)
Multiple sclerosis	NP	NP	NP	1/16 (6,25)
Myelopathy	6 (1,4)	2/53 (3,7)	NP	1/16 (6,25)
Stiff-man syndrome	6 (1,4)	NP	NP	NP
Chorea	3 (0,7)	NP	NP	NP
Neuromyotonia	1 (0,2)	NP	NP	NP
Dystonia	NP	NP	3 (4)	NP
Parkinson disease	NP	NP	2 (2,77)	NP
Epilepsy	1 (0,2)	NP	NP	1/16 (6,25)

* NP= Not provided or not studied

The data from several studies investigating the occurrence of AGA in ataxias have been published and are summarised in table XXIV.

Table XXIII: prevalence of antigliadin antibodies in idiopathic sporadic ataxia

Studies and authors	Sporadic ataxia (%)	Healthy controls (%)	References
Hadjivassiliou and al, UK	47%	149 (12%)	[85]
Hadjivassiliou and al, UK	41%	12%	[89]
Pellecchia and al, Italy	13%	NP	[108]
Bürk and al, Germany	12%	5%	[121]
Bushara and al, USA	27%	NP	[125]
Abele and al, Germany	15%	5%	[122]
Luostarinen and al, Finland	17%	2%	[126]
Ihara and al, Japan	36%	2%	[118]
Anheim and al, France	36%	NP	[127]
Our study	42,85% (n=3/7)	15,78%	-

The prevalence of GS in our ataxic patients is among the highest ones; close to the English [85], Japanese [118], and French [127] series (table XIII). Nonetheless, the lowest prevalence were reported in the Finnish [126] and German [121] series. Actually, the discrepancy in frequency might be explained by several factors including geographical differences, culinary habits, variability in the AGA assays used, referral bias in the selection of patients (for example, some studies categorised patients with cerebellar variant of multisystem atrophy as idiopathic sporadic ataxia), small study size, and absence of controls[2].

Sporadic idiopathic ataxia seems to be more linked to GS than the hereditary ataxia or the sporadic form with multiple system atrophy (MSA). This fact is supported by Hadjivassiliou [67, 68, 89, 128] and Pellecchia [108] and Luostarinen[126], and Abele[122, 129].

In the large study lead in England on 268 patients with ataxia, GS accounted for up to 41% of cases of sporadic idiopathic ataxia which makes it the single most common cause of ataxia in this cohort of patients. Besides, 14% of familial ataxia's cases and 15% of the MSA-C (cerebellar variant of MSA) group had evidence of GS but were not significantly different from the healthy controls (12%) [89]. However, a study from the USA found a high prevalence of AGA positivity in both sporadic (27%) and familial ataxias (37%); however, the numbers screened were small (26 sporadic form and 24 familial form) [130]. On the other hand, all our 3 positive AGA ataxic patients correspond to cerebellar sporadic idiopathic form which is well supported by the literature data above.

Peripheral neuropathy (PN) is the other most common manifestation of GS[2]. Actually, many authors relate that PN is frequently associated with GSE, and it might be detected even in celiac patients under GFD [2, 131, 132]. Otherwise, PN was recognised as an exclusive

manifestation of GS in numerous studies[2, 71, 72, 120]. Concerning our series, 25% of cases (n=4) had evidence of gluten sensitive neuropathies, which is close to the English [71], and Italian [72] and Finnish [131] studies; but remains higher than the American one [120] (table XXIV).

Table XXIV: Prevalence of GS in peripheral neuropathy patients

Studies and authors	Gluten neuropathies n (%)	Control group n (%)	p Value	References
Luostarinen et al, Finland (n=26)	23%	4,3%	<0,001	[131]
Hadjivassiliou et al, UK (n=140)	34%	149 (12%)	<0.001	[71]
Mata et al, Italy (n=330)	21%	1 (1,5%)	<0·0001	[72]
Chin et al, USA (n=400)	Between 2,5% and 8%	1%	<0,001	[120]
Our study	4 (25%)	15,78%	-	-

According to literature, the association of ischemic stroke with GS is less frequent and has not been well documented [74, 75]. A recent study suggested that childhood GSE is associated with a 10-fold increased risk of death from stroke, although it was based on small numbers[133]. However, a nationwide Swedish study that evaluated the risk of stroke in 28,000 patients with GSE concluded that celiac patients are at only a small increased risk of stroke and that CD does not seem to be a major risk factor for stroke[133].

The risk of cardiovascular disease in individuals with GSE has been evaluated by Swedish authors on a large cohort of patients (13 358 individuals diagnosed with GSE and 64 118 age-matched and sex-matched controls without GSE). They found a positive association between GSE and myocardial infarction, angina pectoris, heart failure, brain haemorrhage and ischemic stroke [134].

West and al studied the risk of vascular disease in adults with diagnosed GSE compared with the general population. Consequently, the author found a slight increase in the risk of atrial fibrillation and ischemic stroke. In our series, 3 of 18 ischemic stroke cases were positive for AGA which is important.

Myopathy is considered by Hadjivassiliou [2] and Henriksson [135] as rare neurological manifestation of GS[2]. However, Selva-O'Callaghan and colleagues found that GS might be a probable aetiology for idiopathic and inflammatory myopathies[136]. They supported their statement by the high prevalence of AGA positivity (31%) within inflammatory myopathies compared to the general population, certainly because of the shared HLA class II haplotypes (DQ2) between the two diseases [136, 137]. Moreover, our series showed also a high prevalence of GS since 2 have tested positive for AGA among the 3 myopathy patients.

Several reports have suggested a link between epilepsy and GSE[2, 5, 138, 139] which was first described by Visakorpi and al in 1970 [140]. Nevertheless, some authors didn't confirm these findings, such us *Ranua and al* who found no difference in the prevalence of AGA and anti-EMA and anti-tTG abs between epileptic patients and controls [141]. Moreover, authors disagreed on the frequency of this association; while Hadjivassiliou considered epilepsy as a rare manifestation of GS; It was reported to be common in Italy, Spain, and Argentina suggesting a geographical factor [142]. In our series, 1 of the 7 epileptic patients had evidence of GS.

Further more, the association between GS and relapsing-remitting or secondary-progressive multiple sclerosis was not significant in all studies performed till now[143, 144].

Additionally, clinical evidence of myelopathy without vitamin or other deficiencies (particularly copper) can be a rare manifestation of GS[2, 117]. There have been reports of patients

with neuromyelitis optica (Devic's disease) and GS associated with antibodies to aquaporin-4[145, 146]. In our series, only 1 patient who had myelopathy with negative etiological investigations was positive for AGA abs.

The cases of thrombophlebitis associated with GSE are very scarce[147]. Bahloul *and al* reported a case of GSE who developed cerebral venous thrombosis associated with protein S deficiency[148] . Moreover, a Turkish case-report about GSE associated with deep venous thrombosis of the leg was published[147]. Our series comprises a 38-years old female patient diagnosed with cerebral thrombophlebitis who tested positive for AGA.

Finally, all patients in our series who had dystonia, and anterior horn disease, and Parkinson disease and lymphocytic meningitis were tested negative for AGA. In fact, case reports about a possible association between GS and those conditions are scarce; however, there is no evidence in literature of such association with Parkinson disease. Thus, 1 case of chronic meningitis [149] and 2 cases of dystonia [150, 151] and 3 cases of anterior horn disease [118, 152, 153] revealing GS are reported by the literature.

IV. Clinical and investigations data

1. Gluten Ataxia

The patients with gluten ataxia are usually males, however, female predominance was reported by some authors [121]. Moreover, gluten ataxia has generally an insidious onset with a mean age at diagnosis of 41 years which is in line with Hadjivassiliou and Burk's findings[89, 121]; however, old patients prevailed in a Japanese study[118] (Table XXV).

Table XXV: Characteristics of the patients with gluten ataxia

	Hadjivassiliou et al, 2003, [89] n= 68	Hadjivassiliou et al,1998,[85] n=28	Burk et al, 2001, [121] n=12	Ihara et al, 2006,[118] n=5	Our study, 2012 n=3
M/F sex ratio	1,06	3	0,71	1,5	2
Mean age at study (range)	NP	61 years (21-79 years)	55 years+/- 17,4 (30-76)	69 years (53-88)	41 years (13-69)
Mean age at onset (range)	48 years (14± 78 years)	53,57 years (18-76 years)	44,8 years+/- 23,2 (2-68 years)	NP	NP
Dysarthria	45 (66%)	NP	12 (100%)	NP	3 (100%)
Limb ataxia (LA)	Upper LA n=51(75%) Lower LA n=61(90%)	26 (92,8%)	11 (91,7%)	NP	3 (100%)
Gait ataxia	68 (100%)	28 (100%)	12 (100%)	NP	2 (67%)
Gastrointestinal symptoms	9 (13%)	12 (43%)	2 (16,7%)	NP	-
Loss of proprioception	NP	NP	7 (58,3%)	NP	1 (33,33%)
PN clinical signs	NP	10 (35,7%)	4 (33,3%)	3 (60%)	-
Amyotrophy	-	-	1 (8,3%)	NP	-
Cerebellar atrophy on MRI	n=52 (79%)	6 (21,4%)	12 (100%)	4 (80%)	2 (67%)
White matter hyper-signal on MRI	n=13 (19%)	-	-	NP	-
axonal neuropathy on neurophysiology (EMG)	31 (45%)	10 (35,7%)	2 (16,7%)	3 (60%)	-

In addition, gluten ataxia presents usually with the cerebellar form [2, 89, 121] which matches our results (Table XXV). However, the association between GS and sensory ataxia has been described [121]. Otherwise, the association of ataxia and peripheral neuropathy was reported by authors; usually it's an axonal neuropathy on EMG exploration[85, 118, 121, 154]. This neuropathy is frequently mild and does not contribute to the ataxia[2]; however, none of our

patients diagnosed with gluten ataxia had such signs. Gaze-evoked nystagmus and other ocular signs of cerebellar dysfunction are seen in up to 80% of cases[154].

Besides, cerebellar atrophy on MRI is commonly found in gluten ataxia reaching 100% in some studies [85, 89, 121] (table XXV).

Finally, there is no specific clinical features to enable a confident diagnosis of gluten ataxia, except perhaps in patients with established GSE[108]. The clinical features described in table XXV are also seen in patients with other forms of sporadic and inherited ataxias. This emphasizes the importance to keep in mind the possibility of GS in patients presenting with ataxia[89].

2. Gluten neuropathy

Gluten neuropathy is defined as apparently sporadic idiopathic neuropathy in the absence of an alternative etiology and in the presence of serological evidence of GS. It is a progressive disease affecting mostly young subjects with a mean age at onset of 55 years (range 24–77 years) [71] which supports our findings (mean age at diagnosis: 45 years).

The mean diagnostic delay before introducing GFD is 9 years (range 1–33 years)[2]; this long delay explains the occurrence of neurologic disorders in GS patients[131].

The majority of patients are masculine (male to female sex ratio 3:1) and matches the sex ratio of the whole group of positive AGA patients, which is supported by other studies [117, 120]. Also, Chin *and al [120]* found an important frequency of positive AGA cases in patients with associated digestive symptoms whereas one positive AGA case in our series reported chronic diarrhea; thus, it could be considered as an orientating element.

Positive patients often express pain and paresthesias, and on clinical examination, PN syndrome may be associated with sensory abnormalities (tactile, heat pain and vibratory hypoesthesia), which is consistent with our findings. This provides evidence that peripheral nerve fibres, even small non-myelinated ones, are affected in GS[131]. Otherwise, amyotrophy or handicap were neither found in our study nor reported by authors (Table XXVI).

Symmetrical sensori-motor axonal neuropathy is the prominent electrophysiological finding[2, 71, 155] which is consistent with EMG results of our positive AGA cases. Other types of neuropathies have also been reported such as asymmetrical neuropathy[155], sensory ganglionopathy[156], small fiber neuropathy[157], pure motor neuropathy[71], and autonomic neuropathy[99]. Meanwhile, 2 positive AGA patients, in our series, have polyradiculo-neuropathy for one and elongation of distal latencies with abnormalities of "F" waves for the other.

Brannagan *and al* reported up to 8% of gluten neuropathy with normal electrophysiologic testing [120]. Similar to our results, Hadjivassiliou and Chin didn't find cerebral and/or cerebellar atrophy on neuro-imaging in patients with gluten neuropathy[71, 120].

Table XXVI: Clinical and investigations' characteristics of patients with idiopathic neuropathy associated to positive AGA antibodies

Characteristics	Hadjivassiliou et al, 2006,[71], n=47	Chin et al, 2003,[120],n=28	Our study n=4
Male to female ratio	NP	1,75	3
Mean age at onset of neuropathy	55 years (24–77)	56 years (31-79)	45 years* (40-52)
Mean duration of disease	9 years (range 1–33)	NP	NP
Known GSE	NP	45%	-
Digestive symptoms	NP	NP	25 %
amyotrophy	NP	NP	-
Need walking aid	22%	NP	-
Pain a prominent feature	14%	27%	-
Paresthesias	NP	100%	3/4
Objective sensory abnormalities	NP	85%	2/4 (50%)
Cerebral an/or cerebellar atrophy on MRI	NP	-	-
White matter abnormalities on MRI	NP	-	-
Sensorimotor axonal neuropathy	67%	35%	-
Sensitive axonal polyneuropathy	-	-	1/4 (25%)
Motor neuropathy	9%	-	-
Mononeuropathy multiplex	17%	-	1/4(25%)
Small-fibre neuropathy	7%	-	-
Motor polyradiculoneuropathy	-	-	1/4(25%)
Other EMG findings	-	-	1**
Only antigliadin IgG positive	57%	37%	-
Only antigliadin IgA positive	16%	18%	4/4(100%)
Both antigliadin IgG and IgA positive	27%	45%	-

* Age at diagnosis; ** Elongation of distal latencies with abnormalities of "F" waves; NP=not provided

3. Ischemic stroke

The majority of patients with GS are young [74, 75, 158] and the median of age at onset, in our series, is 40 years ranging between 25 and 74 years. Besides, case-reports about childhood stroke revealing GS have already been published [103, 159]. The medical record of the gluten stroke cases didn't show any cardiovascular risk factors except 1 patient who is masculine. Also, digestive symptoms were absent for all of them. Moreover, recurrent episodes of transient ischemic strokes are reported by authors [100, 160]. The main clinical presentation corresponds to pure and proportional pyramidal syndrome, and rarely pseudo-bulbar syndrome [75], and the right side was mostly concerned in our study.

On neuro-imaging, the middle cerebral artery's area is the most affected with seldom cerebral or cerebellar atrophy[75], however, 2 of the 3 positive cases in our study presented global atrophy. Consistent with literature, echography showed elevated resistance in the right primitive carotids and vertebral arteries in 1 patient and hypertensive cardiomyopathy in another one. In fact, cases of thrombus of the ventricles[100], arteriosclerosis of the coronary artery[100] and dilated cardiomyopathy [159] have been described.

Laboratory evaluations for prothrombotic conditions (including coagulation examinations, full blood count, factor V Leyden and prothrombin mutations, serum homocystein, glycaemia) can be either normal [74, 159] or abnormal [100, 160]. In this disease, AGA frequently coexists with hyper-homocysteinemia and decreased folates' levels [75]. This hyper-homocysteinemia is a known risk factor for atherosclerosis and ischemic strokes [75, 101].

In our series, 3 of 18 ischemic stroke cases had positive AGA which is important regarding the

rare reported cases over the world. One of them has an intermediate homocycteinemia level, 2 patients had hyperglycaemia and 1 had intermediate rate of serum homocysteine; meanwhile, the lipid profile and coagulation examinations were normal for all. Hence, our results are approximate to literature.

4. Myopathy

AGA antibodies have been detected in various clinical forms of myopathies including proximal myopathy due to vitamin E deficiency[161], osteomalacia linked to vitamin D deficiency[162], polymyositis [135], juvenile form of dermatomyositis (DM) [163] and sporadic inclusion body myositis (s-IBM) [135]. Besides, no intestinal symptoms were reported in most cases.

In addition, Spanish authors found that 31% of patients with inflammatory myopathy were AGA positive and the prevalence was significantly more frequent in patients with s-IBM than DM ($P<0.001$)[136].

On neurologic examination, patients usually have bilateral and symmetric myogenic syndrome with progressive muscular atrophy [2]. Moreover, the association with ataxia and neuropathy was described by some authors[164].

Gluten myopathy can be combined to normal or increased CPK rate[136, 164]. On neuro-pathology, inflammatory myopathy is the most common finding[136, 164]. Finally, some authors reported an improvement of the myopathy after GFD introduction [2].

5.1. Epilepsy

Epilepsy associated with GS tends to affect young patients; however, paediatric cases have also been reported [165]. The seizures mostly resist to antiepileptic drugs[142, 166], and may be benign or sometimes evolves into severe epileptic encephalopathy[142].

The epilepsy related to GS is more often focal [139, 165, 167], besides, *Magaudda and al* found that the majority of patients had complex partial seizures linked to the occipital or temporal lobes. In addition, secondarily generalized seizures, or other seizure types, and episodic headaches were also described [138, 168]. This is in line with clinical presentation of our only positive patient who is young (44 years) and had a partial and remittent tonic-clonic status epilepticus.

On neuro-imaging, authors found that cerebral calcifications of the occipital lobe without contrast enhancement are tightly associated with GSE [5, 165, 167, 169]. However, the CT-scan performed for our patient showed a frontal sequellae hypo-density without cerebral atrophy or calcifications.

6. Other less common manifestations

6.1. Thrombophlebitis

The cases of thrombophlebitis associated with GSE have been rarely published[147]. The disease usually affects young patients with no pro-thrombotic risk factors[147], involving different vascular territories: deep venous proximal thrombosis of the leg[147] , portal vein thrombosis[105], and non-ischemic central retinal vein occlusion[170]. Also, *Bahloul and al*

reported a case of GSE who developed cerebral venous thrombosis associated with protein S deficiency[148] . In addition, some patients improved after introduction of GFD[147].

6.2. Dystonia

The case-reports about a possible association between dystonia and GS are rare. *Hall and al* reported a child with biopsy-proven GSE associated to movement disorder since the age of 6 months that evoked paroxysmal non-kinesigenic dystonia (PNKD). This patient had complete resolution of her neurological symptoms after introduction of GFD[151]. Another case-report about 14 years-old girl who developed dystonic movements in her left lower limb and became handicapped; she was diagnosed later with pathology-proven GSE[150]. In our study, one patient with dystonia was admitted and has no evidence of GS after immunological screening.

6.3. Anterior horn disease (AHD)

The amyotrophic lateral sclerosis (ALS) is one of the most common diseases that affect the anterior medullar horn. Extremely few Case-reports about the association of ALS with GS are published [118, 152, 153]. Actually, in a Japanese study, among the 18 recruited patients with ALS, 1 had evidence of GS; he was a 56 years-old man who had an active denervation of the tongue and the 4 extremities on electrophysiological testing, with abnormal T2 signal intensities in the bilateral pyramidal tract on cranial MRI[118]. In addition, *Turner and Brown* published 2 cases of confirmed GSE that manifested by ALS associated with MRI abnormalities. One of them had T2/FLAIR signal-intensity abnormalities in the left cortico-spinal tract and the other had abnormal T2 signal-intensity abnormalities in the bilateral pyramidal tract on cranial MRI. After GFD introduction, the MRI ALS suggesting features showed improvement[152, 153].

Otherwise, our study included 2 female patients with AHD; both of them were negative for AGA and anti-tTG testing.

6.4. Lymphocytic meningitis

The first observation of 56 years-old woman with chronic meningitis revealing GSE is reported by *Cartalat-catel and al*. Seven years after the onset of meningitis, she presented neuralgia of the trigeminal nerve and cerebellar syndrome. The MRI examination showed cerebellar atrophy with leuco encephalopathy[149].

6.5. Myelopathy

Clinical evidence of myelopathy in the absence of vitamin and other deficiencies (particularly copper) can be a rare manifestation of GS[2, 117]. This myelopathy can present with progressive medullar syndrome and is usually associated with normal imaging of the spinal cord[2]. In addition, there have been reports of patients with neuromyelitis optica (Devic's disease) and GS who have antibodies to aquaporin-4[145, 146]; these patients had abnormal MRI of the spinal cord. This form has to be determined whether this is simply an association based on the same genetic susceptibility or due to immunological mechanisms[2].

V. Immunological investigations

1. Global findings

We found an important prevalence of AGA abs among patients with idiopathic neuropathies reaching 26.7% (n=16). This finding is in line with previous studies, some of them are close to our results such as Hadjivassiliou[89]. Other ones show higher frequency [117], and the published prevalence by some German studies are the lowest[121] (Table XXVII).

Even if the association of GS and neuropathies in our series is not significant (*p=0,151*), compared to control individuals, GS can be considered as a substantial aetiology of unknown neuropathies of our patients.

Table XXVII: Immunological findings in series about the association of GS and idiopathic neuropathies

	Hadjivassiliou [117] n(%)	Hadjivassiliou [85] n(%)	Hadjivassiliou [89] n(%)	Chin; [120] n(%)	Burk [121] n(%)	Our study n(%)
Number	53	NP*	176	20	104	60
Only IgG-AGA	6	16	62	4	2	6
Only IgA-AGA	12	6	6	2	6	9
Both IgG and IgA AGA positive	12	6	NP	5	3	1
Total of AGA-positive patients	30 (57%)	28	68 (38,6%)	11 (55%)	11(10,5%)	16(26,7%)
Anti IgA-tTG	NP	NP	NP	8	NP	0

The author reports that he included patients seen in the neurology outpatient department at the Royal Hallamshire Hospital from January 1994, to April 1998 and 28 were diagnosed with GS after immunological screening.

IgA-AGA is the most common isotype that we identified in our gluten neuropathies (16,7%;n=9), versus 10% (n=6) for IgG-AGA. This finding is coherent with Burk's series [121]. However, many authors found that IgG-AGAs were more common in neurologic diseases [85, 89, 120]. Therefore, IgG-AGA isotype is considered to be more important in the context of extra-intestinal manifestations of GS, by comparison to IgA class antibodies, which seems to be more linked to gut clinical forms [2, 114, 171]. This finding can be supported by the fact that IgG-AGA titres are higher than IgA-AGA's ones in our series (figure 11). However, this fact needs further

consideration because of the absence of analogous data.

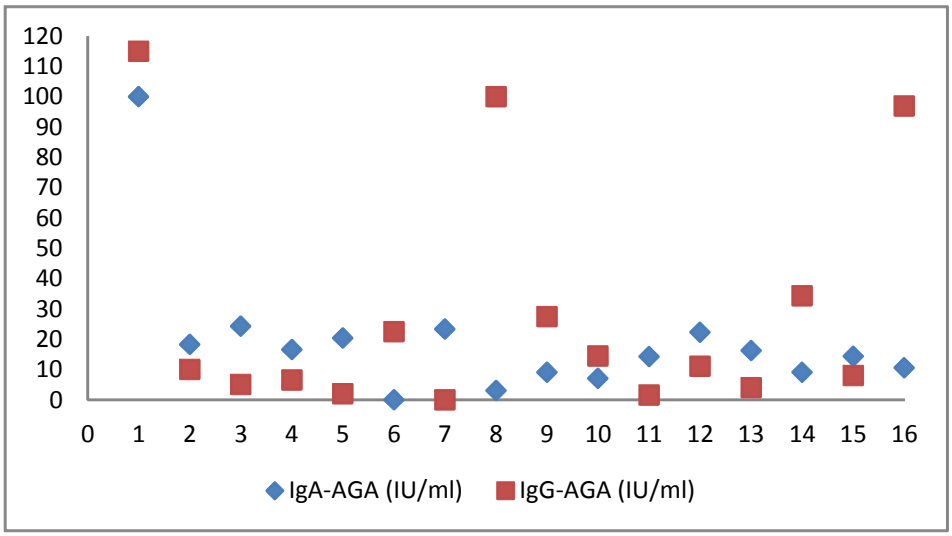


Figure 11: Comparison between IgG-AGA and IgA-AGA titres

Nevertheless, some authors report a non-significant increase of AGA either in ataxia or PN, and no over representation of HLA DQ2 or HLA DQ8 is detected in their series [113, 129]. Lock *and al* argue that it might simply reflect an age related phenomenon or may imply a general heightened responsiveness of the gut immune system in these individuals. Moreover, it could be explained by a gut permeability's impairment or inflammation, and adds that AGA in hereditary ataxias must be an epiphenomenon[113].

The introduction of more specific CD serological markers such as anti-EMA and more recently, tissue transglutaminase abs may help in diagnosing GSE, but their sensitivity as markers of other manifestations of GS (where the bowel is not affected) is low[85]. Hadjivassiliou explained that without overt gastrointestinal involvement, serum antibodies to transglutaminase-2 (TG2) can be absent[2].

Our results are supporting previous findings and all of our patients were negative for anti-tTG IgA, which makes occult CD unlikely.

2. Gluten Ataxia

Two of our ataxic patients have positive IgA-AGA. (14,18 IUI/mL and 22,24 IU/mL), and 1 has both IgA (more than 200 UI/L) and IgG (more than 200 UI/L) AGA. None of them is positive for IgA anti-tTG.

In many studies, patients with idiopathic sporadic ataxias were found to have frequent occurrence of AGA compared with healthy controls (table XXVIII), which makes GS a potential cause for this condition [2, 89, 108, 118, 121]

Table XXVIII: Immunological profile of gluten ataxia.

	Ihara, 2006, [118]	Hadjivassiliou et al, 1998, [85], (n=NP)	Hadjivassiliou et al, 2003,[89] (n=176)	Pellecchia et al, 1999,[108] (n=24)	Burk et al, 2003, [121] (n=104)	Our study n=7
AGA positive (IgG or IgA)	36%	n=28	68 (38,63%)	12,5%	10,5%	N=3
IgG-AGA positive	3 (21,4)	n=16 (57,1%)	62 (35,2%)	3(8,3%)	2 (2%)	N=0
IgA-AGA positive	2 (14,3)	n=6 (21,4%)	6 (3,4%)	0	6 (5,7%)	N=2
Both IgG and IgA positive	-	n=6 (21,4%)	NP	1 (4,1%)	3 (2,9%)	n=1

n: number

IgG-AGAs are better markers of the whole spectrum of GS irrespective of the organ involved and remain the best diagnostic markers for gluten ataxia[89, 130]. Moreover, IgA-AGA and anti-EMA may lack sensitivity and specificity when used in a neurological population[172]. In fact, HLA studies supports theses findings; thus, within a group of patients with gluten ataxia defined by the presence of IgG-AGA antibodies (n=68), authors have found an HLA association similar to

that seen in patients with CD: 72% of patients have the HLA DQ2 (35% in the general population), 6% have the HLA DQ8 and the remainder have HLA DQ1 [89].

However, Burk *and al* found that IgA-AGA was the most frequent isotype among gluten ataxia patients[121] which is similar to our findings (all gluten ataxia patients have the IgA-AGA isotype). The genetic and geographical factors might cause this difference in immunologic profiles but it remains to be demonstrated.

Finally, combined IgA and IgG-AGA abs can be present in those patients, but at a lower proportion compared with the other immunological features (table XXVIII).

IgG-anti-tTG2 in patients with gluten ataxia are found to be more common than IgA, also, IgA-anti-tTG2' titres in patients with gluten ataxia are lower than those seen in celiac patients [2]. In our study, all patients were negative for IgA-anti-tTG but none of them was screened for IgG-anti TG2.

3. Gluten neuropathy

The literature highlights an important prevalence rate of GS in a considerable number of idiopathic axonal PN (table XXIX); suggesting the aetiological link between the two conditions.

Table XXIX: Immunological characteristics of patients with idiopathic PN

Immunological characteristics	Hadjivassiliou et al, 2006,[71] n=140	Chin et al,2003,[120] n=20	Our study n=16
Positive AGA abs (of any isotype)	34%	55%	25%
Positive IgG AGA Only	57%	37%	0
Positive IgA AGA Only	16%	18%	25%
Positive of Both IgG and IgA AGA	27%	45%	0
Positive IgA anti-tTG	36%	40%	0

Moreover, IgG-AGA remains the most frequent isotype among neuropathic patients[2, 71, 120]. However, the IgA-AGA can be the only positive isotype but at lower proportions [71, 120], which is coherent with our results. On the other hand, IgA anti-tTG2 detection is specific for the presence of enteropathy but often not detectable in patients with neurological manifestations[2, 155]. Nevertheless, an Italian study found an important number of patients (68 of 330; 21%) with various types of peripheral neuropathies who were positive for IgA anti-tTG2 compared to controls (1 of 68; 1,5%) ($p<0\cdot0001$) [72]. In addition, the HLA types associated with GSE were seen in 80% of the patients with PN (62% HLA-DQ2, 10% HLA-DQ8, 8% HLA-DR3, HLA-DR5 or HLA-DR7, without HLA-DQ2 or HLA-DQ8) [71], thus, it may offer additional diagnostic value.

4. Ischemic stroke

Even if the published case-reports on the stroke-GS association are scarce, the following remarks are made on the basis of the available literature [74, 75, 103, 160] and our data,

- IgG-AGA isotype is more frequent than IgA-AGA, and it has high titres, which supports the fact that AGA is more specific to GS without gastrointestinal involvement;

- IgA anti-tTG abs and anti-EMA abs are often detected, while, none of our patients was positive

for IgA anti-tTG abs.

Being a potentially treatable cause of ischemic stroke, GS can be considered as a potential aetiology of stroke of unknown cause, particularly in young patients, and even without gastrointestinal manifestations[173].

5. Myopathy

GS is more prevalent in patients with inflammatory myopathies than in the general population [136, 174]. The positive status of HLA-DQ2 allele, which is known to be more frequent in patients with inflammatory myopathies (IM), could explain the high prevalence of AGA in this population[136].

The data available from literature show that IgA-AGA is the prominent isotype[136, 174]. In a study evaluating the titres of auto-antibodies specific to various autoimmune diseases, including GS, in 99 patients with inflammatory myopathies compared with 100 healthy controls, found that IgA-AGA levels were significantly elevated in IM patients compared with controls *($p= 0.017$)* [174]. Also, Selva O'Callaghan and al found that 31% of patients (n=17) were positive for IgA-AGA which were significantly more frequent in patients with inclusion body myositis than dermatomyositis *($p <0.001$)*[136]. However, 2 of 3 patients with myopathy were positive for IgG-AGA isotype.

Furthermore, anti-tTG abs are not necessarily positive in gluten inflammatory myopathies[174], which is coherent with our results. The following factors could contribute to explain these findings[136]. First, low positive values of IgA-class AGA antibodies can be present in patients with autoimmune disease, as has been demonstrated in Sjogren's syndrome and lupus [175].

Therefore, we believe that autoimmune myositis patients might show similar findings, and the negative anti-tTG abs might be due to the antigen binding to the bowel mucosa, making it undetectable in serum. Actually, this hypothesis was suggested in some patients with gluten ataxia [102]. However, compared to patients with normal muscle, the elevated rate of tTG in subjects with sporadic inclusion-body myositis, suggests the possible contribution of these abs in the pathogenesis of myopathy [176]. Nonetheless, more large-based population studies are needed to confirm or reject this hypothesis.

On the basis of these findings, some practical observations were offered by authors [136]. First, a high degree of awareness is required to detect GS in patients with idiopathic inflammatory myopathies (IIM). In fact, intestinal symptoms are usually absent, and AGA abs are mildly positive, and anti-tTG abs, the most specific and sensitive serological screening test for GSE, are usually negative. The HLA-DQ2 haplotype does not seem to help in the diagnosis of GS in these patients because of the shared HLA alleles in both diseases (IIM and GS)[136]. Thus, moderate AGA values (around 7 IU/mL) in these patients may warrant a bowel biopsy to exclude GSE[136]. Secondarily, the risk of cancer, which is increased in patients with PM/DM, may be even higher in patients with associated GSE, particularly gastrointestinal cancer. Consequently, a correct diagnosis of GSE may help to reduce this risk[136]

6. Other less common manifestations

6.1. Multiple sclerosis

An Iranian study, lead on 161 clinically defined MS patients and 166 control group who were screened for IgG and IgA antigliadin abs, showed no significant differences between MS patients

and controls regarding the IgG and IgA-AGA status and anti-tTG abs as well as intestinal biopsy were negative in all positive IgG or IgA AGA [143]. *Nicoletti and al* described similar observations in a case-control (217 patients vs 200 controls) Italian study [177].

In our study, the only 1 patient with MS was positive for IgG-AGA abs and the titre was 97 IU/mL, the IgA-AGA abs and anti-tTG abs were negative.

6.2.Thrombophlebitis

A Turkish study reported 1 patient with deep venous thrombosis of the leg associated to GSE; the diagnosis was made according to the elevated rate of IgA-AGA and IgA-EMA abs along with the jejunal biopsy results[147]. Also, Lee and Pulido described a woman with non-ischemic central retinal vein occlusion associated with GSE and suggested that hyper-viscosity due to circulating AGA abs or dehydration due to diarrhoea might cause the thrombotic event[170].

Saibeni and al found that hyper-homocysteinemia is more frequent in patients with GSE compared with the control group, which results from vitamin deficiency caused by malabsorption and represent a risk factor for thrombosis [178]. Similar to the Turkish study, our corresponding patient had cerebral thrombo-phlebitis and positive IgA-AGA Abs (14,32 UI/mL) but both IgG AGA and tTG were negative; unfortunately, he did not have the serum homocystein testing.

6.3.Myelopathy

Similarly to our study, among 53 unknown etiologic neuropathy patients, Hadjivassiliou included 2 cases of myelopathy. One of them had IgG-AGA abs and the other one had both IgG and IgA-AGA [117]. Two patients with myelopathy were enrolled in our series and the immunological testing showed 1 positive IgG-AGA (34,25 IU/ml), but negative for both IgA-AGA and IgA-tTG.

Finally, IgG-AGA isotype seems more frequent in this condition, nevertheless, the small size of patients with myelopathy in both Hadjivassiliou and our series makes difficult to elaborate concrete conclusions.

CONCLUSION

We conclude that serological evidence of gluten sensitivity is common in neurological diseases of unknown cause and may be etiologically linked.

The diagnosis is based on AGA testing which might be the best marker for gluten neuropathies.

The clinical assessment showed that peripheral neuropathy and ataxia and even ischemic stroke of young adults are commonly associated with GS. Otherwise, the effect of gluten free diet on the neuropathy will be an additional argument for this association and, therefore, offers the prospect of a realistic therapeutic possibility for some untreatable neuropathies.

Indeed, further studies with larger sampling of patients as well as experiments on the effectiveness of the gluten free diet are strongly needed.

ABSTRACTS

Abstract

Gluten sensitivity (GS) is a state of heightened immunological responsiveness to ingested gluten in genetically susceptible individuals. Recently, it has been accepted that GS can have only neurological manifestations.

Objectives: To estimate prospectively the prevalence of GS among idiopathic neurologic diseases and to study their clinical, radiological, electrophysiological, immunological and biological characteristics.

Methods: Prospective screening (using IgA and IgG antigliadin and IgA-anti-tissue transglutaminase antibodies using ELISA system) on 60 patients (mean age: 43 years, ranging between 13 and 76 years and male to female ratio: 0.7) with different idiopathic neuropathies compared to 57 controls. Patients were recruited from Neurology Department (University Hospital of Marrakesh) and controls corresponded to healthy blood donors from the blood transfusion center (Ibn-Sina Military Hospital, Marrakesh).

Results: According to physical examination and specific investigations of the patients, the study included 18 cases of ischemic stroke (28,33%), 16 cases of peripheral neuropathy (PN) (26,7%), 7 cases of epilepsy (11.7%), and 7 with ataxia (11.7%), and 3 with myopathy (6.7%) and 9 had other neuropathies (15%) corresponding to 2 cases of myelopathy and 2 anterior horn disease patients together with 1 case for each of the followings: Parkinson disease, lymphocytic meningitis, multiple sclerosis, cerebral thrombophlebitis, dystonia. After immunological testing, 26.7% of patients (n=16) had positive AGA versus 15.7% in the healthy controls *(p=0,151)* while IgA-tTG was negative for all patients, and positive in only one control. The positive AGA cases corresponded to peripheral neuropathy (n=4), ataxia (n=3), ischemic stroke (n=3) and myopathy (n=2) followed by one case for each of the following conditions: multiple sclerosis, epilepsy, cerebral thrombophlebitis and myelopathy. Among the positive AGA, IgA isotype is more frequent than IgG; however, IgG-AGA titres are higher than IgA-AGA ones.

Conclusion: Regarding the high prevalence of AGA in our series, GS may be considered as potential cause for neurologic diseases of unknown aetiology, particularly peripheral neuropathy and ataxia and ischemic stroke of young adults. Moreover, the AGA testing might represent the best marker for gluten neuropathies.

Key words: gluten sensitivity, neuropathy, antigliadin antibodies, prevalence.

ملخص

الحساسية المفرطة للغلوتين هي استجابة مناعية مبالغة ضد الغلوتين و مشتقاته عند أشخاص ذو استعداد وراثي. و قد بينت الأبحاث الطبية الحديثة أن هذا المرض يمكن أن يظهر بأعراض عصبية فقط دونما عوارض هضمية. و لهذا تأتي هذه الدراسة الاستباقية من أجل تحديد معدل انتشار هذه الحساسية المفرطة في الأمراض العصبية المجهولة السبب و تبيان خواصها السريرية، الإشعاعية، الفيزيولوجية و الإحيائية. تم انجاز هذا البحث على 60 مريضا (متوسط العمر 43 سنة محصورة بين 13 و 76 سنة و نسبة الذكور للإناث: 0,7) في مقابل 57 شاهدا سليما تم انتقاؤهم من بين المتبرعين بالدم. استفاد المشاركون من فحص بدني وفحص بالأشعة و تحاليل مخبرية ضمت قياس تركيز مضادات الأجسام ضد الغلياذين من نوع "أ" و "ج" إضافة إلى مضادات الأجسام ضد ناقلات الغلياذين من نوع "أ".أسفرت هذه الفحوصات عن 18 حالة جلطة دماغية (28,3%)، 16 حالة من مرض اعتلال الأعصاب (26,7 %)، 7 حالات من الصرع (11,7%)،7 حالات من الرنح (11,7%)، 3 حالات من الاعتلال العضلي (6,7%)،حالتان من مرض القرن النخاعي الأمامي و حالة واحدة لكل من متلازمة باركنسون، التهاب السحايا، متلازمة الانضغاط النخاعي، التصلب اللويحي، مرض اعتلال النخاع الشوكي و مرض خلل التوتر العضلي و التهاب الوريد الخثاري. أما التحليل المناعي فأسفر عن تسجيل 16 مريضا (26,7%) و 9 شهود (15,7%) ذو تركيز موجب لمضادات الأجسام ضد الغلياذين (الرقم الاستدلالي =0,151) في حين أن مضادات ناقلات الغلوتامين كانت ذات تركيز موجب عند شاهد واحد. يتوزع المصابون بالحساسية الزائدة للغلوتين على الشكل الآتي: 4 حالات من مرض اعتلال الأعصاب، 3 حالات لكل من الرنح المخيخي و الجلطة الدماغية، حالتين للاعتلال العضلي إضافة الى حالة واحدة لكل من التصلب اللويحي و الصرع و التهاب الأوردة الدماغية الخثاري و متلازمة الانضغاط النخاعي. و قد أثبتت التحاليل المخبرية أن مضادات الغلياذين من نوع "أ" هي الأكثر تردد لكن تركيزها يبقى أقل من مضادات الغلياذين من نوع "ج". نستنتج من كل ما سبق ان معدل الانتشار المهم للحساسية المفرطة للغلوتين تجعلها سببا محتملا للأمراض العصبية المجهولة المصدر و خصوصا مرض اعتلال الأعصاب و الرنح المخيخي إضافة إلى الجلطة الدماغية.

الكلمات الأساسية: الحساسية المفرطة للغلوتين، المرض العصبي، مضادات الأجسام ضد الغلياذين، معدل الانتشار.

Résumé

La sensibilité au gluten (SaG) est un état de réponse immunologique excessive aux protéines ingérées du gluten, chez un individu génétiquement prédisposé. Récemment, il est appar

que la SaG peut se manifester uniquement par des troubles neurologiques en dehors de tout symptôme digestif.

Objectif : Notre étude a pour objectif de mesurer la prévalence de la SaG au cours des neuropathies idiopathiques et de déterminer leurs caractéristiques cliniques, radiologiques, électro-physiologiques et biologiques.

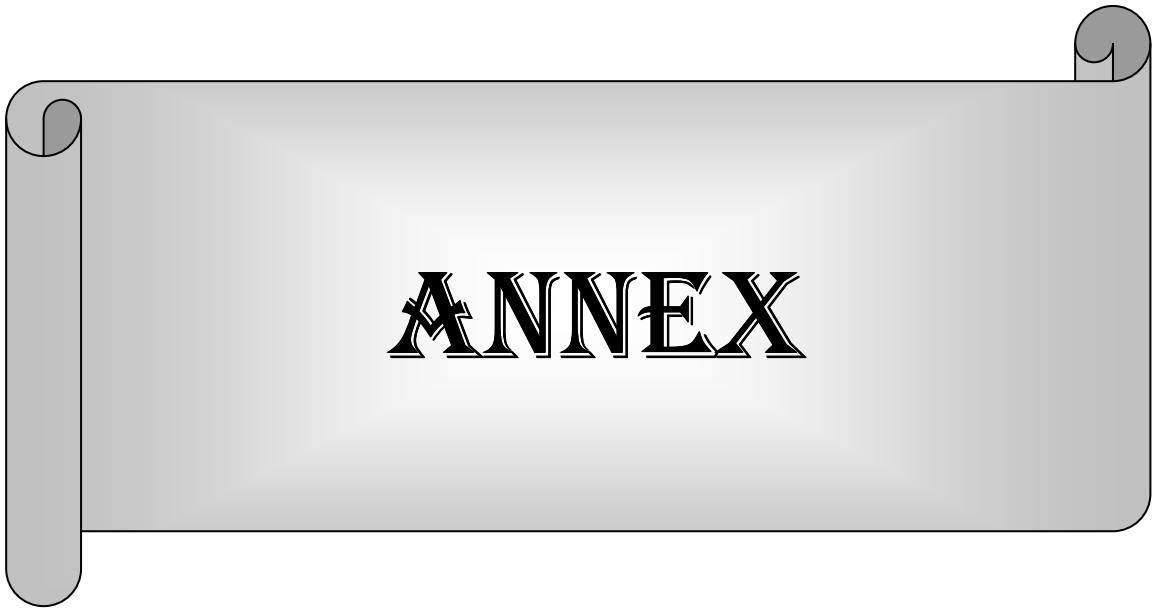
Patients et méthodes : Nous avons recherché des marqueurs de la SaG, représentés par les anticorps anti-gliadine (AGA, IgA et IgG) couplés aux anticorps anti-transglutaminase tissulaire (Ac anti-tTG), chez 60 patients (âge moyen: 43 ans, allant de 13 à 76 ans, sex-ratio M/F: 0,7) recrutés à partir du service de neurologie du Centre Hospitalier Universitaire de Marrakech et 57 témoins sélectionnés parmi des donneurs de sang sains.

Résultats : Selon les données cliniques et para-cliniques, les patients de l'étude correspondaient à 18 cas d'accident vasculaire cérébral ischémique (AVCi) (28,33%), 16 cas de neuropathies périphériques (NP) (26,7%), 7 cas d'épilepsie (11,7%), 7 cas d'ataxie (11,7%), 3 cas de myopathies (6,7%), 2 cas de maladie de la corne antérieure, et 1 cas pour chacune des pathologies suivantes : syndrome de compression médullaire, syndrome parkinsonien, méningite lymphocytaire, sclérose en plaques (SEP), myélopathie, la thrombophlébite cérébrale et la dystonie.

Les AGA étaient positifs chez 26,7% de nos patients contre 15,7% chez les témoins *(p=0,151),* alors que le dosage des anti-tTG était négatif pour tous les patients et positif chez un seul témoin. Les patients AGA positifs correspondaient à 4 cas de NP, 3 cas d'ataxie (n=3), 3 cas d'AVCi, 2 cas de myopathie suivi d'un cas pour chacune des neuropathies suivantes : la Sclérose en plaques , l'épilepsie, la thrombophlébite cérébrale et le syndrome de compression médullaire.

Conclusion : Confrontées aux données de la littérature, les résultats de notre série permettraient d'attribuer l'étiologie des neuropathies idiopathiques à une SaG, essentiellement la NP, l'ataxie et l'AVCi du sujet jeune. En plus, le dosage des AGA constituerait un meilleur marqueur pour les neuropathies au gluten.

Mots clés : Sensibilité au gluten, neuropathie, anticorps antigliadin, prévalence.



The Questionnaire

1-Identity

Full name : …… …… Sex : M : ☐ F : ☐

…….. Age : ….

Origin : Rural ☐ Urban ☐ Occupation : ……

Department : ……..

Intellectual level : Illiterate ☐ Primary ☐ Secondary ☐ university ☐

Inclusion date : ……..

2-Medical Record

Diabetes	Type 1	Type 2	Treatment :		
			Insulin	Pills	Diet
HBP		Treatment Yes ☐ No ☐			
Cardiopathy		Type:			
Tobaccoc		……P.Y			

Coagulation dysfunction	type :
Systemic diseases	Type:

Alcoholism	Amount :
Nephropathy	Type :
Drug's Intoxication	Type :
nutrition deficiency	Type :
Tuberculosis	yes No:
Treatment for tuberculosis	Yes: No:
Recent viral infection	Type :
Celiac disease of the parents	Yes : No :
Celiac disease in the family	Yes : No :
Similar cases in the family	Yes : No :

3-Disease's evolution:

Mode of onset	Acute	

	Chronic	
Evolution	remittent	
	progressive	
	One Episode	

-Introduction age of gluten ……..
- Gluten free diet Yes ☐ No☐
- Reasons for GFD ……

4-Clinical analysis :

A. Ataxias

Proprioceptive	
Cerebellar	
Peripheral vestibular	
Central vestibular	

B. Ischemic stroke

- Motor signs :
- Sensitive signs :
- Consciousness and Glasgow score :
- Seizures : yes ☐ No ☐ Type :…….
- Topography :
- Dysarthria :

C. Peripheral neuropathies

Weakness		Proximal		Distal
Paresthesia		Distal		Radicular
Hypoesthesia		Superficial		Tactile
		Profound		Vibratory
		Heat and pain		
		arthrocinetic		
Cranial nerves dysfunction		Type : …… ……		
Complications :		Respiratory failure		
		Swallowing dysfunction		

D. Myopathies

- Weakness :
  Bilateral : Yes ☐ No ☐
  Symmetric : Yes ☐ No ☐
- Dermatologic signs : yes ☐ No ☐
  description…….....

5-Investigations

A/ Neuro-Imaging

Brain scanner :

MRI :

Echography-Echo Doppler :

B/Electro-physiological explorations :

- EMG :

Axonal :

Demyelinating :
Mononeuropathy :
Polyneuropathy
Mononeuropathy multiplex :
Polyradiculoneuropathy :
Motor :
Sensitive :
Other features :

- EEG :
- PEV :
- PEA :

C/ Biology

HgB :	Urea :
WBC :	Serum creatinine :
CRP :	SR :
Serum glycaemia :	HIV serology
Lipid Profile Triglycerids : Total Cholesterol HDL : LDL : VLDL :	**Liver function** ALAT : ASAT : Total Bilirubin: Unconjugated Bilirubin: Conjugated Bilirubin: alkaline phosphatase : Gamma GT :
Apo A : …… …. ApoB :…… ……..	**Muscle enzymes** CPK: **CSF exploration** Cells : Proteins : Glucose : Bactériology : Abnormal cells research
Serum proteins electrophoresis	AAN :…… Anti SSb :…… Anti SSa :…….. AntiDNA :……..

Measurement of IgG-AGA:

Positive ☐ Negative ☐
The rate : ……..

Measurement of IgA anti-tTG:

Positive ☐ Negative ☐

IgA deficiency: yes ☐ No ☐
The rate of IgA-tTG: ……
The rate of IgG-tTG: ……...

CONCLUSION: .....

REFERENCES

[1] B.Admou MS, F.Bienvenu, L.Chabaa. Immunologic diagnosis of celiac disease in children. Report progress. 2009.
[2] Hadjivassiliou M SD, et al. Gluten sensitivity: from gut to brain. Lancet Neurol. 2010;9:318–30.
[3] Dowd B. WSJ, Gee S. Aretaeus, and the Coeliac Affection. Br Med J. 1974;2(5909):45-7
[4] FW. P. From Aretaeus to Crosby: a history of coeliac disease. BMJ. 1988; (297): 1646-9
[5] Gobbi G BF, Greco L et al. Coeliac disease, epilepsy, and cerebral calcifications. Lancet. 1992;340(8817): 439–43.
[6] SV. H. Celiac disease, its specific treatment andcure without nutritional relapse.JAMA. 1932: 99: 448.
[7] Dicke WK. Simple dietary treatment for the syndrome of GheeHerter. Ned Tijdschr Geneeskd. 1941; 85:1715.
[8] Van De Kamer JH WH, Dicke WK. . An investigation into the injurious constituents of wheat in connection with their action on patients with coeliac disease. Acta Paediatr 1953;42: 232.
[9] JW. P. Observation on the aetiology of idiopathic steatorrhoea; jejunal and lymph-node biopsies. . Br Med J 1954(4900): 1318-21.
[10] Sakula j SM. celiac disease with atrophy of the small-intestine mucosa. Lancet 1957(273):876-7.
[11] Koning F SD, Cerf-Bensussan N, Sollid M.L. Pathomechanisms in celiac disease. Best Practice and Research Clinical Gastroenterology 2005;19,(3): 373-87.
[12] A. E. Coeliac disease: previous family studies. *Genetics of coeliac disease*. Lancaster: MTP:197–200.
[13] Greco L RR, Coto I et al. The first large population based twin study of coeliac disease. . Gut. 2002(50):624–8.
[14] Shewry P.R. TA. The prolamin storage proteins of cereal seeds: structure and evolution. . Biochem J 1990(276): 1–12.
[15] Holopainen P AM, Sistonen P et al. CD28/CTLA4 gene region on chromosome 2q33 confers genetic susceptibility to celiac disease. A linkage and family-based association study. Tissue Antigens 1999(53):470–5.
[16] Rioux JD KH, Kocher K et al. . Genomewide search and association studies in a Finnish celiac disease population: Identification of a novel locus and replication of the HLA and CTLA4 loci. Am J Med Genet 2004(130):345–50.
[17] Neuhausen SL FM, Camp NJ et al. Genome-wide linkage analysis for celiac disease in North American families. Am J Med Genet 2002(111): 1.
[18] Greco L BM, Corazza GR et al. . Existence of a genetic risk factor on chromosome 5q in Italian coeliac disease families. Ann Hum Genet 2001(65):35.
[19] Folk JE CS. Transglutaminases. . Meth Enzymol 1985(113): 358–75.
[20] Piacentini M RC, Farrace MG & Autuori F. Tissue transglutaminase in animal development. . Int J Dev Biol 2002(44.): 655–62.
[21] Aeschlimann D TV. Protein crosslinking in assembly and remodelling of extracellular matrices: the role of transglutaminases. . Connect Tissue Res 2000(41): 1–27.
[22] Lorand L. GR. Transglutaminases: crosslinking enzymes with pleiotropic functions. . Nat Rev Mol Cell Biol 2003(4):140–56.
[23] Haroon ZA HJ, Lai TS et al. . Tissue transglutaminase is expressed, active, and directly involved in rat dermal wound healing and angiogenesis. . FASEB J 1999(13): 1787–815.
[24] Molberg Ø MS, Ko¨rner R et al. . Tissue transglutaminase selectively modifies gliadin peptides that are recognized by gut derived T cells in celiac disease. . Nat Med 1998(4): 713–7.
[25] Van de Wal Y KY, van Veelen P et al. . Selective deamidation by tissue transglutaminase strongly enhances gliadin-specific T cell reactivity. J Immunol 1998(161):1585–8.

[26] Sjostrom H LK, Molberg Ø et al. Identification of a gliadin T cell epitope in coeliac disease: general importance of gliadin deamidation for intestinal T cell recognition. Scandanavian J Immunol. 1998(48):111–5.
[27] Vader W dRA, van de Wal Y et al. . Specificity of tissue transglutaminase explains cereal toxicity in celiac disease. J Exp Med 2002(195):2002.
[28] VaderW KY, van Veelen P et al. . The gluten response in children with recent onset celiac disease. A highly diverse response towards multiple gliadin and glutenin derived peptides. . Gastroenterology. 2002(122):1729–37.
[29] Meresse B CZ, Ciszewski C et al. . Coordinated Induction by IL15 of a TCR-Independent NKG2D signaling pathway converts CTL into Lymphokine-activated killer cells in celiac disease. . Immunity 2004;21:357–66.
[30] Hu¨e S MJ-J, Monteiro RC et al. . A direct role for NKG2D/MICA interaction in villous atrophy during celiac disease. . Immunity. 2004(21):367-77.
[31] M.Rewers. Epidemiology of Celiac Disease: What Are the Prevalence, Incidence, and Progression of Celiac Disease? . Gastroenterology. 2005(128):S47–S51.
[32] Catassi C RI, Gandolfi L, Pratesi R, Fabiani E, El Asmar R, Frijia M, Bearzi I, Vizzoni L. Why is coeliac disease endemic in the people of the Sahara? Lancet 1999;354:647–8.
[33] S.Ridouane MB. Profil épidemiologique, clinique et évolutif de la maladie coeliaque dans la région de Marrakech Marrakech: Université Cadi Ayyad 2008.
[34] J W. Coeliac disease. Gastroenterology. 2007 April;35(4):226-30.
[35] Abu-Zekry M DM, Catassi C and Fasano A. Prevalence of Celiac Disease in Egyptian Children Disputes the East-West Agriculture-dependent Spread of the Disease. J Pediatr Gastroenterol Nutr. 2008 August;47(2):136-40.
[36] Ben Hariz M K-SM, Kallel L, Lahmer A, Halioui S, Bouraoui S, Laater A, Sliti A, Mahjoub A, Zouari B, Makni S, Maherzi A. Prevalence of celiac disease in Tunisia: mass-screening study in schoolchildren. Eur J Gastroenterol Hepatol. 2007 August;19(8):687-94.
[37] Fasano A CC. Current approaches to diagnosis and treatment of celiac disease: an evolving spectrum. Gastroenterology 2001;120:636–51.
[38] Book L HA, Black J, Feolo M, Zone JJ, Neuhausen SL. Prevalence and clinical characteristics of celiac disease in Down's syndrome in a US study. Am J Med Genet. 2001;98:70–4.
[39] Giannotti A TG, Castro M, Virgilii F, Colistro F, Ferretti F, Digilio MC et al. Coeliac disease in Williams syndrome. J Med Genet 2001;38:767–8.
[40] Murray JA VDC, Plevak MF, Dierkhising RA, Zinsmeister AR, Melton LJ. Trends in the identification and clinical features of celiac disease in a North American community, 1950–2001. Clin Gastroenterol Hepatol. 2003;1:19–27.
[41] Cook B OR, Chapman B, Whitehead M, Burt M. A thirty-year (1970–1999) study of coeliac disease in the Canterbury region of New Zealand. N Z Med J. 2004;117:U772.
[42] Roux K. Formes cliniques de la maladie coeliaque en Pédiatrie. [Thèse de mèd.]. DIJON: Faculté de Médecine de DIJON; 2002.
[43] Holtmeier W cWF. Celiac disease. 2005 [cited; Available from: http://www.orphanet.net/data/patho/GB/uk-CD.pdf
[44] S.Guandalini PA, Vallee. Celiac Disease. [cited; Available from: http://emedicine.medscape.com/article/932104-overview
[45] Farell RJ KC. Celiac sprue. N Engl J Med. 2002;346(3):180-2.
[46] Sanders DS CM, Hurlstone DP et al. . Association of adult coeliac disease with irritable bowel syndrome: a case-control study in patients fulfilling ROME II criteria referred to secondary care. Lancet. 2001;358(9292):1504–8.
[47] DieterichW LE, Schopper H et al. Autoantibodies to tissue transglutaminase as predictors of celiac disease. Gastroenterology. 1998;115(6):1317–21.
[48] Rostom A DC, Cranney A et al. Celiac disease. . Celiac disease. In: Quality MAfHRa, ed.

Evidence Report/Technology Assessment: AHRQ Publication No. 04-E029-2. Rockville 2004.

[49] Clemente MG MM, Frau F et al. . Antitissue transglutaminase antibodies outside celiac disease. J Pediatr Gastroenterol Nutr 2002; 34(1): 31–4.

[50] Freeman HJ. Strongly positive tissue transglutaminase antibody assays without celiac disease. Can J Gastroenterol 2004;18(1):25–8.

[51] Dahele AV AM, Humphreys K & Ghosh S. Serum IgA tissue transglutaminase antibodies in coeliac disease and other gastrointestinal diseases. QJM 2001. 2001;94(4):195–205.

[52] Weiss B BY, Avidan B et al. Positive tissue transglutaminase antibodies with negative endomysial antibodies. Isr Med Assoc J 2004;6(1):9–12.

[53] Rittmeyer C. RJ. IgA deficiency causes false-negative endomysial antibody results in celiac disease. J Pediatr Gastroenterol Nutr. 1996;23(4):504–6.

[54] Cataldo F MV, Bottaro G et al. Celiac disease and selective immunoglobulin A deficiency. J Pediatr. 1997;131(2):306–8.

[55] Dickey W HDMS. Reliance on serum endomysial antibody testing underestimates the true prevalence of coeliac disease by one fifth. Scand J Gastroenterol. 2000;35(2):181–3.

[56] Dahele A KK, Bode J et al. Anti-endomysial antibody negative celiac disease: does additional serological testing help? . Dig Dis Sci 2001;46(1):214–21.

[57] Johnson TC DB, Memeo L et al. Relationship of HLA-DQ8 and severity of celiac disease: comparison of New York and Parisian cohorts. Clin Gastroenterol Hepatol. 2004;2(10):888–94.

[58] Ploski R EJ, Thorsby E & Sollid LM. On the HLA-DQ(alpha 1*0501, beta 1*0201)-associated susceptibility in celiac disease: a possible gene dosage effect of DQB1*0201. Tissue Antigens. 1993;41(4):173–7.

[59] Kaukinen K PJ, Maki M & Collin P. HLA-DQ typing in the diagnosis of celiac disease. Am J Gastroenterol. 2002;97(3):695–9.

[60] Thijs WJ vBJ, Kleibeuker JH & Kolkman JJ. Duodenal versus jejunal biopsies in suspected celiac disease. Endoscopy 2004;36(11):993–6.

[61] Dandalides SM CW, Petras R & Achkar E. Endoscopic small bowel mucosal biopsy: a controlled trial evaluating forceps size and biopsy location in the diagnosis of normal and abnormal mucosal architecture Gastrointest Endosc. 1989;35(3):197–200.

[62] Mariaud de Serre NP VV, Cellier C et al. Diagnostic étiologique d'une atrophie villositaire. Ann Pathol. 2001;21:319–33.

[63] Masafumi Ihara FM, Hideyuki Sawada, Takahiro Mezaki, Kotaro Mizutani,, Hiroshi Nakase MM, Hidekazu Tomimoto and Shun Shimohama. Gluten Sensitivity in Japanese Patients with adult-onset cerebellar ataxia. Internal Medicine. 2005;1351(.45).

[64] M.Hadjivassiliou DSS, et al. Gluten sensitivity: from gut to brain. Lancet Neurol. 2010;9:318–30.

[65] Holmes G. Neurological and psychiatric complications in celiac disease. In: Gobbi G, Anderman F, Naccarato S, Banchini G, eds. Epilepsy and other neurological disorders in coeliac disease. London: John Libbey 1997.

[66] Briani C ZG, Alaedini A, et al. Neurological complications of coeliac disease and autoimmune mechanisms: a prospective study. J Neuroimmunol. 2008(195):171–75.

[67] Hadjivassiliou M BS, Tongiorgi E, et al. Immune mediated acquired ataxias: Elsevier (in press).

[68] Hadjivassiliou M BS, Tongiorgi E, et al. Cerebellar ataxia as a possible organ specific autoimmune disease. Mov Disord. 2008;23:1370–77.

[69] Luostarinen L HS, Luostarinen M, Collin P, Pirttila T. Neuromuscular and sensory disturbances in patients with well treated celiac disease J Neurol Neurosurg Psychiatry 2003;74:490–94.

[70] Ludvigsson JF OT, Ekbom A, Montgomery SM. A population based study of celiac disease,

neurodegenerative and neuroinflammatory diseases. Aliment Pharmacol Ther 2007;25:1317–27.
[71] Hadjivassiliou M GR, Kandler RH, et al. Neuropathy associated with gluten sensitivity. J Neurol Neurosurg Psychiatry. 2006;77:1262–66.
[72] Mata S RD, Pinto F, Calabro A. Anti-tissue transglutaminase IgA antibodies in peripheral neuropathy and motor neuronopathy. Acta Neurol Scand. 2006;114:54–8.
[73] Chin RL SH, Brannagan TH, et al. Celiac neuropathy. Neurology 2003;60:1581–85.
[74] rachid belfkih ea. Accident vasculaire cérébral ischémique révélant une maladie coeliaque. Pan African Medical Journal. 2009;5(2).
[75] S. Audia a, C. Duchêne a, M. Samsona, G. Muller a, P. Bielefeld a, F. Ricolfi b, M. Giroud c, J.-F. Besancenot. Accident vasculaire cérébral ischémique de l'adulte jeune au cours de la maladie coeliaque. À propos de deux observations. La Revue de médecine interne. 2008;29:228-31.
[76] M Hadjivassiliou AG, G A B Davies-Jones, A J Lobo, T J Stephenson, A Milford-Ward. Does cryptic gluten sensitivity play a part in neurological illness? The Lancet. 1996 February 10;347.
[77] Cooke WT HG. Neurological and psychiatric complications in coeliac disease. Churchill Livingstone. 1984:197-213.
[78] Mayer M GL, Troncone R, Auricchio S, Marsh MN. Compliance of adolescents with coeliac disease with a gluten free diet. Gut. 1991;32:881-85.
[79] Hadjivassiliou M BS, Davies-Jones GA, Grunewald RA, Not T, Sanders DS, et al. . The humoral response in the pathogenesis of gluten ataxia. . Neurology. 2002;58:1221–6.
[80] Alaedini A OH, Briani C, et al. Immune cross-reactivity in coeliac disease: antigliadin antibodies bind to neuronal symapsin I. J Immunol 2007;178:6590–95.
[81] Alaedini A LN. Transglutaminase-independent binding of gliadin to intestinal brush border membrane and GM1 ganglioside. J Neuroimmunol 2006;177:167–72.
[82] Cervio E VU, Verri M, et al. Sera from patients with celiac disease and neurologic disorders evoke a mitochondrial-dependent apoptosis in vitro. Gastroenterol 2007;133:195–206.
[83] Hadjivassiliou M DSS, Richard A Grünewald, Nicola Woodroofe, Sabrina Boscolo, Daniel Aeschlimann. Gluten sensitivity: from gut to brain. Lancet Neurol. 2010;9:318-30.
[84] Cooke WT T-SW. Neurological disorders associated with adult coeliac disease. Brain 1966;89:683–722.
[85] Hadjivassiliou M GRA, Chattopadhyay A K. Clinical, radiological, neurophysiological, and neuropathological characteristics of gluten ataxia. Lancet. 1998;352:1582–85.
[86] Rao DG HM. Sensory neuronopathy due to gluten sensitivity. Ann Indian Acad Neurol 2007;10 (suppl 2):16.
[87] Finelli PF MW, Ambler M, Kestenbaum D. Adult celiac disease presenting as cerebellar syndrome. Neurology 1980;30:245–49.
[88] Kaplan JG PD, Horoupian D, DeSouza T, Brin M, Schaumburg H. . Distal axonopathy associated with chronic gluten enteropathy: a treatable disorder. Neurology. 1988;38:642–45.
[89] Hadjivassiliou M GR, Sharrack B,Sanders D et al. Gluten ataxia in perspective: epidemiology, genetic susceptibility and clinical characteristics. Brain. 2003;126:685-91.
[90] Hadjivassiliou M SD, Woodroofe N, Williamson C, Grunewald RA. . Gluten ataxia. Cerebellum 2008;7:494–98.
[91] Pereira AC EM, Buttery PC, et al. Choreic syndrome and coeliac disease: a hitherto unrecognised association. Mov Disord. 2004;19:478–82.
[92] Hadjivassiliou M AP, Sanders DS, et al. Antibodies against TG6 as the only serological marker of gluten ataxia. Proceedings of the 13th International Coeliac Disease Symposium; 2009 April 6–8, 2009; Amsterdam; 2009.
[93] Luostarinen LK CP, Paraaho MJ, Maki MJ, Pirttila TA. Coeliac disease in patients with cerebellar ataxia of unknown origin. Ann Med. 2001;33:445–49.

[94] Wilkinson ID HM, Dickson JM et al. Cerebellar abnormalities on proton MR spectroscopy in gluten ataxia. J Neurol Neurosurg Psychiatry. 2005;76:1011-13.
[95] Wilkinson ID HM, Dickson JM, et al. Cerebellar abnormalities on proton MR spectroscopy in gluten ataxia. J Neurol Neurosurg Psychiatry 2005;76:1011–13.
[96] Chin RL SH, Brannagan TH, Green PH, Hays AP, Alaedini A, Latov N. Celiac neuropathy. Neurology. 2003;60:1581–5.
[97] Kelkar P RM, Murray J. Mononeuropathy multiplex associated with celiac disease. Muscle Nerve 1996;19:234–36.
[98] Brannagan TH HA, Chin SS, et al. Small-fiber neuropathy/ neuronopathy associated with celiac disease: skin biopsy findings. Arch Neurol. 2005;62:1574–78.
[99] Gibbons CH FR. Autonomic neuropathy and celiac disease. J Neurol Neurosurg Psychiatry 2005;76:579–81.
[100] Gefel D. DM, Ben-Valid E., Daraushe A.E., Lugassy G, Ben-Ami S. Recurrent stroke in a young patient with celiac disease and hyperhomocysteinemia. IMAJ 2002;4:222-3.
[101] El-Khairy L UPM, Nygard O, Refsum H., Vollset SE. Lifestyle and cardiovascular disease risk factors as determinants of total homocysteine in plasma: the Hordaland Homocysteine Study. Am J Clin Nutr 1999;70:1016±24.
[102] Hadjivassiliou M MM, Sanders DS, Williamson CA, Grunewald RA, Woodroofe NM, et al. Autoantibody targeting of brain and intestinal transglutaminase in gluten ataxia. . Neurology 2006;66:373–7.
[103] Goodwin FC BR, Millar J, Kirkham FJ. Celiac disease and childhood stroke. Pediatr Neurol 2004;31:139–42.
[104] Curione M BM, De Biase L, Viola F, Lo Russo L, Cardi E. Prevalence of coeliac disease in idiopathic dilated cardiomyopathy. Lancet. 1999;354:222-3.
[105] Karoui S SS, Kallel M, Boubaker J, Makni S, Filali A. Syndrome des antiphospholipides révélé par une thrombose porte au cours d'une maladie coeliaque. Rev Med Interne 2004;25:471–3.
[106] Dickson BC SC, Chetty R. Coeliac disease: an update for pathologists. J Clin Pathol. 2006;59(10):1008-16.
[107] Baudon JJ JC, Absalon YB, Morgant G, Cabrol S, Mougenot JF. Diagnosing celiac disease: a comparison of human tissue transglutaminase antibodies with antigliadin and antiendomysium antibodies. Arch Pediatr Adolesc Med. 2004 Jun;158(6):584-8.
[108] Pellecchia MT SR, Filla A, De Michele G, Ciacci C, Barone P. Idiopathic cerebellar ataxia associated with celiac disease: lack of distinctive neurological features. J Neurol Neurosurg Psychiatry 1999;66:32–5.
[109] Schrodl D KF, Peter-Zimmer K, et al. Intrathecal synthesis of autoantibodies against tissue transglutaminase. J Autoimmun. 2004;22:335–40.
[110] Hadjivassiliou M AP, Sanders DS, et al. Antibodies against TG6 as the only serological marker of gluten ataxia. Proceedings of the 13th International Coeliac Disease Symposium April 6–8, 2009. 09.1; Amsterdam
[111] Kaukinen K C, P, Laurila, K et al. Resurrection of gliadin antibodies in celiac disease. Deamidated gliadin peptide antibody test provides additional diagnostic benefit. Scand J Gastroenterol. 2007;42:1428–33.
[112] Karoui S SM, Laatar AB, Zitouni M, Matri S, Laadhar L, et al. Prevalence of anticardiolipin and antibeta2-glycoprotein I antibodies in celiac disease. Dig Dis Sci. 2007;52:1096–100.
[113] R J Lock DSNAPT, D J Unsworth, J J Ward, A J Wills. Ataxia, peripheral neuropathy, and anti-gliadin antibody. Guilt by association? J Neurol Neurosurg Psychiatry. 2005(76):1601-3.
[114] Hadjivassiliou M, Williamson C.A, Woodroofe N. The immunology of gluten sensitivity: beyond the gut. Trends in immunology. 2004 November;25(11).
[115] Neto J I S VCACL, Magalhães F G, Silva G S. NEUROLOGICAL MANIFESTATIONS OF CELIAC DISEASE. Arq Neuropsiquiatr. 2004;62(4):969-72.

[116] Lahat E BE, Leshem M, Evans S, Scapa E. Prevalence of Celiac Antibodies in Children With Neurologic Disorders. Pediatr Neurol. 2000;22:393-6.
[117] Hadjivassiliou M GA, Davies-Jones GAB, et al. Does cryptic gluten sensitivity play a part in neurological illness? Lancet. 1996(347):369–71.
[118] Ihara M MF, Sawada H, et al. Gluten sensitivity in Japanese patients with adult-onset cerebellar ataxia. Intern Med 2006;45:135–40.
[119] Hadjivassiliou M DGR, S.B. Wharton, D.S. Sanders, R.A. Grunewald, Davies-Jones,MD. Sensory ganglionopathy due to gluten sensitivity. Neurology. 2010 September 14(75):1003-08.
[120] Chin RL SH, Brannagan TH, et al. Celiac neuropathy. Neurology. 2003(60):1566-68.
[121] Bürk K BS, Müller CA, et al. Sporadic cerebellar ataxia associated with gluten sensitivity. Brain. 2001;124:1013–19.
[122] Abele M SL, Schwartz S, Klockgether T. Prevalence of antigliadin antibodies in ataxia patients. Neurology 2003;60:1674–75.
[123] D. Wong MD, M. Schulzer, M. Nimmo, B.R. Leavitt, S.D. Spacey. Ataxia and the role of antigliadin antibodies. Can J Neurol Sci. 2007;34:193-6.
[124] Burk K M-LF, Georg Lamprecht,Guenter Roth, Patrice Decker,Michael Weller, Hans-Georg Rammensee, Wolfang Oertel. Neurological Symptoms in Patients with Biopsy Proven Celiac Disease. Mov Disord. 2009;24(16):2358-62.
[125] BUSHARA KO. Neurologic Presentation of Celiac Disease. GASTROENTEROLOGY 2005;128:S92–S97. 2005;128:S92–S7.
[126] Luostarinen LK CP, Paraaho MJ, Maki MJ, Pirttila TA. Coeliac disease in patients with cerebellar ataxia of unknown origin. Ann Med 2001;33:445–49.
[127] Anheim M DB, Echaniz-Laguna A, Fleury M, Grucker M, Tranchant C. Ataxia associated with gluten sensitivity, myth or reality? . Rev Neurol 2006;162: 214–21.
[128] Hadjivassiliou M GA, Davies-Jones GAB, Lobo A, Stephenson TJ, Milford-Ward A. Is cryptic gluten sensitivity an important cause of neurological illness? . Lancet 1996;347:369–71.
[129] Abele M BK, Schöls L, et al. The aetiology of sporadic adult onset ataxia. Brain. 2002;125:961–68.
[130] Bushara KO GS, Shill H, Goldfarb LG, Hallett M. Gluten sensitivity in sporadic and hereditary ataxia. Ann Neurol. 2001;49(540–43):540–43.
[131] Luostarinen L HS, Luostarinen M, Collin P, Pirttila T. Neuromuscular and sensory disturbances in patients with well treated celiac disease. J Neurol Neurosurg Psychiatry 2003;74:490–94.
[132] Ludvigsson JF OT, Ekbom A, Montgomery SM. A population based study of celiac disease, neurodegenerative and neuroinfl ammatory diseases. Aliment Pharmacol Ther. 2007;25:1317–27.
[133] Ludvigsson JF WJ, Card T, Appelros P. Risk of Stroke in 28,000 Patients with Celiac Disease: A Nationwide Cohort Study in Sweden. J Stroke Cerebrovasc Dis. 2011 Jul 4.
[134] Ludvigsson JF. DFU, Ekbom A., Montgomery SM. Vascular disease in a population-based cohort of individuals hospitalised with coeliac disease. Heart. 2007;93:1111-5.
[135] Henriksson KG HC, Norrby K, Walan A. Polymyositis and adult celiac disease. Acta Neurol Scand 1982(65):301–19.
[136] Selva-O'Callaghan A CF, De Torres I, Palou E, Grau-Junyent JM, Villardell-Tarres M. Celiac disease and antibodies associated with celiac disease in patients with inflammatory myopathy. Muscle Nerve 2007(35):49–54.
[137] Farre´ C HP, Vilar P, Varea V, Aldeguer X, Carnicer J, et al. Serological markers and HLA-DQ2 haplotype among first-degree relatives of celiac patients. Dig Dis Sci 1999;44:2344-9.
[138] Cronin CC JL, Feighery C, Shanahan F, Abuzakouk M, Ryder DQ, Whelton M, Callaghan N. . Coeliac disease and epilepsy. QJM 1998;91:303–8.

[139] Gobbi G AP, Zaniboni MG, Lambertini A, Ambrosioni G, Tassinari CA. . Celiac disease, posterior cerebral calcifications and epilepsy. Brain Dev 1992(14):23-9.
[140] Visakorpi J KP, Pelkonen P. Intestinal malabsorption: a clinical study of 22 children over 2 years of age. Acta Paediatr Scand 1970(59):273–80.
[141] Ranua J LK, Auvinen A, et al. Celiac disease-related antibodies in an epilepsy cohort and matched reference population. Epilepsy Behav 2005(6):388–92.
[142] Gobbi G. Coeliac disease, epilepsy and cerebral calcifications. Brain Dev 2005 Apr;27(3):189-200.
[143] Haghighi AB AN, Mokhtari M, Geramizadeh B, Lankarani KB. Multiple sclerosis and gluten sensitivity. Clin Neurol Neurosurg 2007(109):651-53.
[144] Hadjivassiliou M SD, Grunewald RA. Multiple sclerosis and occult gluten sensitivity. Neurology 2004;62:2326–27.
[145] Jacob S ZM, Kenton A, Allroggen H. Gluten sensitivity and neuromyelitis optica: two case reports. J Neurol Neurosurg Psychiatry. 2005;76:1028–30.
[146] Jarius S JS, Waters P, Jacob A, Littleton E, Vincent A. Neuromyelitis optica in patients with gluten sensitivity associated with antibodies to aquaporin-4. J Neurol Neurosurg Psychiatry. 2008;79:1084.
[147] Esin Beyan MP, Cengiz Beyan. Deep vein thrombosis associated with celiac disease. Brastil Lek Listy. 2009;110(4):263-4.
[148] Bahloul M CA, Khlaf-Bouaziz N et al. Celiac disease, cerebral venous thrombosis and protein S deficiency, a fortuitous association? J Mal Vasc. 2005;30:228-30.
[149] Cartalat-Carel S PP, Carpentier A, Delattre JY. Chronic meningitis before diagnosis of celiac disease. Rev Neurol (Paris). 2002;158(4):467-9.
[150] Sobstyl M ZM, Dzierzęcki S, Mossakowski Z, Szczałuba K. Successful bilateral pallidal stimulation in a patient with isolated lower limb dystonia coexistent with Langerhans cell histiocytosis and coeliac disease. Neurol Neurochir Pol. 2011 Sep-Oct;45(5):514-9.
[151] Hall DA PJ, Benke T. Paroxysmal nonkinesigenic dystonia and celiac disease. Mov Disord. 2007 Apr 15;22(5):708-10.
[152] K.J. Brown VJ, H. Herfarth, M. Castillo. White Matter Lesions Suggestive of Amyotrophic Lateral Sclerosis Attributed to Celiac Disease. Am J Neu Rad 2010 May;31:880-1.
[153] Turner M CG, Quaghebeur G, et al. A case of celiac disease mimicking amyotrophic lateral sclerosis. Nat Clin Pract Neurol. 2007;3:581–84.
[154] Hadjivassiliou M SD, Woodroofe N, Williamson C, Grunewald RA. Gluten ataxia. Cerebellum. 2008(7):494–98.
[155] Chin RL TV, Green PHR, Sander HW, Brannagan TH, Latov N. Multifocal axonal polyneuropathy in celiac disease. Neurology 2006(66):1923–25.
[156] Rao DG HM. Sensory neuronopathy due to gluten sensitivity. Ann Indian Acad Neurol. 2007;10(suppl 2):16.
[157] Brannagan TH HA, Chin SS, et al. Small-fi ber neuropathy/ neuronopathy associated with celiac disease: skin biopsy findings. Arch Neurol 2005;62:1574–78.
[158] Goodwin FC BR, Millar J, Kirkham FJ. Celiac Disease and Childhood Stroke. Pediatr Neurol. 2004;31:139-43.
[159] Doğan M. PE, Cagan E., Akbayram S, Acikgoz M, Caksen H, Uner A, Cesur Y. Stroke and dilated cardiomyopathy associated with celiac disease. World J Gastroenterol 2010;16(18):2302-4.
[160] El Moutawakil B CN, Sibai M, Moutawakil F, Rafai M, Bourezgui, Sissi I. Celiac disease and ischemic stroke. Rev Neurol. 2009 Nov;165(11):962-6.
[161] Kleopa KA KK, Zamba-Papanicolau E, Kyriakides T. Reversible inflammation and vacuolar myopathy with vitamin. Muscle Nerve. 2005;31:260 –5.
[162] Kozanoglu E BS, Goncu MK. Proximal myopathy as an unusual presenting feature of celiac disease. Clin Rheumatol. 2005;24:76 –8.

[163] Marie I LF, Hachulla E, Antonietti M, François A, Levesque H, et al. An uncommon association: celiac disease and dermatomyositis in adults. Clin Exp Rheumatol. 2001;19:201-3.
[164] Hadjivassiliou M CA, Grünewald RA, et al. Myopathy associated with gluten sensitivity Muscle Nerve 2007;35:443–50.
[165] Fois A VM, Di Bartolo RM, Di Marco V. Celiac disease and epilepsy in pediatric patients. Childs Nerv Syst 1994;10:450–54.
[166] Toti P BP, Cano M, et al. Celiac disease with cerebral calcium and silica deposits: X-ray spectroscopic findings, an autopsy study. Neurology 1996;46:1088–92.
[167] Magaudda A DBB, De Marco P, Sfaello Z, Longo M, Colamaria V, Daniele O, Tortorella G, Tata MA, Di Perri R, et al. Bilateral occipital calcification, epilepsy and coeliac disease: clinical and neuroimaging features of a new syndrome. J Neurol Neurosurg Psychiatry. 1993(56):885-9.
[168] Luostarinen L DP, Collin P, Peraaho M, Maki M, Erila T, Pirttila T. Association between coeliac disease, epilepsy and brain atrophy. 2001(46):187–91.
[169] Paltola M KK, Dastidar P, et al. Hippocampal sclerosis in refractory temporal lobe epilepsy is associated with gluten sensitivity. J Neurol Neurosurg Psychiatry 2009(80):626–30.
[170] Lee ES PJ. Non ischemic central retinal vein occlusion associated with celiac disease. Rev Med Interne. 2005;80(2):157.
[171] Marzari Rea. Molecular dissection of the tissue transglutaminase autoantibody response in coeliac disease. J Immunol. 2001;166:4170-6.
[172] Fasano A CC. Current approaches to diagnosis and treatment of celiac disease: an evolving spectrum. [Review]. Gastroenterology. 2001;120:636±51.
[173] El Moutawakil B CN, Sibai M, Moutaouakil F, Rafai M, Bourezgui M, Slassi I. Ischemic stroke and celiac disease. Rev Neurol (Paris). 2009 Nov;165(11):962-6.
[174] Orbach H AN, Barzilai O, Boaz M, Ram M, Zandman-Goddard G, Shoenfeld Y. Autoantibody screen in inflammatory myopathies high prevalence of antibodies to gliadin. Ann N Y Acad Sci. 2009;1173:174-9.
[175] Iltanen S CP, Korpela M, Holm K, Partanen J, Polvi, A, et al. Celiac disease and markers of celiac disease latency in patients with primary Sjogren's syndrome. Am J Gastroenterol. 1999;94:1042-6.
[176] Choi Y-C PG, Kim T-S, Sunwoo I-N, Steinert PM, Kim S-Y. Sporadic inclusion body myositis correlates with increased expression and cross-linking by transglutaminases 1 and 2. J Biol Chem. 1999;275:8703–10.
[177] Nicoletti A PF, Lo Fermo S, Sciacca A, Laisa P, Liberto A, Lanzafame S, Contraffatto D, D'Agate C, Russo A, Zappia M. Frequency of celiac disease is not increased among multiple sclerosis patients. Mult Scler. 2008;14(5):698-700.
[178] Saibeni S LA, Meucci G et al. Prevalence of hyperhomocysteinemia in adult gluten-sensitive enteropathy at diagnosis: role of B12, folate and genetics. Clin Gastroenterol Hepatol. 2005;3(6):574-80.

اقَسِمُ باللهِ العَظِيمْ

أن أراقبَ اللّه في مِهنَتِي .

وأن أصُونَ حياة الإنسان في كافّةِ أدوَارهَا. في كل الظروف والأحوال بَاذِلاً وسْعِي في استنقاذها مِن الهَلاكِ والمرَضِ والألَم والقَلق .

وأن أَحفَظ لِلنّاسِ كَرَامَتهُم ، وأستر عَوْرَتهُم ، وأكتمَ سِرَّهُمْ .

وأن أكونَ عَلى الدوَام من وسائِل رحمة الله ، باذلا رِعَايَتي الطبية للقريب والبعيد ، للصالح والخاطئ ، والصديق والعدو .

وأن أثابر على طلب العلم، أُسَخِره لنفعِ الإنسَان لا لأذَاه .

وأن أُوَقّرَ مَن عَلَّمَني، وأُعَلّمَ مَن يَصْغرَني، وأكون أخاً لِكُلّ زَميلٍ في المِهنَةِ الطُبّيّة مُتعَاونِينَ عَلى البرِّ والتقوى .

وأن تكون حياتي مِصْدَاق إيمَاني في سِرّي وَعَلانيَتي ، نَقيّةً مِمّا يُشينهَا تجَاهَ الله وَرَسُولِهِ وَالمؤمِنين.

والله على ما أقول شهيد

جامعة القاضي عياض
كلية الطب و الصيدلة
مراكش

سنة 2012 **أطروحة رقم 84**

الحساسية المفرطة للغلوتين وأمراض الجهاز العصبي
دراسة مغربية للحالاَتِ و الشَّواهِد

الأطروحة

قدمت ونوقشت علانية يوم

من طرف

السيد محمد رضى بورمان
المزداد في22 مارس 1985 بمراكش

لنيل شهادة الدكتوراة في الطب

الكلمات الأساسية :
الحساسية المفرطة للغلوتين، المرض العصبي، مضادات الأجسام ضد الغليادين، معدل الانتشار

اللجنة

السيد	ع.العلوي اليزيدي أستاذ في علم أمراض الجهاز التنفسي مدير مختبر الأبحاث PCIM	الرئيس
السيد	ا. أدمو أستاذ مبرز في علم المناعة	المشرف
السيد	ن. كساني أستاذ في علم أمراض الجهاز العصبي	القضاة
السيد	م. بوالروس أستاذ مبرز في طب الأطفال –تخصص الأعصاب	
السيدة	ل. شبعى أستاذة في علم الأحياء	
السيد	م.أمين أستاذ مبرز في علم الاحصاء	

مركز الأبحاث

PCIM