'The Neurological UnderBelly of the Gluten-free Lifestyle: Potential Benefits, Devastating Dangers'

October 30, 2015

Tom O'Bryan, DC, CCN, DACBN
www.theDr.com

Dietary Influences on Chronic and Autoimmune Thyroid Disease

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- Since 2004, Teaching Clinician for international audiences of Healthcare Practitioners,
- Adjunct Faculty the Institute for Functional Medicine
- Adjunct Faculty National University of Health Sciences.
- Scientific Advisory Committee of the International and American Association of Clinical Nutritionists
- Medical Advisory Board of the National Association of Nutritional Professionals

What's Coming Your Way in the next 90 minutes?

7 Premises To Consider

3 Case Reports

- Conjunctival Tumor diagnosed as Karposi's sarcoma
- Gluten Psychosis in a 14 year old
- Amyotrophic Lateral Sclerosis

Premise #1

Food Sensitivities may have a lasting, significant impact on CNS function

Detective Adrian Monk

EDITORIALS

NEJM 348;25 June 19,2003

Celiac Disease — How to Handle a Clinical Chameleon

Alessio Fasano, M.D.

Celiac disease is an immune-mediated enteropathy triggered by the ingestion of gluten-containing grains (including wheat, rye, and barley) in genetically susceptible persons. The disease is associated with HLA-DQ2 in 90 to 95 percent of cases and with HLA-DQ8 in 5 to 10 percent of cases and is self-perpetuating in the continued presence of gluten.[1] It is the interplay between genes (both HLA and other types) and environment (i.e., gluten) that leads to the intestinal damage that is typical of the disease.[2] Under physiologic circumstances, this inter-

Celiac Disease is one of the most common lifelong disorders in both Europe and the US

and the subsequent abnormal passage of gluten into the lamina propria. The protein is deamidated by tissue transglutaminase in the lamina propria and is then recognized by antigen-presenting cells bearing HLA-DQ2 or DQ8, thereby triggering the autoimmune reaction of celiac disease.[3] Given the undisputable role of gluten in causing inflammation and immune-mediated tissue damage, celiac disease represents a unique model of autoimmunity in which, in contrast to all other autoimmune diseases, a close genetic association with HLA-DQ2, DQ8, or both; a highly specific humoral autoimmune response (autoantibodies against tissue transglutaminase); and most important, the triggering environmental factor (gluten) have all been identified. This information provides the rationale for the treatment of the disease based on complete avoidance of gluten-containing grains, a task complicated by the lack of a clear food-labeling policy.

Epidemiologic studies conducted during the past decade, using specific and sensitive serologic tests, have revealed that celiac disease is one of the most common lifelong disorders in both Europe[4] and the United States.[5] The clinical presentation of this condition can range from the typical syndrome of malabsorption (chronic diarrhea, weight loss, and abdominal distention) to symptoms and conditions that can affect any organ system (Table 1).[5] Since the onset of celiac disease may be atypical or even silent, many cases remain undiagnosed and

with HLA typing, the authors screened a cohort of children whose serum samples had been collected seven years earlier. Fifty-six had positive serologic tests, only 10 (18 percent) of whom had been given a diagnosis of celiac disease between the serum

Table 1. Atypical Clinical Manifestations of Celiac Disease.

Diabetes
Anemia
Osteoporosis or other bone diseases
Chronic fatigue
Autoimmune disorders
Gastrointestinal cancer
Dermatitis herpetiformis
Behavioral changes
Irritable bowel
Miscarriage
Neurologic symptoms (including ataxia)

36% of patients with Celiac Disease referred for a neurological opinion have substantial structural and functional brain deficit and show significant brain abnormality on MR imaging

J Neurol Neurosurg Psychiatry 2012;83:1216–1221

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RESEARCH PAPER

Should we be 'nervous' about coeliac disease? Brain abnormalities in patients with coeliac disease referred for neurological opinion

Patients with coeliac disease had three main types of neurological complaint:
(1) balance disturbance;
(2) headache and
(3) sensory loss.
Balance disturbance comprised gait ataxia with patients having difficulty tandem walking and standing on one leg in turn during clinical examination.

uk

grey matter density, cerebellar volume, cerebellar

allows assessment of white matter abnormalities

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(36%) of patients demonstrated WMAs unexpected for the patient's age, with the highest incidence occurring in the headache subgroup.

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patients with coeliac disease referred for neurological opinion and evaluate MR imaging sequences as biomarkers for neurological dysfunction, given the lack of readily available serological markers of neurological disease in this cohort.

Methods Retrospective examination of a consecutive cohort of patients (n=33, mean age=44±13 years (range 19–64)) with biopsy proven coeliac disease referred for neurological opinion. Patients were divided into subgroups based on their primary neurological complaint (balance disturbance, headache and sensory loss). 3T MR was used to evaluate differences in brain grey matter density, cerebellar volume, cerebellar

…n that …of the population,[5] the health and economic burden arising as a consequence of neurological dysfunction is potentially substantial. Characterisation of brain abnormality in these patients is fundamental to understanding the pattern and extent of disease. There is the additional need for reproducible biomarkers as there is no readily available specific serological indicator for neurological dysfunction in this cohort.

Single-voxel proton MR spectroscopy provides an insight into the underlying chemical environment of a particular brain region. T2-weighted imaging allows assessment of white matter abnormalities

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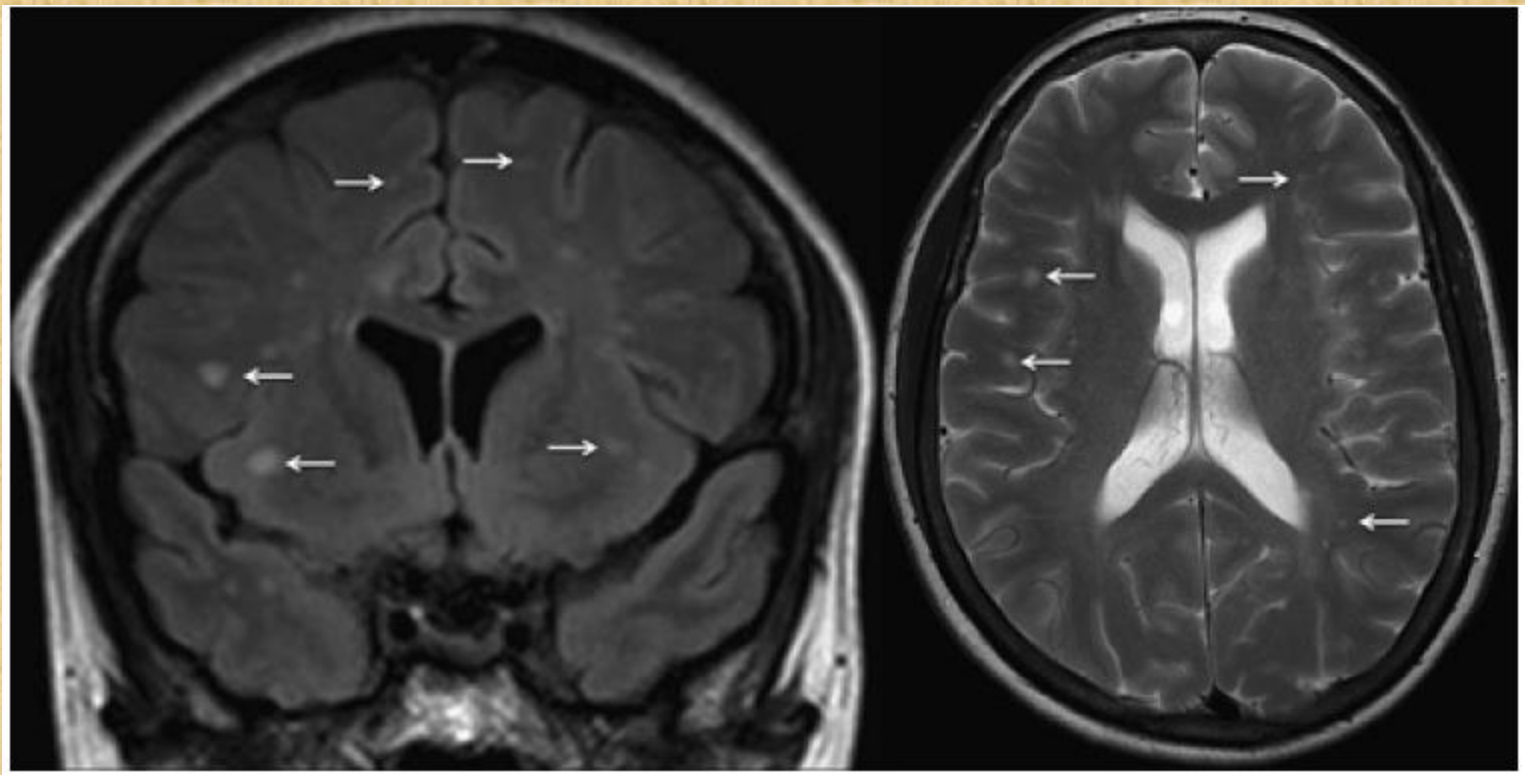

Figure 3 Typical example of white matter abnormalities found in the patient group. Coronal fluid attenuated inversion recovery (FLAIR) (left) and axial T2-weighted (right) images of a 57-year-old woman with coeliac disease who complained of recurrent headaches. Predominantly frontal subcortical white matter T2-weighted hyperintensities are indicated by arrows.

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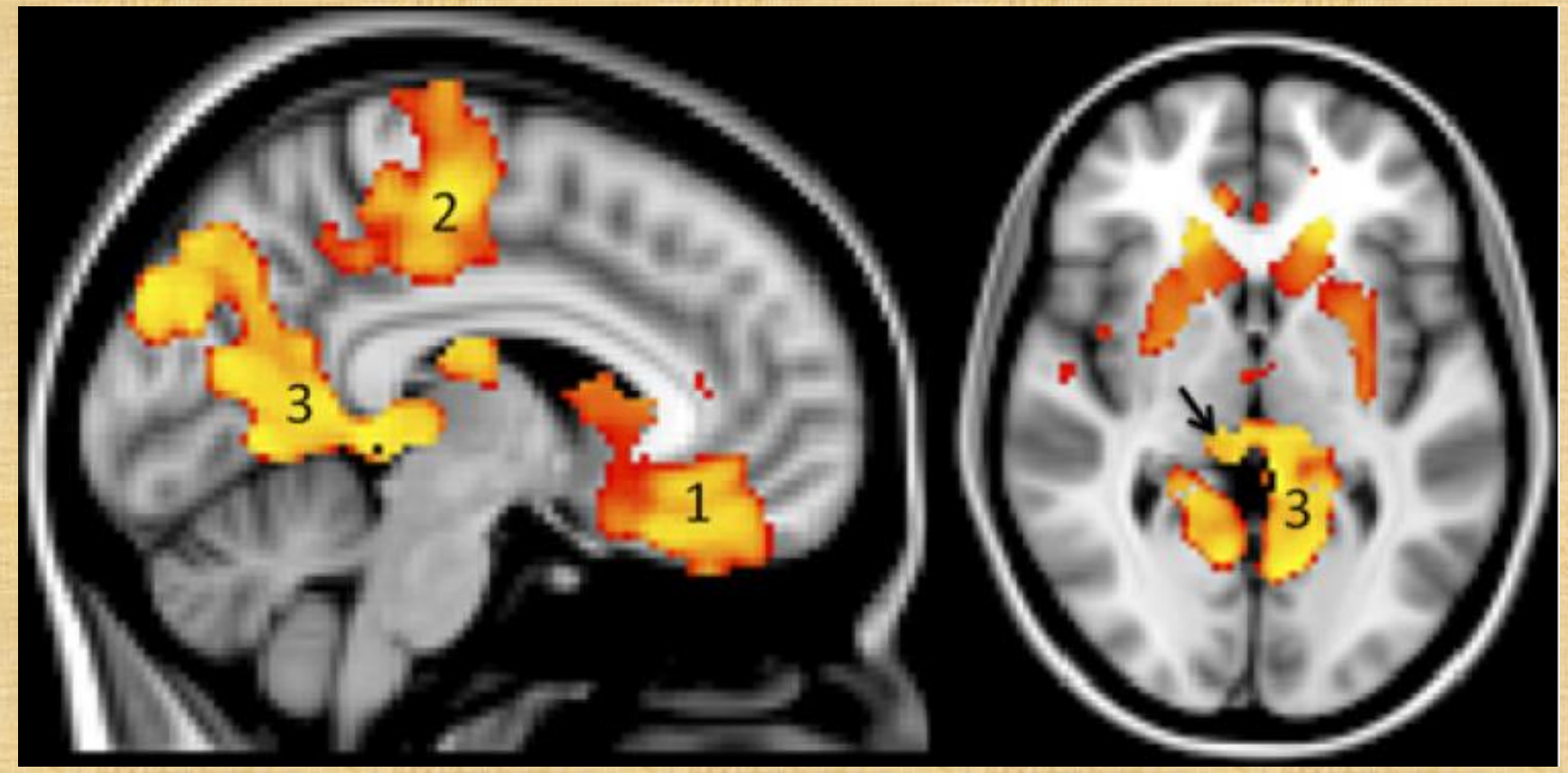

Highlighted areas depict cortical and subcortical brain regions that show statistically significant lower grey matter concentrations in patients with coeliac disease compared with age- and sex-matched controls,

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Conclusion: Patients with established coeliac disease referred for neurological opinion have substantial structural and functional brain deficit and show significant brain abnormality on MR imaging. MR imaging may provide valuable biomarkers of disease in this patient cohort.

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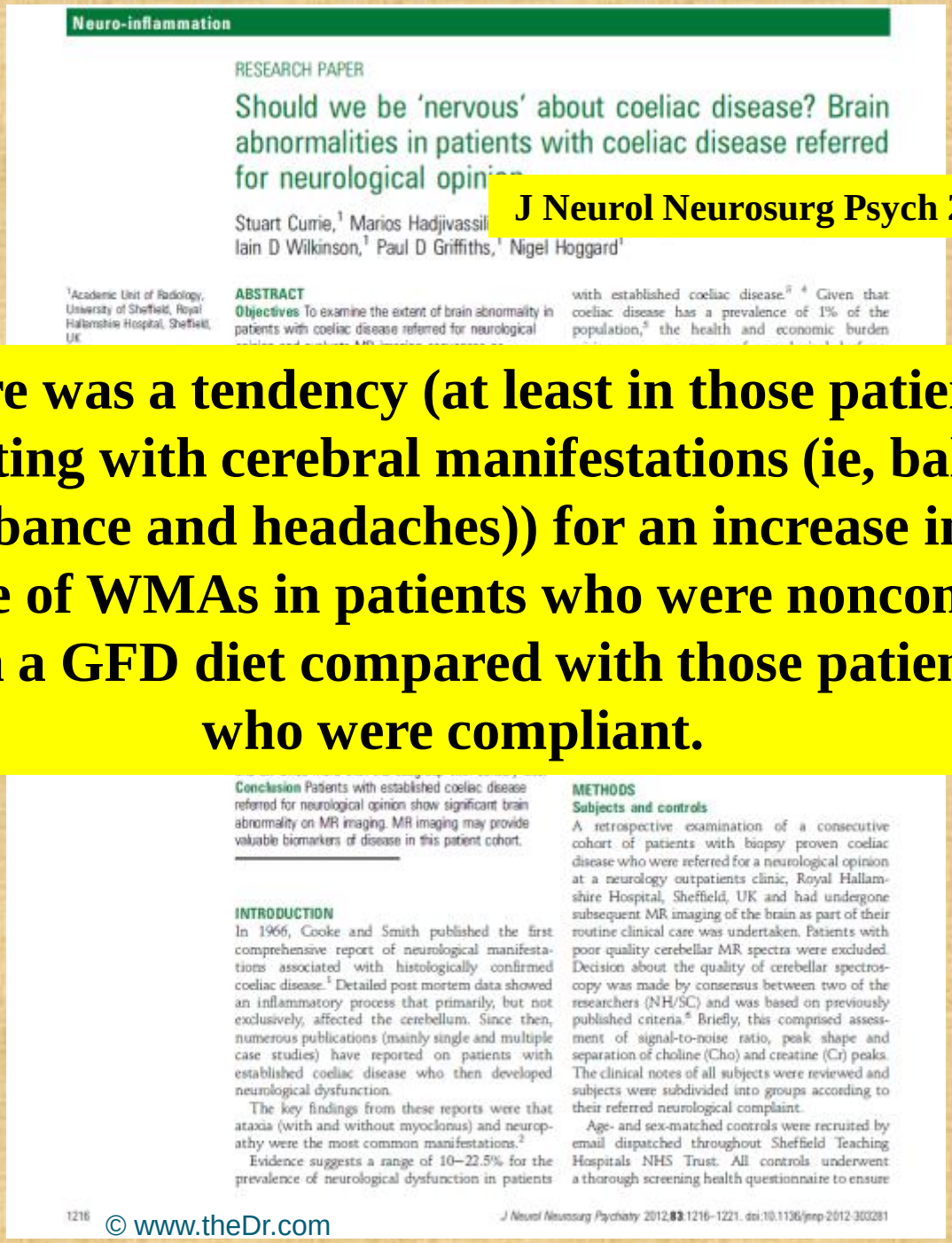

Neuro-inflammation

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ABSTRACT

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Conclusion Patients with established coeliac disease referred for neurological opinion show significant brain abnormality on MR imaging. MR imaging may provide valuable biomarkers of disease in this patient cohort.

There was a tendency (at least in those patients presenting with cerebral manifestations (ie, balance disturbance and headaches)) for an increase in the incidence of WMAs in patients who were noncompliant with a GFD diet compared with those patients who were compliant.

INTRODUCTION

In 1966, Cooke and Smith published the first comprehensive report of neurological manifestations associated with histologically confirmed coeliac disease.[1] Detailed post mortem data showed an inflammatory process that primarily, but not exclusively, affected the cerebellum. Since then, numerous publications (mainly single and multiple case studies) have reported on patients with established coeliac disease who then developed neurological dysfunction.

The key findings from these reports were that ataxia (with and without myoclonus) and neuropathy were the most common manifestations.[2]

Evidence suggests a range of 10–22.5% for the prevalence of neurological dysfunction in patients

METHODS

Subjects and controls

A retrospective examination of a consecutive cohort of patients with biopsy proven coeliac disease who were referred for a neurological opinion at a neurology outpatients clinic, Royal Hallamshire Hospital, Sheffield, UK and had undergone subsequent MR imaging of the brain as part of their routine clinical care was undertaken. Patients with poor quality cerebellar MR spectra were excluded. Decision about the quality of cerebellar spectroscopy was made by consensus between two of the researchers (NH/SC) and was based on previously published criteria.[6] Briefly, this comprised assessment of signal-to-noise ratio, peak shape and separation of choline (Cho) and creatine (Cr) peaks. The clinical notes of all subjects were reviewed and subjects were subdivided into groups according to their referred neurological complaint.

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The incidence of WMA in patients with CD presenting with headaches and compliant with a GFD was 50%.

ABSTRACT

Objectives To examine the extent of brain abnormality in patients with coeliac disease referred for neurological

complaint (balance disturbance, headache and sensory loss). 3T MR was used to evaluate differences in brain grey matter density, cerebellar volume, cerebellar neurochemistry and white matter abnormalities (WMAs) between subjects and controls.

Results Cerebellar volume was significantly less in the patient group than in controls (6.9±0.7% vs 7.4±0.9% of total intracranial volume, p<0.05). Significantly less grey matter density was found in multiple brain regions, both above and below the tentorium cerebelli, than in controls (p<0.05). 12 (36%) patients demonstrated WMAs unexpected for the patient's age, with the highest incidence occurring in the headache subgroup. This subgroup averaged almost twice the number of WMAs per MR imaging than the subgroup with balance disturbance and six times more than the subgroup with sensory loss.

Conclusion Patients with established coeliac disease referred for neurological opinion show significant brain abnormality on MR imaging. MR imaging may provide valuable biomarkers of disease in this patient cohort.

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insight into the underlying chemical environment of a particular brain region. T2-weighted imaging allows assessment of white matter abnormalities (WMAs) and three-dimensional T1-weighted datasets can be used to evaluate atrophy.

This study evaluated retrospectively the MR features of a consecutive cohort of patients with biopsy proven coeliac disease who were referred for neurological opinion. Brain grey matter volume, cerebellar volume, cerebral WMAs and cerebellar MR spectroscopy data of patients were compared with data of age- and sex-matched controls. The data suggest that patients with established coeliac disease referred for neurological opinion have substantial structural and functional brain deficit.

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Results from this study show that patients with coeliac disease and neurological complaints have significant cerebral and cerebellar abnormalities in comparison with age- and sex matched healthy volunteers.

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matter density was found in multiple brain regions, both above and below the tentorium cerebelli, than in controls ($p<0.05$). 12 (36%) patients demonstrated WMAs unexpected for the patient's age, with the highest incidence occurring in the headache subgroup. This subgroup averaged almost twice the number of WMAs per MR imaging than the subgroup with balance disturbance and six times more than the subgroup with sensory loss.

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Especially, when compared with the control cohort this group of patients with coeliac disease and neurological complaints has significantly smaller cerebellar volume and has significantly reduced grey matter volume in multiple brain regions, including the cerebellum.

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incidence occurring in the headache subgroup. This subgroup averaged almost twice the number of WMAs per MR imaging than the subgroup with balance disturbance and six times more than the subgroup with sensory loss. **Conclusion** Patients with established coeliac disease referred for neurological opinion show significant brain abnormality on MR imaging. MR imaging may provide valuable biomarkers of disease in this patient cohort.

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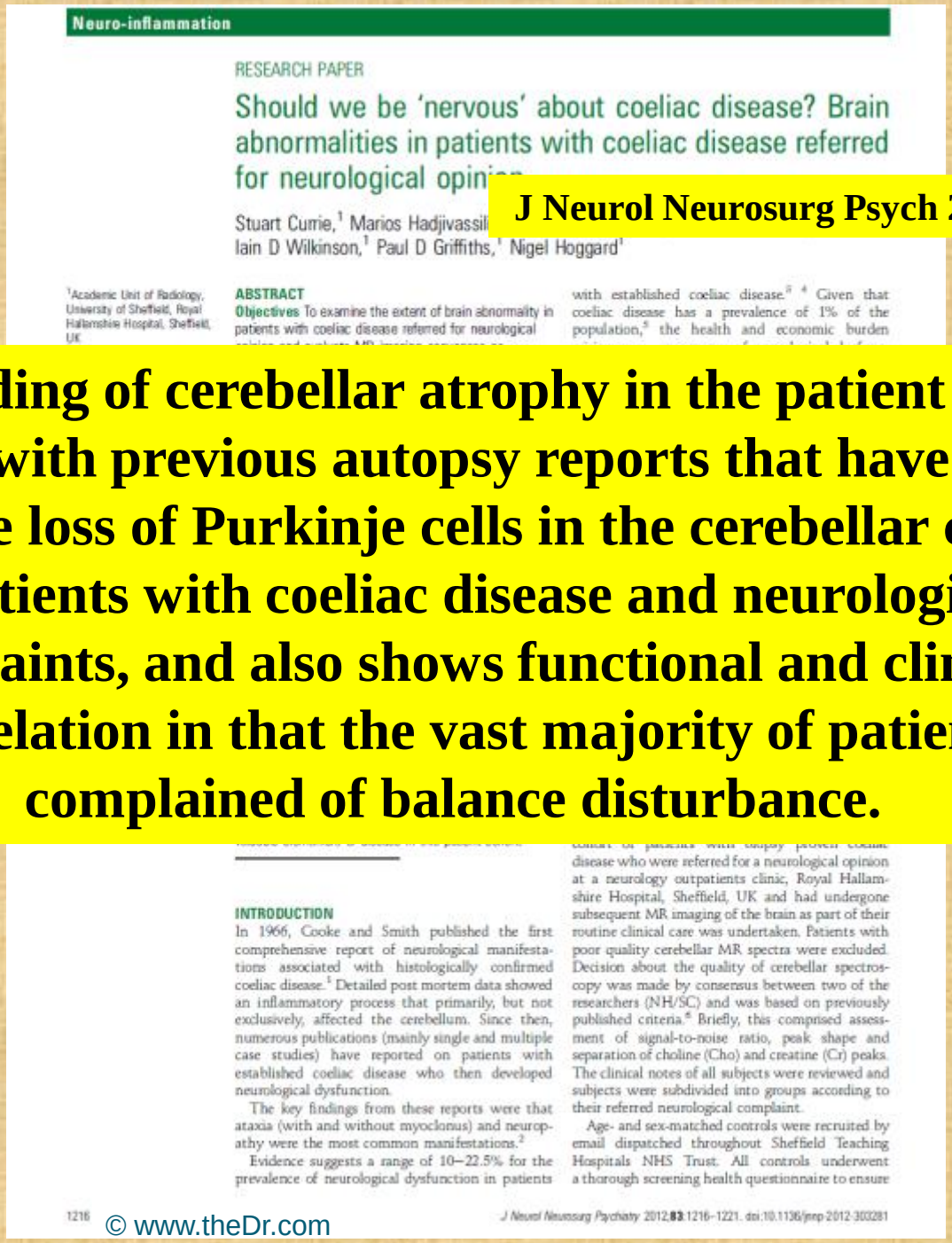

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Our finding of cerebellar atrophy in the patient group concurs with previous autopsy reports that have shown selective loss of Purkinje cells in the cerebellar cortex of patients with coeliac disease and neurological complaints, and also shows functional and clinical correlation in that the vast majority of patients complained of balance disturbance.

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The mechanisms underlying Purkinje cell loss in relation to gluten sensitivity are yet to be fully elucidated. However, current theory tends towards an immune-mediated cellular destruction.

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Immune Response to Dietary Proteins, Gliadin and Cerebellar Peptides in Children with Autism

A. VOJDANI[a,b,*], T. O'BRYAN[c], J.A. GREEN[d], J. MCCANDLESS[e], K.N. WOELLER[f], E. VOJDANI[g], A.A. NOURIAN[a]

"We conclude that a subgroup of patients with autism produces antibodies against Purkinje cells and gliadin peptides, which may be responsible for some of the neurological symptoms in autism."

The mechanisms behind autoimmune reaction to nervous system antigens in autism are not understood. We assessed the reactivity of sera from 50 autism patients and 50 healthy controls to specific peptides from gliadin and the cerebellum. A significant percentage of autism patients showed elevations in antibodies against gliadin and cerebellar peptides simultaneously. For examining cross-reaction between dietary proteins and cerebellar antigens, antibodies were prepared in rabbits, and binding of rabbit anti-gliadin, anti-cerebellar peptides, anti-MBP, anti-milk, anti-egg,

INTRODUCTION

Autism is a complex developmental disorder with unknown etiology. As with many complex diseases, genetic and environmental factors including diet, infections and xenobiotics play a critical role in the development of autism (Ivarsson *et al.*, 1990; Wakefield *et al.*, 1998; Edelson and Cantor, 2000; Fatemi *et al.*, 2002; Kibersti and Roberts, 2002; Vojdani *et al.*,

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We found that children with autism had significantly higher levels of both gluten and cerebellar peptide antibodies in more than 80% of the cases. If gluten antibodies were elevated, cerebellar peptide antibodies were also high.

The mechanisms behind autoimmune reaction to nervous system antigens in autism are not understood. We assessed the reactivity of sera from 50 autism patients and 50 healthy controls to specific peptides from gliadin and the cerebellum. A significant percentage of autism patients showed elevations in antibodies against gliadin and cerebellar peptides simultaneously. For examining cross-reaction between dietary proteins and cerebellar antigens, antibodies were prepared in rabbits, and binding of rabbit anti-gliadin, anti-cerebellar peptides, anti-MBP, anti-milk, anti-egg,

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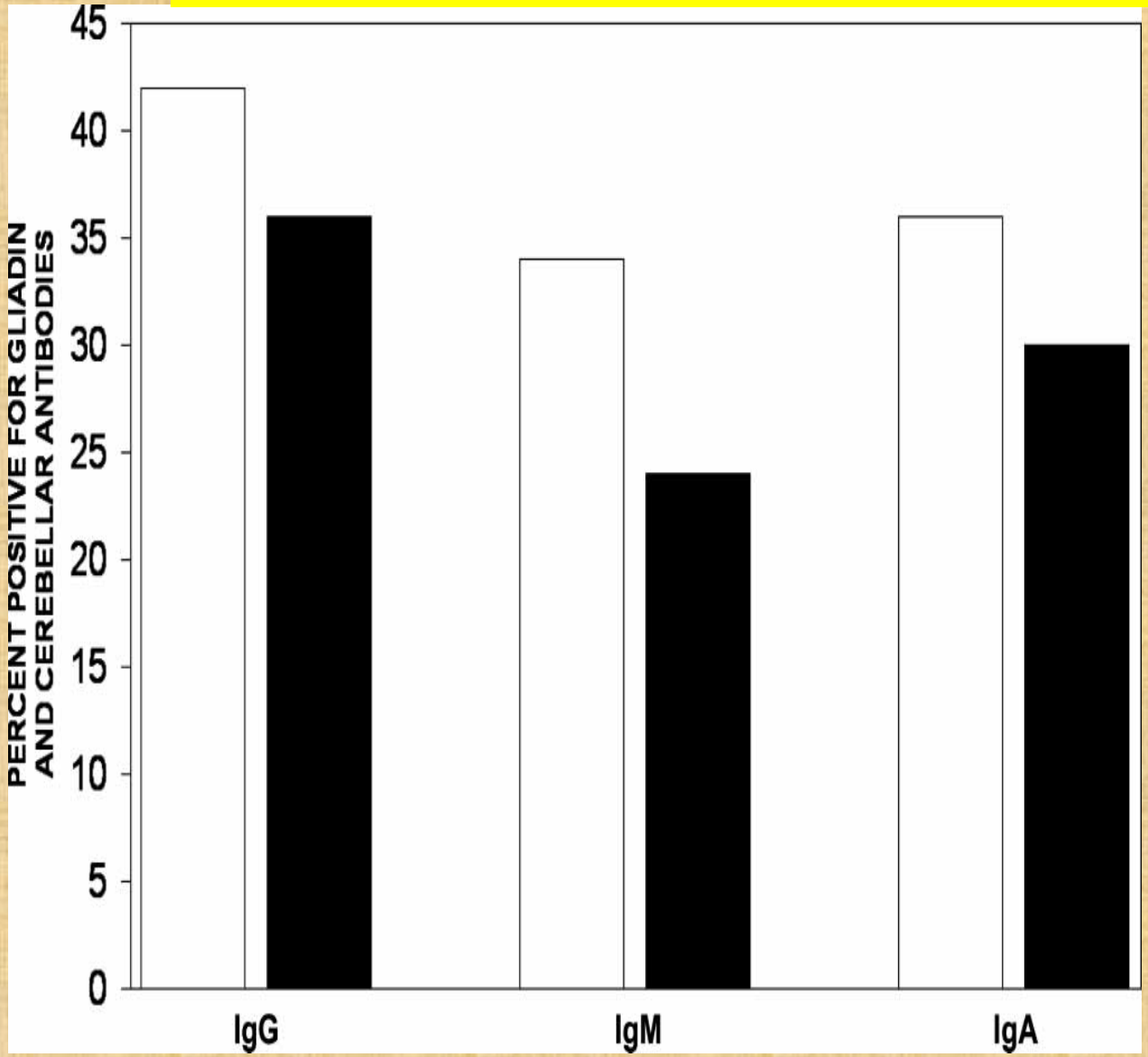

FIGURE 3 Percent positive sera from patients with Autism for IgG, IgM, and IgA antibodies against gliadin □ and cerebellar peptides ■.

Neuro-inflammation

RESEARCH PAPER

Should we be 'nervous' about coeliac disease? Brain abnormalities in patients with coeliac disease referred for neurological opini

Stuart Currie,[1] Marios Hadjivassil
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Other areas of the brain including the gyrus rectus and anterior cingulate gyrus also showed significant grey matter loss in the subject group.

ABSTRACT

Objectives To examine the extent of brain abnormality in patients with coeliac disease referred for neurological

between subjects and controls.

Results Cerebellar volume was significantly less in the patient group than in controls (6.9±0.7% vs 7.4±0.9% of total intracranial volume, p<0.05). Significantly less grey matter density was found in multiple brain regions, both above and below the tentorium cerebelli, than in controls (p<0.05). 12 (36%) patients demonstrated WMAs unexpected for the patient's age, with the highest incidence occurring in the headache subgroup. This subgroup averaged almost twice the number of WMAs per MR imaging than the subgroup with balance disturbance and six times more than the subgroup with sensory loss.

Conclusion Patients with established coeliac disease referred for neurological opinion show significant brain abnormality on MR imaging. MR imaging may provide valuable biomarkers of disease in this patient cohort.

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INTRODUCTION

In 1966, Cooke and Smith published the first comprehensive report of neurological manifestations associated with histologically confirmed coeliac disease.[1] Detailed post mortem data showed an inflammatory process that primarily, but not exclusively, affected the cerebellum. Since then, numerous publications (mainly single and multiple case studies) have reported on patients with established coeliac disease who then developed neurological dysfunction.

The key findings from these reports were that ataxia (with and without myoclonus) and neuropathy were the most common manifestations.[2]

Evidence suggests a range of 10–22.5% for the prevalence of neurological dysfunction in patients with established coeliac disease.[3 4] Given that coeliac disease has a prevalence of 1% of the population,[5] the health and economic burden

datasets can be used to evaluate atrophy.

This study evaluated retrospectively the MR features of a consecutive cohort of patients with biopsy proven coeliac disease who were referred for neurological opinion. Brain grey matter volume, cerebellar volume, cerebral WMAs and cerebellar MR spectroscopy data of patients were compared with data of age- and sex-matched controls. The data suggest that patients with established coeliac disease referred for neurological opinion have substantial structural and functional brain deficit.

METHODS

Subjects and controls

A retrospective examination of a consecutive cohort of patients with biopsy proven coeliac disease who were referred for a neurological opinion at a neurology outpatients clinic, Royal Hallamshire Hospital, Sheffield, UK and had undergone subsequent MR imaging of the brain as part of their routine clinical care was undertaken. Patients with poor quality cerebellar MR spectra were excluded. Decision about the quality of cerebellar spectroscopy was made by consensus between two of the researchers (NH/SC) and was based on previously published criteria.[6] Briefly, this comprised assessment of signal-to-noise ratio, peak shape and separation of choline (Cho) and creatine (Cr) peaks. The clinical notes of all subjects were reviewed and subjects were subdivided into groups according to their referred neurological complaint.

Age- and sex-matched controls were recruited by email dispatched throughout Sheffield Teaching Hospitals NHS Trust. All controls underwent a thorough screening health questionnaire to ensure

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Abnormalities in these regions have been shown to be associated with executive and psychomotor symptoms, and grey matter loss in these areas was found in patients with depression.

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The extent and pattern of grey matter loss in patients with coeliac disease receiving a gluten-free diet compared with controls raises important questions about possible subclinical neurological disease in these patients and the need for <u>early</u> diagnosis and treatment with a <u>strict</u> gluten-free diet.

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Kieslich,M., Pediatrics Vol.108 No.2, August 2001

Brain White-Matter Lesions in Celiac Disease: A Prospective Study of 75 Diet-Treated Patients

Matthias Kieslich, MD*; Germán Errázuriz, MD*; Hans Georg Posselt, MD*;
Walter Moeller-Hartmann, MD‡; Friedhelm Zanella, MD‡; and Hansjosef Boehles, MD*

ABSTRACT. *Objective.* Celiac disease (CD), or gluten sensitivity, is considered to be a state of heightened immunologic responsiveness to ingested gluten proteins in genetically predisposed individuals. The gastrointestinal manifestation suggests a severe enteropathy of the small intestine with malabsorption, steatorrhea, and weight loss because of a deranged mucosal immune response. Neurologic complications occur, especially epilepsy, possibly associated with occipital calcifications or folate deficiency and cerebellar ataxia. There have been reports of brain white-matter lesions as an extraintestinal manifestation in Crohn disease and ulcerative colitis but not in CD.

Methods. In this study, 75 diet-treated mainly pediatric patients with biopsy-proven CD underwent prospectively clinical neurologic examinations, laboratory investigations, electroencephalography, computed to-

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In this study, 75 diet-treated mainly pediatric patients with biopsy-proven CD underwent prospectively clinical neurologic examinations, laboratory investigations, electroencephalography, computed tomography, and magnetic resonance imaging. The age range was 2.8 to 24.2 years with a mean of 11.6 years. The mean period of gluten exposure was 2.4 years.

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Methods. In this study, 75 diet-treated mainly pediatric patients with biopsy-proven CD underwent prospectively clinical neurologic examinations, laboratory investigations, electroencephalography, computed to-

T2-hyperintensive white-matter lesions in 15 patients (20%). There was no correlation between these lesions and dietary compliance or neurologic or electroencephalographic abnormalities. The mean gluten exposure time of these patients was slightly increased (not significant).

Conclusions. Focal white-matter lesions in the brain may represent an extraintestinal manifestation of CD. They may be ischemic in origin as a result of a vasculitis or caused by inflammatory demyelination. They seem to be more typical of pediatric CD than cerebral calcifications. Their prognostic value is unclear and needs to be elucidated in additional studies. CD should be suggested as a differential diagnosis in children with unclear white-matter lesions even without intestinal symptoms.
Pediatrics 2001;108(2). URL: http://www.pediatrics.org/cgi/content/full/108/2/e21; *celiac disease, neurologic complications, brain white-matter lesions, child.*

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Neurologic disorders or findings were found in 51.4% patients with CD.

myositis; neuromyotonia; myasthenic syndrome; myelopathy; and dementia accompanied by brain atrophy in adults.[6–10] The aim of this study was to investigate the spectrum, incidence, and risk factors of neurologic involvement of CD in a mainly pediatric cohort.

METHODS

Seventy-five diet-treated patients who attended the pediatric outpatient clinic of Frankfurt University between 1997 and 1999 were enrolled in this prospective study. The age range was 2.8 to 24.2 years with a median of 10.7 years and a mean of 11.6 years (standard deviation: 5.13). Informed consent was obtained from the patients or their parents. For all patients, the diagnosis was based on biopsies of the small intestine combined with gluten exposition. Fifty-two female patients (69%) and 23 male patients (31%) underwent clinical neurologic examination, laboratory investigation, electroencephalography (EEG), computed tomography (CT), and magnetic resonance imaging (MRI). Medical history concerning concomitant diseases and perinatal problems was evaluated. The quality of dietary compliance was analyzed by a questionnaire, confirmed by the presence of gliadin antibodies (IgA) and classified into 3 groups: 1) good: no dietary mistakes, 2) moderate: 1 or 2 dietary mistakes per week, or 3) poor: more than 2 dietary mistakes per week. IgA were measured in arbitrary units (AU) by the gluten-IgA-enzyme immunometric assay (Pharmacia, Erlagen, Germany). The gluten exposure time was defined as age at diagnosis minus the age at the beginning of gluten-containing nutrition plus the time of diagnostic gluten exposition. EEG re-

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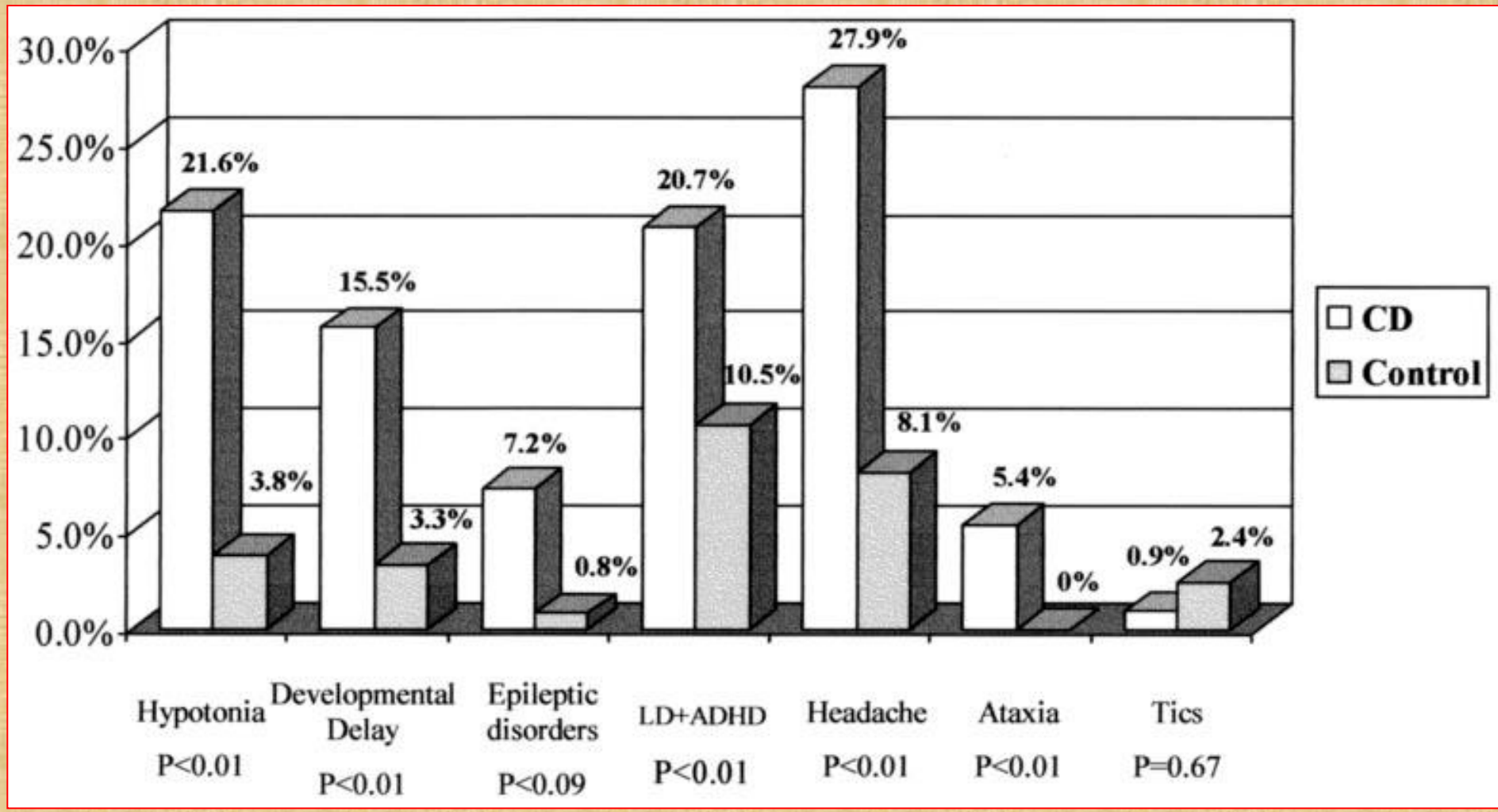

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Of 75 biopsy-proven mainly pediatric celiac patients, 20% of them had MRI detected unilateral and bilateral T2-hyperintensive white-matter lesions

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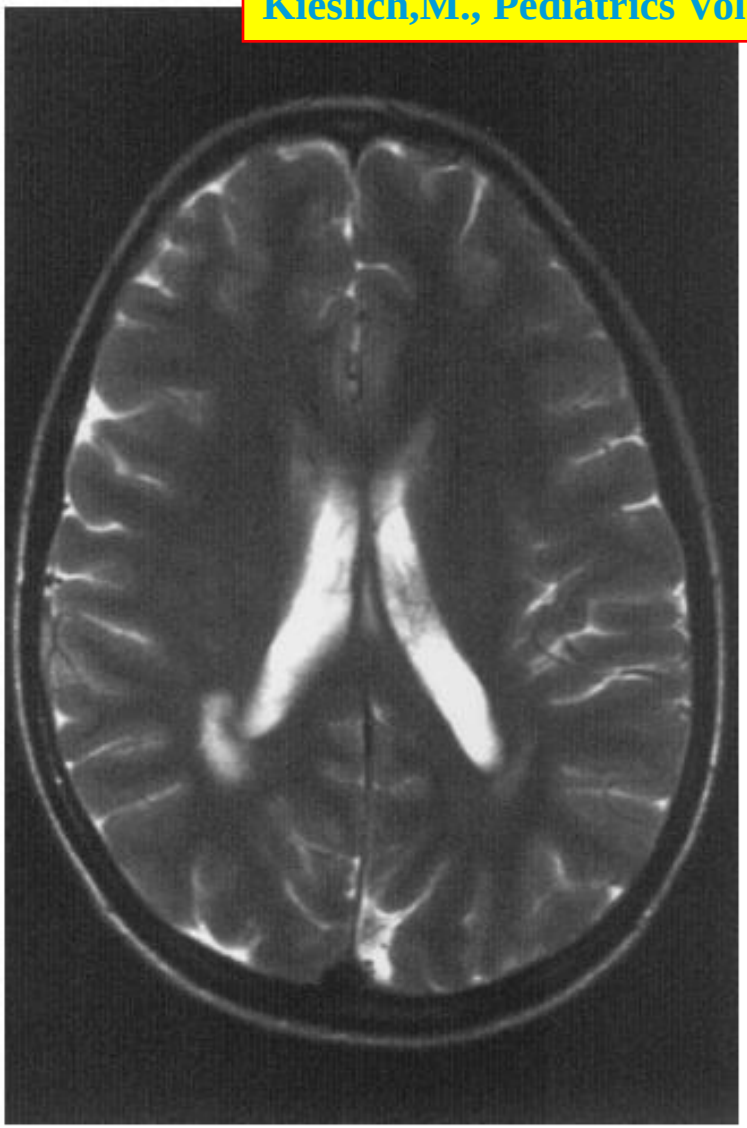

Fig 1. Larger bilateral periventricular white-matter lesions (T2 spin-echo sequence).

CASE STUDY #1

Conjunctival Tumor diagnosed as Kaposi's Sarcoma

Indian J Ophthalmol: 2010;58:433-434

Regression of conjunctival tumor during dietary treatment of celiac disease

Samuray Tuncer, Baris Yeniad, Gonul Peksayar

A 3-year-old girl presented with a hemorrhagic conjunctival lesion in the right eye. The medical history revealed premature cessation of breast feeding, intolerance to the ingestion of baby foods, anorexia, and abdominal distention. Prior to her referral, endoscopic small intestinal biopsy had been carried out under

CD and the conjunctival tumor showed complete regression during gluten-free dietary treatment. The clinical fleshy appearance of the lesion with spider-like vascular extensions and subconjunctival hemorrhagic spots, possible association with an acquired immune system dysfunction due to CD, and spontaneous regression by a gluten-free diet led us to make a presumed diagnosis of conjunctival Kaposi sarcoma.

Key words: Celiac disease, conjunctiva, gluten-free diet, Kaposi sarcoma

Indian J Ophthalmol: 2010;58:433-434

DOI: 10.4103/0301-4738.67071

steroids, and hence, excisional biopsy was suggested. The patient was referred to our clinic to get a second opinion.

Her past medical history revealed premature cessation of breast feeding, intolerance to the ingestion of baby foods, anorexia, and abdominal distention since 2 months. Her weight and height percentiles were subnormal compared to her age group. From 26 months of age, she had recurrent serous otitis media treated with systemic antibiotics. However, the primary etiology could not be determined by her pediatrician in the first 3 years of life.

Our initial visit showed that the visual acuities were 20/20 in both eyes. Slit-lamp examination of the right eye revealed

A 3-year-old girl presented with a hemorrhagic conjunctival lesion in the right eye.

possible diagnosis of CD in another hospital. Therefore, her parents did not want their child to undergo general anesthesia for the second time for the excisional biopsy. We decided to follow the patient without any intervention until all systemic investigations were concluded.

The blood test for HIV antibody was negative. Serology showed high anti-gliadin and anti-endomysial immunoglobulin A antibody levels. Endoscopic intestinal biopsy demonstrated partial villous atrophy, intraepithelial lymphocytosis, and crypt hyperplasia consistent with CD. Genetic testing of the family members revealed high maternal autoantibody titers for CD.

After the diagnosis of CD, gluten-free diet was instituted. The conjunctival lesion gradually regressed [Fig. 1B] and

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Our initial visit showed that the visual acuities were 20/20 in both eyes. Slit-lamp examination of the right eye revealed a reddish, elevated, and highly vascular spider-like lesion on the superior bulbar conjunctiva, measuring 12x4x2 mm [Fig. 1A].

Key words: Celiac disease, conjunctiva, gluten-free diet, Kaposi sarcoma

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DOI: 10.4103/0301-4738.67071

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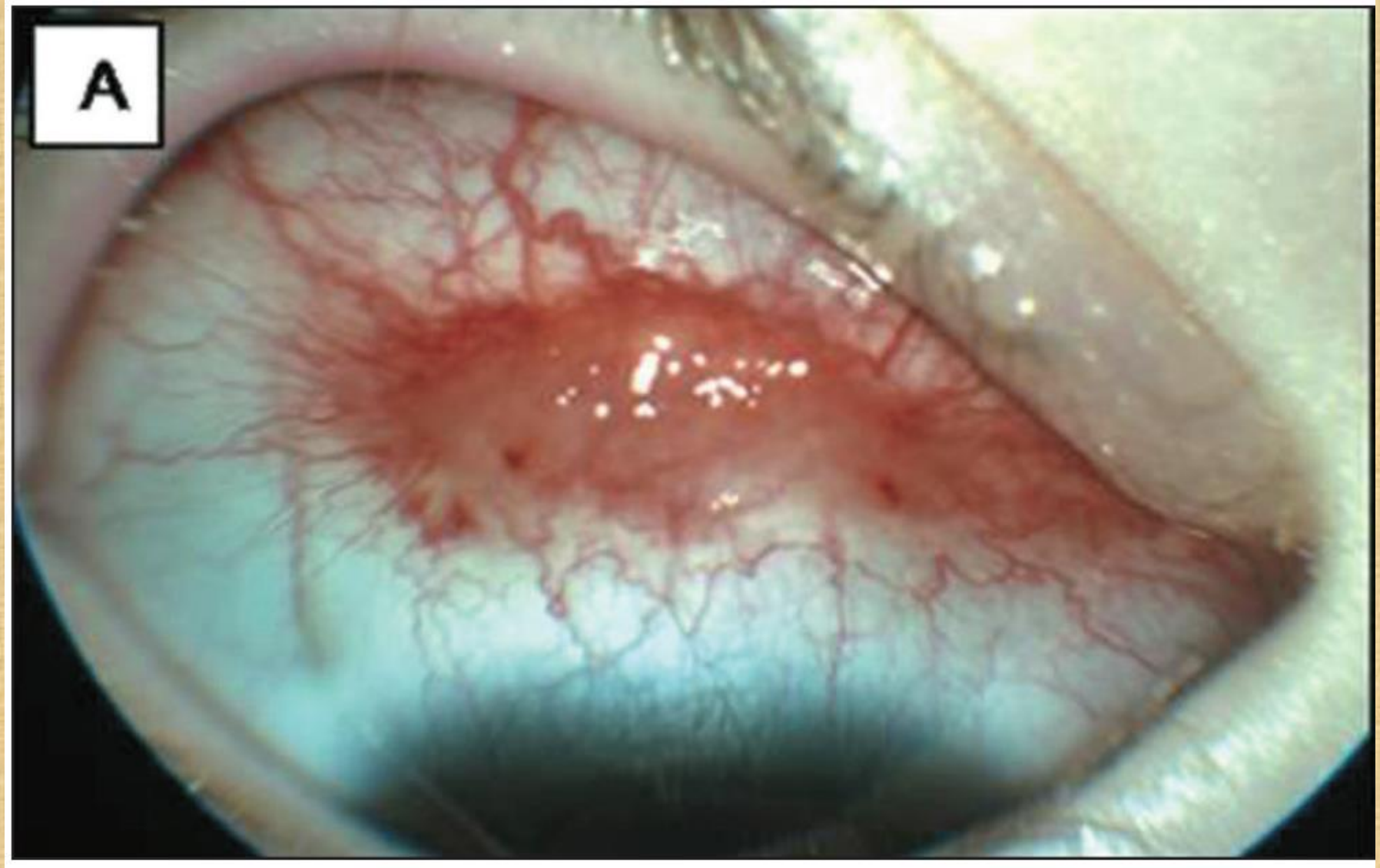
After the diagnosis of CD, gluten-free diet was instituted. The conjunctival lesion gradually regressed [Fig. 1B] and

Indian J Ophthalmol: 2010;58:433-434



Indian J Ophthalmol: 2010;58:433-434

Regression of conjunctival tumor during dietary treatment of celiac disease

Samuray Tuncer, Baris Yeniad, Gonul Peksayar

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The blood test for HIV antibody was negative. Serology showed high anti-gliadin and anti-endomysial immunoglobulin A antibody levels. Endoscopic intestinal biopsy demonstrated partial villous atrophy, intraepithelial lymphocytosis, and crypt hyperplasia consistent with CD. Genetic testing of the family members revealed high maternal autoantibody titers for CD.

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1 week of GFD

2 months of GFD

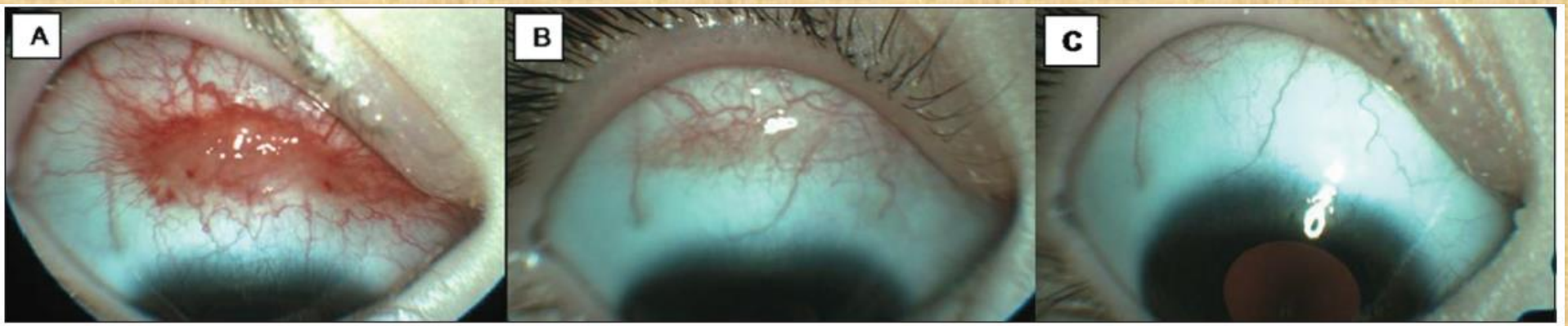

Figure 1: A 3-year-old girl, who had a 3-months history of hemorrhagic tear episodes, presented with a painless and reddish conjunctival lesion in the right eye. (A) Anterior segment photograph of the right eye showing reddish, fleshy, and highly vascular spider-like lesion on the superior bulbar conjunctiva. (B) After one week of follow-up with a gluten-free diet, spontaneous regression of the conjunctival lesion was noted. (C) After 2 months of follow-up, the conjunctival lesion disappeared completely

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Our initial visit showed that the visual acuities were 20/20 in both eyes. Slit-lamp examination of the right eye revealed

She was completely asymptomatic and the conjunctival lesion did not recur after 9 months of follow-up.

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The blood test for HIV antibody was negative. Serology showed high anti-gliadin and anti-endomysial immunoglobulin A antibody levels. Endoscopic intestinal biopsy demonstrated partial villous atrophy, intraepithelial lymphocytosis, and crypt hyperplasia consistent with CD. Genetic testing of the family members revealed high maternal autoantibody titers for CD.

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Premise #2

Gluten Sensitivity is not yet recognized by Practitioners as a <u>Primary Presentation</u> in Their Offices

Detective Adrian Monk

How many Know or Suspect you may have a Sensitivity to Gluten?

A UK study assessing the population prevalence of self-reported gluten sensitivity and referral characteristics to secondary care

Imran Aziz[a], Nina R. Lewis[a], Marios H
Nathan Rugg[a], Alan Kelsall[a], Laurence Newrick[a] and David S. Sanders[a]

Eur J of Gastro & Hepatology 2014, Vol 26 No 1

Background Reports suggest that gluten sensitivity (GS) exists in the absence of coeliac disease (CD). This clinical entity has been termed noncoeliac gluten sensitivity (NCGS).

Objectives To determine the population prevalence of self-reported GS and referral characteristics to secondary care.

Patients and methods A UK population-based

were found to have CD and 93% to have NCGS. All CD patients were human leucocyte antigen DQ2 or DQ8 positive compared with 53% of NCGS cases ($P=0.0003$). Nutritional deficiencies ($P \leq 0.003$), autoimmune disorders (23.1 vs. 9.7%, $P=0.0001$) and a lower mean BMI (23.7 vs. 25.8, $P=0.001$) were significantly associated with CD compared with NCGS.

There is an emerging problem encountered in clinical practice of patients complaining of gluten-related symptoms despite the absence of diagnostic markers for CD, such as negative coeliac serology and normal duodenal biopsies.

Introduction

Coeliac disease (CD) is a chronic inflammatory disorder of the small bowel, which affects 1% of the population [1,2]. The condition can be defined as a state of heightened immunological responsiveness to ingested gluten (from wheat, barley or rye) in genetically susceptible individuals [2,3]. The diagnosis of CD is based on the demonstration of histological abnormalities on duodenal biopsies in accordance with the modified Marsh classification [4,5]. Corroborative evidence used to support the diagnosis comes from positive coeliac serology in the form of endomysial antibody (EMA) and tissue transglutaminase antibody (TTG) [3,6]. The cornerstone of treatment for CD is lifelong adherence to a strict gluten-free diet (GFD), which in the majority leads to an improved clinical outcome, psychological well-being and quality of life [3,7].

However, the consumption of a GFD seems greatly out of proportion to the projected number of patients with CD. Marketers have estimated that 15–25% of North American consumers want gluten-free foods [8,9], although recently published data would suggest this to be an overestimation [10,11]. A National Health and Nutrition Examination Survey in the USA, involving 7798 people aged 6 years or older, suggests that 0.63% of the American public consume a GFD, although the majority of these do not have CD [10]. The prevalence of serologically diagnosed CD in this study was found to be 0.71%, yet up to 80% were previously unaware of the diagnosis of CD and not taking a GFD. Elsewhere, work from New Zealand has found that CD affects 1% of children, yet 5% report gluten avoidance [11]. Consistent with these findings is the emerging problem encountered in clinical practice of patients complaining of gluten-related symptoms despite the absence of diagnostic markers for CD, such as negative coeliac serology and normal duodenal biopsies. These patients pose a clinical dilemma to healthcare professionals and in the past have

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0.8% known to have a doctor diagnosis of CD. Individuals with GS had an increased prevalence of fulfilling the Rome III criteria for irritable bowel syndrome, in comparison with those without GS (20 vs. 3.89%, odds ratio 6.23, $P<0.0001$). In secondary care 200 GS patients (female 84%, mean age 39.6 years) were investigated, in whom 7% were found to have CD and 93% to have NCGS. All CD patients were human leucocyte antigen DQ2 or DQ8 positive compared with 53% of NCGS cases ($P=0.0003$). Nutritional deficiencies ($P \leq 0.003$), autoimmune disorders (23.1 vs. 9.7%, $P=0.0001$) and a lower mean BMI (23.7 vs. 25.8, $P=0.001$) were significantly associated with CD compared with NCGS.

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Received 26 July 2013 Accepted 3 September 2013

These patients pose a clinical dilemma to healthcare professionals and in the past have been described as belonging to a 'no man's land' due to the diagnostic uncertainty

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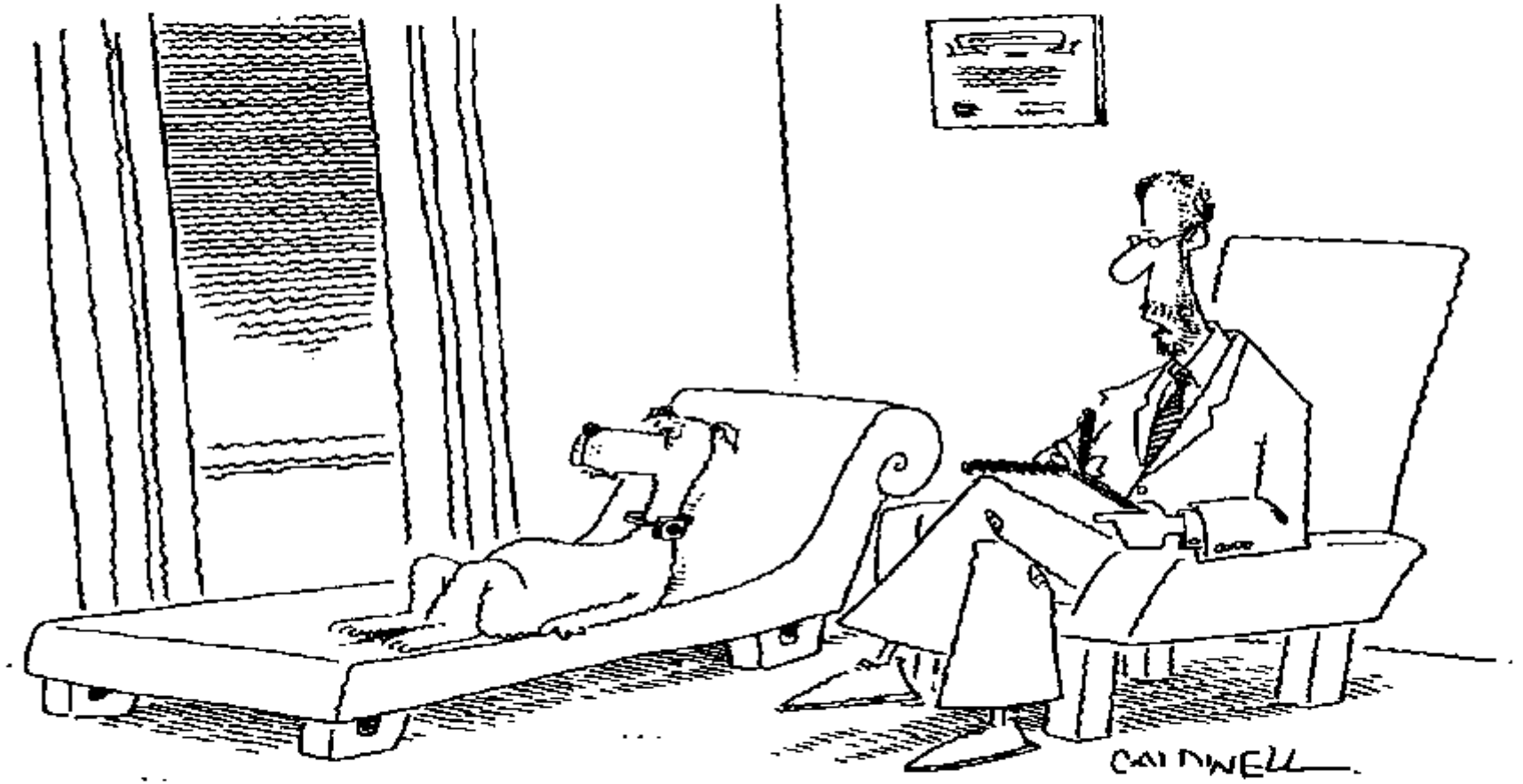


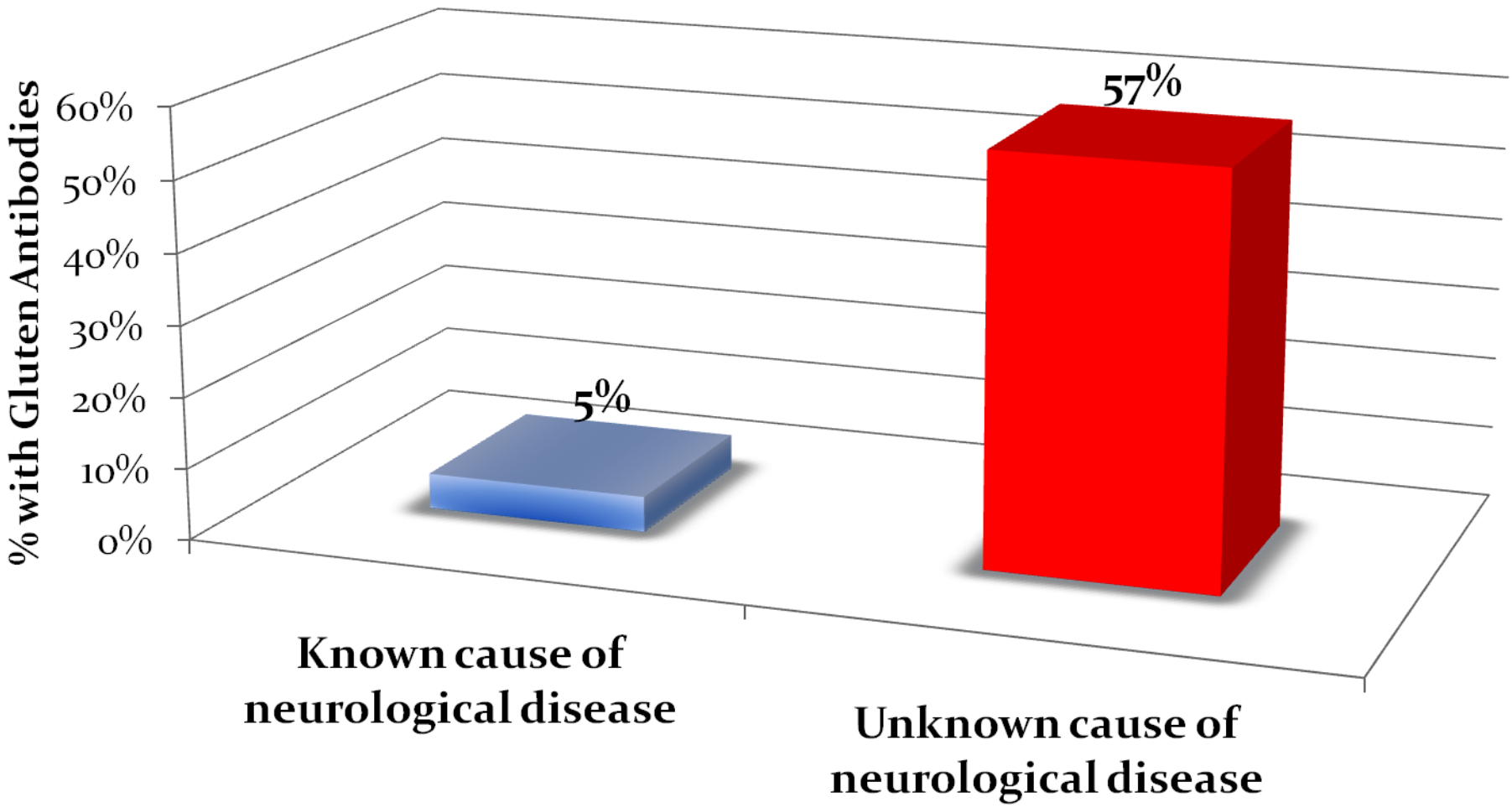
"Please…tell me more about this imaginary fence."

How many Know or Suspect you may have a Sensitivity to Gluten?

And How many Know or Suspect that IF you have an inadverdent exposure to Gluten, it seems to affect your Brain?

Do you think the percentages in this room are different than the percentages in your Practice?

J Neurol Neurosurg Psychiatry 2002 72: 560-563



When the cause of a neurological disease is known, the percentage of those patients with elevated antibodies to gluten is 5%. When the cause of a neurological disease is unknown, the the percentage of those patients with elevated antibodies to gluten is 57%.

62

How many Know or Suspect you may have a Sensitivity to Gluten?

And How many Know or Suspect that IF you have an inadverdent exposure to Gluten, it seems to affect your Brain?

And how many of you with a suspected sensitivity will have a ‘little gluten’ once in awhile?

Thus it would seem the disconnect is not only on awareness of frequency, but also acceptance of relevancy?

Mortality in patients with coeliac disease and their relatives: a cohort study

Giovanni Corrao, Gino Roberto Corazza, Vincenzo Bagnardi, Giovanna Brusco, Carolina Ciacci, Mario Cottone, Carla Sategna Guidetti, Paolo Usai, Pietro Cesari, Maria Antonietta Pelli, Silvano Loperfido, Umberto Volta, Antonino Calabró, Maria Certo, for the Club del Tenue Study Group

Lancet.Vol.358, August 4, 2001

Summary

Background Although previous studies have shown increased mortality in patients with coeliac disease and their relatives, no data are available in relation to different patterns of clinical presentation. We assessed mortality in patients with coeliac disease and their first-degree relatives.

Methods We enrolled, in a prospective cohort study, 1072 adult patients with coeliac disease consecutively diagnosed in 11 gastroenterology units between 1962 and 1994, and their 3384 first-degree relatives. We compared the number of deaths up to 1998 with expected deaths and expressed the

Introducti

Findings fro... the true frequency of coeliac disease is high even in countries where it was thought to be rare.[2] An increased overall and cancer mortality has been reported in adult patients with coeliac disease[3,4] and their relatives,[3] which lends support to the clinical importance of this disorder. Improved knowledge of the wide clinical spectrum of coeliac disease[5,7] and the use of powerful screening tests[8,9] have radically changed the pattern of presentation of this disorder. Previous mortality could be underestimated by the inclusion of subclinical and symptom-free patients, but no information is available on the prognosis of the

Enrolled 1072 adult celiacs and 3384 first-degree relatives

SMR (standardized mortality ratio) of 2.0:1

20+ year follow-up

diagnosis, between Jan 1, 1962, and 31 Dec, 1994, at 11 gastroenterology units. These units, evenly distributed through Italy, were selected from those participating in the Italian Club del Tenue study in accordance with the following inclusion criteria: completeness of clinical records (all the diagnoses of coeliac disease reported from the start of specific diagnostic activity), and reliability of the diagnoses throughout the entire period of activity. Units flagged patients by comparing records with the corresponding small-bowel pathology lists.

We obtained information on vital status, sex, age at time of diagnosis, date of initial presentation, diagnostic delay (time from onset of symptoms to intestinal biopsy), and dietary adherence (adherent or not adherent) recorded at presentation or during subsequent clinical surveillance. We classified patients into three subtypes of coeliac disease according to clinical presentation:[11] severe, with symptoms of malabsorption such as diarrhoea, weight loss, or both that led the patient to seek medical care; mild, with only trivial, transient, or seemingly

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Methods We enrolled, in a prospective cohort study, 1072 adult patients with coeliac disease consecutively diagnosed in 11 gastroenterology units between 1962 and 1994, and their 3384 first-degree relatives. We compared the number of deaths up to 1998 with expected deaths and expressed the comparison as standardised mortality ratio (SMR) and relative survival ratio.

Introducti

Findings from[illegible] the true frequency of coeliac disease is high even in countries where it was thought to be rare.[2] An increased overall and cancer mortality has been reported in adult patients with coeliac disease[3,4] and their relatives,[3] which lends support to the clinical importance of this disorder. Improved knowledge of the wide clinical spectrum of coeliac disease[5,7] and the use of powerful screening tests[8,9] have radically changed the pattern of presentation of this disorder. Previous mortality could be underestimated by the inclusion of subclinical and symptom-free patients, but no information is available on the prognosis of the new forms of coeliac disease. Additionally, the reported 1·9-fold[3] and 3·4-fold[4] increases in mortality might be

Adherence to gluten-free diet						
Likely	627 (59%)	3794	5	10·5	0·5 (0·2–1·1)	0·16
Not likely	155 (15%)	998	26	4·3	6·0 (4·0–8·8)	<0·0001
Uncertain	290 (27%)	1652	22	11·1	2·0 (1·2–3·0)	0·005
					Test for heterogeneity: p<0·0001	

SMR=standardised mortality ratio. *Unknown in 68 patients (clinical records lacking this information) and not applicable in 67 patients with symptomless disease. Test for trend does not include this category.

Table 1: **Demographics, clinical features, and overall mortality of patient cohort**

improvement after gluten-free diet. We enrolled 1072 consecutive patients older than 18 years at the time of diagnosis, between Jan 1, 1962, and 31 Dec, 1994, at 11 gastroenterology units. These units, evenly distributed through Italy, were selected from those participating in the Italian Club del Tenue study in accordance with the following inclusion criteria: completeness of clinical records (all the diagnoses of coeliac disease reported from the start of specific diagnostic activity), and reliability of the diagnoses throughout the entire period of activity. Units flagged patients by comparing records with the corresponding small-bowel pathology lists.

We obtained information on vital status, sex, age at time of diagnosis, date of initial presentation, diagnostic delay (time from onset of symptoms to intestinal biopsy), and dietary adherence (adherent or not adherent) recorded at presentation or during subsequent clinical surveillance. We classified patients into three subtypes of coeliac disease according to clinical presentation:[11] severe, with symptoms of malabsorption such as diarrhoea, weight loss, or both that led the patient to seek medical care; mild, with only trivial, transient, or seemingly

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Mortality in patients with coeliac disease and their relatives: a cohort study

Lancet.Vol.358, August 4, 2001

Giovanni Corrao, Gino Roberto Corazza, Vincenzo Bagnardi, Giovanna Brusco, Carolina Ciacci, Mario Cottone, Carla Sategna Guidetti, Paolo Usai, Pietro Cesari, Maria Antonietta Pelli, Silvano Loperfido, Umberto Volta, Antonino Calabró, Maria Certo, for the Club del Tenue Study Group

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Introduction

Findings from population-based studies have shown that the true frequency of coeliac disease is high[1] even in countries where it was thought to be rare.[2] An increased overall and cancer mortality has been reported in adult patients with coeliac disease[3,4] and their relatives,[3] which lends support to the clinical importance of this disorder. Improved knowledge of the wide clinical spectrum of coeliac disease[5–7] and the use of powerful screening tests[8,9] have radically changed the pattern of presentation of this disorder. Previous mortality could be underestimated by the inclusion of subclinical and symptom-free patients, but no information is available on the prognosis of the new forms of coeliac disease. Additionally, the reported

Death was most significantly affected by diagnostic delay, pattern of presentation, and adherence to the GFD…Non-adherence to the GFD, defined as eating gluten once-per-month increased the relative risk of death 6-fold

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Nearly 50% of patients were diagnosed with mild or symptomless celiac disease. There was a significant excess of deaths among patients who presented with only malabsorption symptoms.

Introducti

Findings fro

the true frequency of coeliac disease is high even in countries where it was thought to be rare.[2] An increased overall and cancer mortality has been reported in adult patients with coeliac disease[3,4] and their relatives,[3] which lends support to the clinical importance of this disorder. Improved knowledge of the wide clinical spectrum of coeliac disease[5,7] and the use of powerful screening tests[8,9] have radically changed the pattern of presentation of this disorder. Previous mortality could be underestimated by the inclusion of subclinical and symptom-free patients, but no information is available on the prognosis of the new forms of coeliac disease. Additionally, the reported

diagnostic criteria were subtotal or severe partial villous atrophy and crypt hyperplasia, and histological improvement after gluten-free diet. We enrolled 1072 consecutive patients older than 18 years at the time of diagnosis, between Jan 1, 1962, and 31 Dec, 1994, at 11 gastroenterology units. These units, evenly distributed through Italy, were selected from those participating in the Italian Club del Tenue study in accordance with the following inclusion criteria: completeness of clinical records (all the diagnoses of coeliac disease reported from the start of specific diagnostic activity), and reliability of the diagnoses throughout the entire period of activity. Units flagged patients by comparing records with the corresponding small-bowel pathology lists.

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Premise #3

Gluten Sensitivity with or without the enteropathy Celiac Disease is a systemic autoimmune disease

Journal of Alzheimer's Disease 45 (2015) 349–362

Detective Adrian Monk

Lancet Neurol 2010; 9: 318–30

Personal View

Gluten sensitivity: from gut to brain

Marios Hadjivassiliou, David S Sanders, Richard A Grünewald, Nicola Woodroofe, Sabrina Boscolo, Daniel Aeschlimann

Lancet Neurol 2010; 9: 318–30

Gluten sensitivity is a systemic autoimmune disease with diverse manifestations. This disorder is characterised by abnormal immunological responsiveness to ingested gluten in genetically susceptible individuals. Coeliac disease, or

Gluten sensitivity is a systemic autoimmune disease with diverse manifestations. This disorder is characterised by abnormal immunological responsiveness to ingested gluten in genetically susceptible individuals. Coeliac disease, or gluten-sensitive enteropathy, is only one aspect of a range of possible manifestations of gluten sensitivity.

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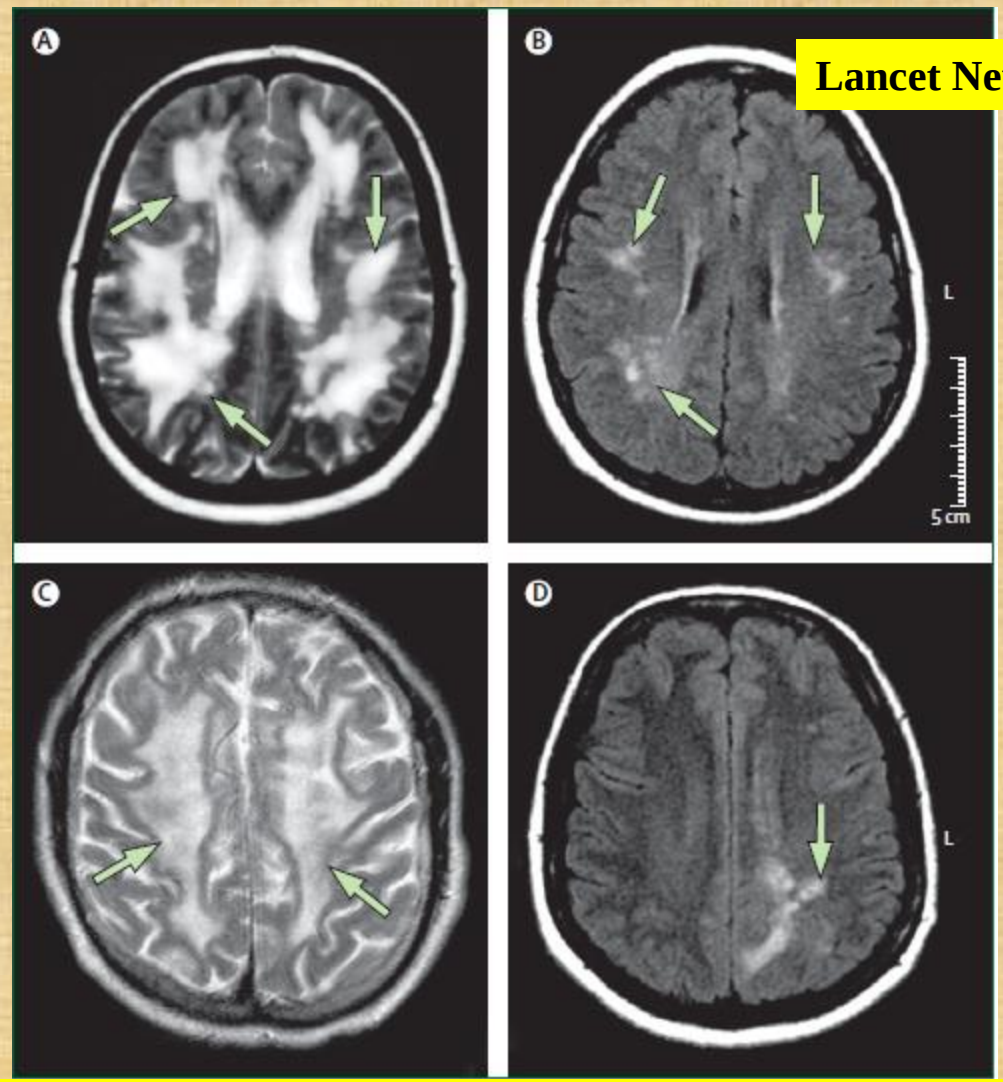
was transcribed to coeliac. The study of coeliac disease was renewed by Gee[2] in 1888. His lecture on the coeliac affection described the disease according to his observations while treating children with the disease. Although clinicians began to recognise and diagnose coeliac disease, its aetiology remained obscure until 1953 when Dicke and colleagues[3] reported "the presence

neurological dysfunction continued to be published.[8–17] The key findings from these reports were that ataxia (with and without myoclonus) and neuropathy were the most common manifestations; neurological manifestations were usually reported in the context of established coeliac disease and were almost always attributed to malabsorption of vitamins and the effects of dietary



Lancet Neurol 2010; 9: 318–30

The extent and variability of white matter abnormalities caused by gluten sensitivity can be seen in these four patients (A–D). A and C show diffuse white matter changes, whereas B and D show more focal and patchy changes.

Gluten-free diet results in complete resolution of the headaches but the white matter changes do not reverse. Repeat scanning while on the diet shows no progression.

Lancet Neurol 2010; 9: 318–30

Personal View

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Departments of Neurology, Clinical Neurosciences Research Centre, Sheffield Hallam University, Sheffield, UK (N Woodroofe PhD); Department of Life Sciences, University of Trieste, Trieste, Italy (S Boscolo PhD); and Matrix Biology and Tissue Repair Research Unit, School of Dentistry, Cardiff University, Cardiff, UK (D Aeschlimann PhD)

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Gluten sensitivity is a systemic autoimmune disease with diverse manifestations. This disorder is characterised by abnormal immunological responsiveness to ingested gluten in genetically susceptible individuals. Coeliac disease, or

The distribution of white matter abnormalities is more suggestive of a vascular rather than a demyelinating etiology.

accepted. In this Personal View, we review the range of neurological manifestations of gluten sensitivity and discuss recent advances in the diagnosis and understanding of the pathophysiological mechanisms underlying neurological dysfunction related to gluten sensitivity.

Introduction

Coeliac disease was first described in 100 AD by the Greek doctor Aretaeus,[1] who used the term abdominal diathesis. When his extant works were first published in Latin in 1552, the Greek word for abdominal, koiliaki, was transcribed to coeliac. The study of coeliac disease was renewed by Gee[2] in 1888. His lecture on the coeliac affection described the disease according to his observations while treating children with the disease. Although clinicians began to recognise and diagnose coeliac disease, its aetiology remained obscure until 1953 when Dicke and colleagues[3] reported "the presence

involved other parts of the CNS and peripheral nervous system. This finding favoured an immune-mediated pathogenesis.

Single and multiple case reports of patients with established coeliac disease who then developed neurological dysfunction continued to be published.[10–29] The key findings from these reports were that ataxia (with and without myoclonus) and neuropathy were the most common manifestations; neurological manifestations were usually reported in the context of established coeliac disease and were almost always attributed to malabsorption of vitamins; and the effects of dietary

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Association Between Migraine and Celiac Disease: Results From a Preliminary Case-Control and Therapeutic Study

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Cristiano Padalino, M.D., Marcello Candelli,
Mario Giacovazzo, M.D., Giovanni Gasbarrin

Department of Internal Medicine; and Department of Pathology, Catholic University of the Sacred Heart, Gemelli Hospital, Rome; and Department of Internal Medicine, La Sapienza University, Rome, Italy

Am J Gastroenter,Vol.98,No.3 2003 626-9

OBJECTIVES: Subclinical celiac disease (CD) has been associated with various neurological disorders, the most common being neuropathy and cerebellar ataxia. The aims of the present study were to assess the following: 1) the prevalence of CD in patients affected by migraine; 2) whether there are regional cerebral blood flow abnormalities in migraine pa-

diet.

RESULTS: Four of 90 (4.4%; 95% CI = 1.2–11.0) migraine patients were found to have CD compared with 0.4% (95% CI = 0.01–2.3) blood donor controls ($p < 0.05$). During the 6 months of gluten free diet, one of the four patients had no migraine attacks, and the remaining three patients experienced an improvement in frequency, duration, and intensity of migraine. Single photon emission CT studies showed a regional baseline reduction in brain tracer uptake in all four patients. Such reduction in uptake completely resolved at follow-up.

CONCLUSIONS: Our results suggest that a significant proportion of patients with migraine may have CD, and that a gluten free diet may lead to a improvement in the migraine in these patients. (Am J Gastroenterol 2003;98:625–629. © 2003 by Am. Coll. of Gastroenterology)

Serum IgA Anti-Gliadin antibodies from patients with CD have been recently shown to (cross) react strongly with blood vessel structures in the human brain

INTRODUCTION

Epidemiological studies using serology tests have shown celiac disease (CD) to be more common than previously realized, showing a prevalence in Europe of 0.33%. Because CD is often asymptomatic, the detection rate can be increased by using serology, *i.e.*, the antiendomysial antibody test (1, 2).

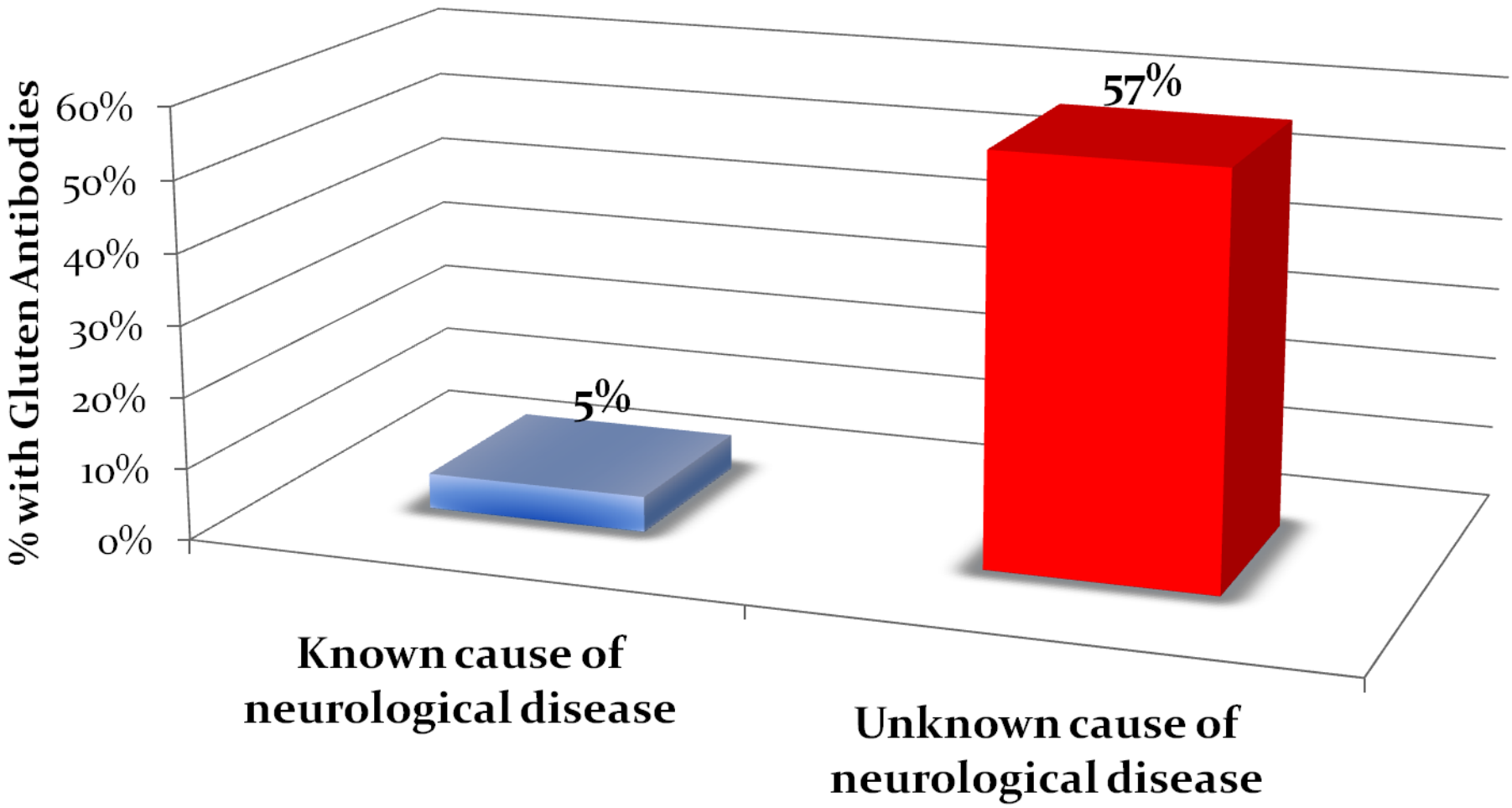
Migraine is the most frequent subtype of primary headache, affecting about 15–18% of women and 6% of men in the general population (3). According to the criteria estab-

reports have suggested a possible causative association between CD and migraine (6, 7).

A disordered vascular tone of particular arterial distributions has been invoked to explain the pathogenetic pathway of migraine. However, conflicting data exist on this topic. Some studies on blood flow in migraine patients, obtained by ^{99m}Tc hexemethyl-propyleneamineoxime single photon emission CT (SPECT) technique, showed that an impaired regional vascular self-regulation may exist even during headache free intervals, revealing clear interhemispheric asymmetry in the upper frontal and occipital regions (8). Other investigators reported no significant asymmetries in regional cerebral blood flow in patients with migraine outside or during the attacks (9). Moreover, a recent report showed a region of severe hypoperfusion of the left frontal area in a patient with CD and schizophrenic symptoms that both completely resolved after a gluten free diet (10).

The aims of the study were: 1) to assess the prevalence of CD in patients with migraine by means of serology and intestinal biopsy samples and to compare this prevalence with that of a control group; 2) to determine whether SPECT abnormalities are present in migraine patients with CD; and

J Neurol Neurosurg Psychiatry 2002 72: 560-563



When the cause of a neurological disease is known, the percentage of those patients with elevated antibodies to gluten is 5%. When the cause of a neurological disease is unknown, the the percentage of those patients with elevated antibodies to gluten is 57%.

74

Brain (2003), 126, 685±691

DOI: 10.1093/brain/awg050 *Brain* (2003), **126**, 685–691

Gluten ataxia in perspective: epidemiology, genetic susceptibility and clinical characteristics

Marios Hadjivassiliou,[1] Richard Grünewald,[1] Basil Sharrack,[1] David Sanders,[2] Alan Lobo,[2] Clare Williamson,[3] Nicola Woodroofe,[3] Nicholas Wood[4] and Aelwyn Davies-Jones[1]

Departmen... artment of Royal Hall... Hospital, Sciences, S... [4]Departme... Neurology, ... Neurosurgery, Queen Square, London, UK

Two hundred and twenty-four patients with various causes of ataxia

Summary

We previously have described a group of patients with gluten sensitivity presenting with ataxia (gluten ataxia) and suggested that this disease entity may account for a large number of patients with sporadic idiopathic ataxia. We have therefore investigated the prevalence of gluten sensitivity amongst a large cohort of patients with sporadic and familial ataxia and looked at possible genetic predisposition to gluten sensitivity amongst these groups. Two hundred and twenty-four patients with various causes of ataxia from North Trent (59 familial and/or positive normal controls. The prevalence in the sporadic idiopathic group from London was 14 out of 44 (32%). The difference in prevalence between the idiopathic sporadic groups and the other groups was highly significant ($P < 0.0001$ and $P < 0.003$, respectively). The clinical characteristics of 68 patients with gluten ataxia were as follows: the mean age at onset of the ataxia was 48 years (range 14–81 years) with a mean duration of the ataxia of 9.7 years (range 1–40 years). Ocular signs were observed in 84% and dysarthria in 66%. Upper limb ataxia was evident in

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The prevalence of (elevated) antigliadin antibodies:

- **8 out of 59 (14%) in the familial atrophy group**
- **54 out of 132 (41%) in the sporadic idiopathic group,**
- **5 out of 33 (15%) in the Multiple System Atrophy group**

with gluten sensitivity presenting with ataxia (gluten ataxia) and suggested that this disease entity may account for a large number of patients with sporadic idiopathic ataxia. We have therefore investigated the prevalence of gluten sensitivity amongst a large cohort of patients with sporadic and familial ataxia and looked at possible genetic predisposition to gluten sensitivity amongst these groups. Two hundred and twenty-four patients with various causes of ataxia from North Trent (59 familial and/or positive pathic group from London was 14 out of 44 (32%). The difference in prevalence between the idiopathic sporadic groups and the other groups was highly significant ($P < 0.0001$ and $P < 0.003$, respectively). The clinical characteristics of 68 patients with gluten ataxia were as follows: the mean age at onset of the ataxia was 48 years (range 14–81 years) with a mean duration of the ataxia of 9.7 years (range 1–40 years). Ocular signs were observed in 84% and dysarthria in 66%. Upper limb ataxia was evident in

CASE STUDY #2

A 14 year old girl misdiagnosed with psychosis

Nutrients 2015, 7, 5532-5539

Nutrients **2015**, *7*, 5532-5539; doi:10.3390/nu7075235

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ISSN 2072-6643

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Case Report

Gluten Psychosis: Confirmation of a New Clinical Entity

Elena Lionetti [1,*], Salvatore Leonardi [1], Chiara Franzonello [1], Margherita Mancardi [2], Martino Ruggieri [1] and Carlo Catassi [3,4]

In recent studies, NCGS has been related to the appearance of neuro-psychiatric disorders, such as autism, schizophrenia and depression.

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Case Report

Gluten Psychosis: Confirmation of a New Clinical Entity

A 14-year-old girl came to our outpatient clinic for psychotic symptoms that were apparently associated with gluten consumption.

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Case Report

Gluten Psychosis: Confirmation of a New Clinical Entity

In May 2012, after a febrile episode, she became increasingly irritable and reported daily headache and concentration difficulties. One month after, her symptoms worsened presenting with severe headache, sleep problems, and behavior alterations, with several unmotivated crying spells and apathy.

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Case Report

Gluten Psychosis: Confirmation of a New Clinical Entity

Her school performance deteriorated, as reported by her teachers. The mother noted severe halitosis, never suffered before. The patient was referred to a local neuropsychiatric outpatient clinic, where a conversion somatic disorder was diagnosed and a benzodiazepine treatment (*i.e.*, bromazepam) was started.

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Case Report

Gluten Psychosis: Confirmation of a New Clinical Entity

In June 2012, during the final school examinations, psychiatric symptoms, occurring sporadically in the previous two months, worsened. Indeed, she began to have complex hallucinations. The types of these hallucinations varied and were reported as indistinguishable from reality (she saw people coming off the television to follow and scare her).

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Case Report

Gluten Psychosis: Confirmation of a New Clinical Entity

She also presented weight loss (about 5% of her weight) and gastrointestinal symptoms such as abdominal distension and severe constipation. She was admitted to a psychiatric ward.

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Case Report

A computed tomography scan of the brain and a blood pressure holter were also performed and resulted normal. Electroencephalogram (EEG) showed mild nonspecific abnormalities and slow-wave activity. Due to the abnormal autoimmune parameters and the recurrence of psychotic symptoms, autoimmune encephalitis was suspected, and steroid treatment was initiated.

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Case Report

In September 2012, shortly after eating pasta, she presented crying spells, relevant confusion, ataxia, severe anxiety and paranoid delirium. Then she was again referred to the psychiatric unit. A relapse of autoimmune encephalitis was suspected and treatment with endovenous steroid and immunoglobulins was started. During the following months, several hospitalizations were done, for recurrence of psychotic symptoms.

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Nutrients 2015, 7, 5532-5539

Nutrients **2015**, *7*, 5532-5539; doi:10.3390/nu7075235

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Case Report

Cerebral and spinal cord magnetic resonance imaging, lumbar puncture, and fundus oculi examination did not show any pathological signs. Several EEG were performed confirming bilateral slow activity. The laboratory tests showed only mild microcytic anemia with reduced levels of ferritin and a slight increase in fecal calprotectin values.
All markers for CD were negative.

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Case Report

In September 2013, she presented with severe abdominal pain, associated with asthenia, slowed speech, depression, distorted and paranoid thinking and suicidal ideation up to a state of pre-coma. The clinical suspicion was moving towards a fluctuating psychotic disorder. Treatment with a second-generation anti-psychotic (*i.e.*, olanzapine) was started, but psychotic symptoms persisted.

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Case Report

November 2013, due to gastro-intestinal symptoms and further weight loss (about 15% of her weight in the last year), a nutritionist was consulted, and a gluten-free diet (GFD) was recommended for symptomatic treatment of the intestinal complaints; unexpectedly, within a week of gluten-free diet, the symptoms (both gastro-intestinal and psychiatric) dramatically improved, and the GFD was continued for four months.

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Case Report

Until a few years ago, the spectrum of gluten-related disorders included only CD and wheat allergy, therefore our patient would be turned back home as a "psychotic patient" and receive lifelong treatment with anti-psychotic drugs. Recent data, however, suggested the existence of another form of gluten intolerance, known as NCGS

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Case Report

Due to parental choice, the girl did not continue assuming gluten and she started a gluten-free diet with a complete regression of all symptoms within a week. Her mother finally recalled that she was returned a "normal girl". Nine months after definitely starting the GFD, she is still symptoms-free.

E-Mail: margheritamancardi@ospedale-gaslini.ge.it

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Case Report

It has been hypothesized that some neuro-psychiatric symptoms related to gluten may be the consequence of the excessive absorption of peptides with opioid activity that formed from incomplete breakdown of gluten. Increased intestinal permeability, also referred to as "leaky gut syndrome", may allow these peptides to cross the intestinal membrane, enter the bloodstream, and cross the blood brain barrier, affecting the endogenous opiate system and neurotransmission within the nervous system.

MassGeneral Hospital for Children, 55 Fruit Street, Boston, MA 02114, USA

Premise #4

Food selection has a direct impact on dysbiosis and may be an initiating factor in an autoimmune cascade

Detective Adrian Monk

The ISME Journal (2010) 4, 232–241

The ISME Journal (2010) 4, 232–241

www.nature.com/ismej

ORIGINAL ARTICLE

Interactions between gut microbiota, host genetics and diet relevant to development of metabolic syndromes in mice

Diet has a dominating role in shaping gut microbiota and changes of some key populations may transform the gut microbiota into a pathogen-like entity, despite a complete host genome.

Both genetic variations and diet-disrupted gut microbiota can predispose animals to metabolic syndromes (MS). This study assessed the relative contributions of host genetics and diet in shaping the gut microbiota and modulating MS-relevant phenotypes in mice. Together with its wild-type (Wt) counterpart, the *Apoa*-I knockout mouse, which has impaired glucose tolerance (IGT) and increased body fat, was fed a high-fat diet (HFD) or normal chow (NC) diet for 25 weeks. DNA fingerprinting and bar-coded pyrosequencing of 16S rRNA genes were used to profile gut microbiota structures and to identify the key population changes relevant to MS development by Partial Least Square Discriminate Analysis. Diet changes explained 57% of the total structural variation in gut microbiota, whereas genetic mutation accounted for no more than 12%. All three groups with IGT had significantly different gut microbiota relative to healthy Wt/NC-fed animals. In all, 65 species-level phylotypes were identified as key members with differential responses to changes in diet, genotype and MS phenotype. Most notably, gut barrier-protecting *Bifidobacterium* spp. were nearly absent in all animals on HFD, regardless of genotype. Sulphate-reducing, endotoxin-producing bacteria of the family, *Desulfovibrionaceae*, were enhanced in all animals with IGT, most significantly in the Wt/HFD group, which had the highest calorie intake and the most serious MS phenotypes. Thus, diet has a dominating role in shaping gut microbiota and changes of some key populations may transform the gut microbiota of Wt animals into a pathogen-like entity relevant to development of MS, despite a complete host genome.
The ISME Journal (2010) 4, 232–241; doi:10.1038/ismej.2009.112; published online 29 October 2009

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www.nature.com/ismej

ORIGINAL ARTICLE

Interactions between gut microbiota, host genetics and diet relevant to development of metabolic syndromes in mice

Chenhong Zhang[1], Mingkun Zhang[1], Shengxiu Wang[2], Ruijin Han[3], Yanfang Cao[1]

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Shanghai, PR China and [2]Shanghai Centre for Systems Biomedicine, Shanghai, PR China

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Nutrients 2013, 5, 162-207

Review

Nutrition of the Critically Ill—A 21st-Century Perspective

Stig Bengmark

Division of Surgery & Interventional Science, University College London, 4th floor, 74 Huntley

Foods rich in proteotoxins such as gluten, casein, zein, and proteins, have been observed to have endotoxin-like effects that can contribute to dysbiosis

year to undergo major surgery, of which approximately 3 million will never return home from the hospital. Furthermore, the quality of life is reported to be significantly impaired for the rest of the lives of those who, during their hospital stay, suffered life-threatening infections/sepsis. Severe infections are strongly associated with a high degree of systemic inflammation in the body, and intimately associated with significantly reduced and malfunctioning GI microbiota, a condition called dysbiosis. Deranged composition and function of the gastrointestinal microbiota, occurring from the mouth to the anus, has been found to cause impaired ability to maintain intact mucosal membrane functions and prevent leakage of toxins—bacterial endotoxins, as well as whole bacteria or debris of bacteria, the DNA of which are commonly found in most cells of the body, often in adipocytes of obese individuals or in arteriosclerotic plaques. Foods rich in proteotoxins such as gluten, casein and zein, and proteins, have been observed to have endotoxin-like effects that can contribute to dysbiosis. About 75% of the food in the Western diet is of limited or no benefit to the microbiota in the lower gut. Most of it, comprised specifically of refined carbohydrates, is already absorbed in the upper part of the GI tract, and what eventually reaches the large intestine is of limited value, as it contains only small amounts of the minerals, vitamins and other nutrients necessary for maintenance of the microbiota. The consequence is that the microbiota of modern humans is greatly reduced, both in terms of numbers and diversity when compared to the diets of our paleolithic forebears and the individuals living a rural lifestyle today. It is the artificial treatment provided in modern medical care—unfortunately often the only alternative provided—which constitute the main contributors to a poor outcome. These treatments include artificial ventilation, artificial nutrition, hygienic measures, use of skin-penetrating devices, tubes and catheters,

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About 75% of the food in the Western diet is of limited or no benefit to the microbiota in the lower gut.

Abstract: Health care-induced diseases constitute a fast-increasing problem. Just one type of these health care-associated infections (HCAI) constitutes the fourth leading cause of death in Western countries. About 25 million individuals worldwide are estimated each year to undergo major surgery, of which approximately 3 million will never return home from the hospital. Furthermore, the quality of life is reported to be significantly impaired for the rest of the lives of those who, during their hospital stay, suffered life-threatening infections/sepsis. Severe infections are strongly associated with a high degree of systemic inflammation in the body, and intimately associated with significantly reduced and malfunctioning GI microbiota, a condition called dysbiosis. Deranged composition and function of the gastrointestinal microbiota, occurring from the mouth to the anus, has been found to cause impaired ability to maintain intact mucosal membrane functions and prevent leakage of toxins—bacterial endotoxins, as well as whole bacteria or debris of bacteria, the DNA of which are commonly found in most cells of the body, often in adipocytes of obese individuals or in arteriosclerotic plaques. Foods rich in proteotoxins such as gluten, casein and zein, and proteins, have been observed to have endotoxin-like effects that can contribute to dysbiosis. About 75% of the food in the Western diet is of limited or no benefit to the microbiota in the lower gut. Most of it, comprised specifically of refined carbohydrates, is already absorbed in the upper part of the GI tract, and what eventually reaches the large intestine is of limited value, as it contains only small amounts of the minerals, vitamins and other nutrients necessary for maintenance of the microbiota. The consequence is that the microbiota of modern humans is greatly reduced, both in terms of numbers and diversity when compared to the diets of our paleolithic forebears and the individuals living a rural lifestyle today. It is the artificial treatment provided in modern medical care—unfortunately often the only alternative provided—which constitute the main contributors to a poor outcome. These treatments include artificial ventilation, artificial nutrition, hygienic measures, use of skin-penetrating devices, tubes and catheters,

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Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa

PNAS | August 17, 2010 | vol. 107 | no. 33

Carlotta De Filippo[a], Duccio Cavalieri[a], Monica Di Paola[b], Matteo Ramazzotti[c], Jean Baptiste Poullet[d], Sebastien Massart[d], Silvia Collini[b], Giuseppe Pieraccini[e], and Paolo Lionetti[b,1]

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Edited* by Daniel L. Hartl, Harvard University, Cambridge, MA, and approved June 30, 2010 (received for review April 29, 2010)

Gut microbial composition depends on different dietary habits just as health depends on microbial metabolism, but the association of microbiota with different diets in human populations has not yet been shown. In this work, we compared the fecal microbiota of European children (EU) and that of children from a rural African village of Burkina Faso (BF), where the diet, high in fiber content, is similar to that of early human settlements at the time of the birth of agriculture. By using high-throughput 16S rDNA sequencing and biochemical analyses, we found significant differences in gut microbiota between the two groups. BF children showed a significant enrichment in Bacteroidetes and depletion in Firmicutes ($P < 0.001$), with a unique abundance of bacteria from the genus *Prevotella* and *Xylanibacter*, known to contain a set of bacterial genes for cellulose and xylan hydrolysis, completely lacking in the EU children. In addition, we found significantly more short-chain fatty acids ($P < 0.001$) in BF than in EU children. Also, *Enterobacteriaceae* (*Shigella* and *Escherichia)* were significantly underrepresented in BF than in EU children ($P < 0.05$). We hypothesize that gut microbiota coevolved with the polysaccharide-rich diet of BF individuals, allowing them to maximize energy intake from fibers while also protecting them from inflammations and noninfectious colonic diseases. This study investigates and compares human intestinal microbiota from children characterized by a modern western diet and a rural diet, indicating the importance of preserving this treasure of microbial diversity from ancient rural communities worldwide.

created selective pressure that favored pathogens specialized in colonizing human hosts and probably produced the first wave of emerging human diseases (5). It has been hypothesized that bacteria specialized in human-associated niches, including our gut commensal flora, underwent intense transformation during the social and demographic changes that took place with the first Neolithic settlements (6).

Western developed countries successfully controlled infectious diseases during the second half of the last century, by improving sanitation and using antibiotics and vaccines. At the same time, a rise in new diseases such as allergic, autoimmune disorders, and inflammatory bowel disease (IBD) both in adults and in children has been observed (5), and it is hypothesized that improvements in hygiene together with decreased microbial exposure in childhood are considered responsible for this increase (7). The GI microflora plays a crucial role in the pathogenesis of IBD (8), and recent studies demonstrate that obesity is associated with imbalance in the normal gut microbiota (9, 10).

The aim of this study was to compare the gut microbiota of children aged 1–6 y living in a village of rural Africa in an environment that still resembles that of Neolithic subsistence farmers with the gut microbiota of western European children of the same age, eating the diet and living in an environment typical of the developed world. These two childhood populations provided an attractive model for assessing the impact of many environ-

PNAS | August 17, 2010 | vol. 107 | no. 33

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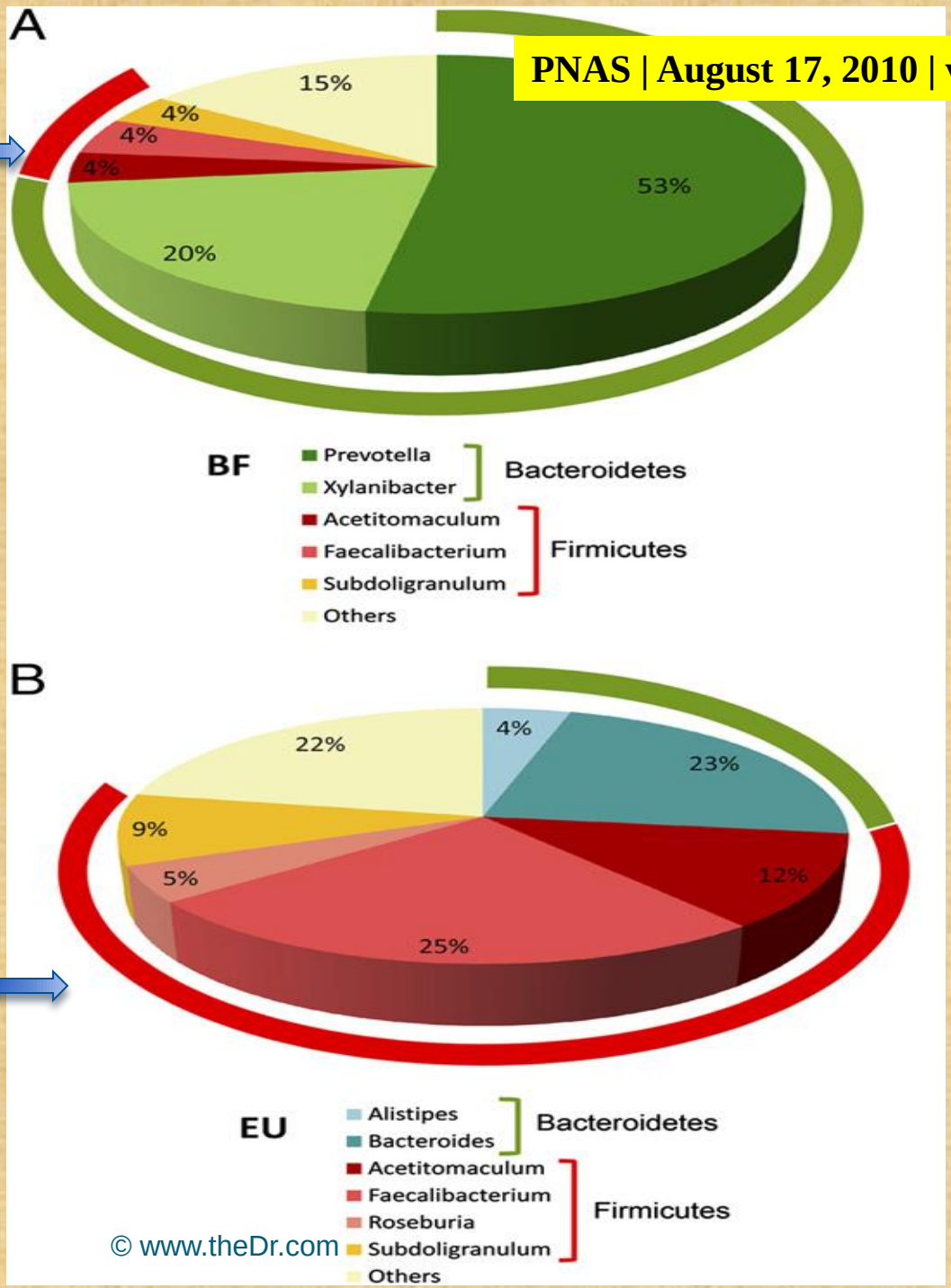

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Review

Nutrition of the Critically Ill—A 21st-Century Perspective

Stig Bengmark

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Attempts to reconstitute a normal microbiome by supply of probiotics have often failed as they are almost always undertaken as a complement to—and not as an alternative to—existing treatment schemes, especially those based on antibiotics, but also other pharmaceuticals.

functions and prevent leakage of toxins—bacterial endotoxins, as well as whole bacteria or debris of bacteria, the DNA of which are commonly found in most cells of the body, often in adipocytes of obese individuals or in arteriosclerotic plaques. Foods rich in proteotoxins such as gluten, casein and zein, and proteins, have been observed to have endotoxin-like effects that can contribute to dysbiosis. About 75% of the food in the Western diet is of limited or no benefit to the microbiota in the lower gut. Most of it, comprised specifically of refined carbohydrates, is already absorbed in the upper part of the GI tract, and what eventually reaches the large intestine is of limited value, as it contains only small amounts of the minerals, vitamins and other nutrients necessary for maintenance of the microbiota. The consequence is that the microbiota of modern humans is greatly reduced, both in terms of numbers and diversity when compared to the diets of our paleolithic forebears and the individuals living a rural lifestyle today. It is the artificial treatment provided in modern medical care—unfortunately often the only alternative provided—which constitute the main contributors to a poor outcome. These treatments include artificial ventilation, artificial nutrition, hygienic measures, use of skin-penetrating devices, tubes and catheters,

Silently
Point to 2 People
Close By

1) **What recommendations do you currently give in your Practice to enhance the microbiome**

Premise #5

Both Parkinson's and Alzheimer's diseases involve the formation of transmissible self-propagating prion-like proteins.

Journal of Alzheimer's Disease 45 (2015) 349–362

Detective Adrian Monk

‘Transmissible’ from where

Detective Adrian Monk

Cell. Mol. Life Sci. (2013) 70:55–69
DOI 10.1007/s00018-012-1028-z

Cellular and Molecular Life Sciences

Cell. Mol. Life Sci. (2013) 70:55–69

REVIEW

Voices from within: gut microbes and the CNS

Paul Forsythe · Wolfgang A. Kunze

Received: 8 March 2012 / Revised: 3 May 2012 / Accepted: 7 May 2012 / Published online: 27 May 2012

There is now robust evidence that gut bacteria influence the enteric nervous system, an effect that may contribute to afferent signaling to the brain.

and centrally. Effects of commensal gut bacteria in adult animals include protection from the central effects of infection and inflammation as well as modulation of normal behavioral responses. There is now robust evidence that gut bacteria influence the enteric nervous system, an effect that may contribute to afferent signaling to the brain. The vagus nerve has also emerged as an important means of communicating signals from gut bacteria to the CNS. Further understanding of the mechanisms underlying

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Microbiota–gut–brain axis

It is now well established that the brain and the gut are engaged in constant bi-directional communication. Most individuals are made aware of such communication when alteration in gastrointestinal function is communicated to the brain bringing about the perception of visceral events such as nausea, satiety, and pain or when, in turn, stressful experiences lead to altered gastrointestinal secretions and motility [1].

The mechanisms underlying gut–brain axis communication involve neural pathways as well as immune and endocrine mechanisms. The gastrointestinal tract is a point of interaction between the body's largest concentration of immune cells, a vast network of 500 million neurons and the gut microbiota. With an estimated mass of 1–2 kg, the approximately 100 trillion bacteria that constitute the human gut microbiota consist of at least 1,800 genera and up to 40,000 species of bacteria [2] and together possess 100 times the number of genes in the human genome [3]. Given the scale of the metabolic and genetic coding capacity of this "virtual organ", it is not surprising that the gut microbiota impacts various aspects of host physiology [4–7]. It is now clear that these influences include modulation of gut–brain communication. Indeed, it is emerging

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There is now strong evidence that gut microorganisms can activate the vagus nerve, and that such activation plays a critical role in mediating effects on the brain and, subsequently, behavior.

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Increased Intestinal Permeability Correlates with Sigmoid Mucosa alpha-Synuclein Staining and Endotoxin Exposure Markers in Early Parkinson's Disease

Christopher B. Forsyth[1]*, Kathleen M. Shannon[2], Jeffrey H. Kordower[3], Robin M. Voigt[1], Maliha Shaikh[1], Jean A. Jaglin[2], Jacob D. Estes[4], Hemraj B. Dodiya[3], Ali Keshavarzian[1]

1 Department of Internal Medicine, Section of Gastroenterology, Rush University Medical Center, Chicago, Illinois, United States of America, 2 Department of Neurological Sciences, Rush University Medical Center, Chicago, Illinois, United States of America, 3 Center for Brain Repair, Rush Medical College, Chicago, Illinois, United States of America, 4 AIDS and Cancer Virus Program, SAIC-Frederick, Inc., National Cancer Institute-Frederick, Frederick, Maryland, United States of America

Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disorder of aging. The pathological hallmark of PD

negative bacteria and tissue oxidative stress. Our study may thus shed new light on PD pathogenesis as well as provide a new method for earlier diagnosis of PD and suggests potential therapeutic targets in PD subjects.

Trial Registration: Clinicaltrials.gov NCT01155492

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Over the last decade there has been mounting evidence that supports a role for the GI tract and the enteric nervous system (ENS) in the pathogenesis of PD

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The GI system and the brain are directly linked anatomically with the dorsal motor nucleus of the vagus nerve, a brain region proposed to express Lewy pathology very early in the disease process.

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Gut leakiness in patients with a genetic susceptibility to PD may be a pivotal early step promoting a pro-inflammatory/oxidative environment contributing to the initiation and/or progression of the PD process.

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Indeed, it has been suggested that the GI tract might be a portal of entry for a putative PD pathogen, triggering pathological changes in the submucosal/myenteric neurons, which then spread through the vagus nerve to the medulla oblongata

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From there, pathological changes may move rostrally, ultimately resulting in the clinically-defining motor symptoms of PD when there is extensive involvement in the middle portion of the disease at the level of the midbrain substantia nigra.

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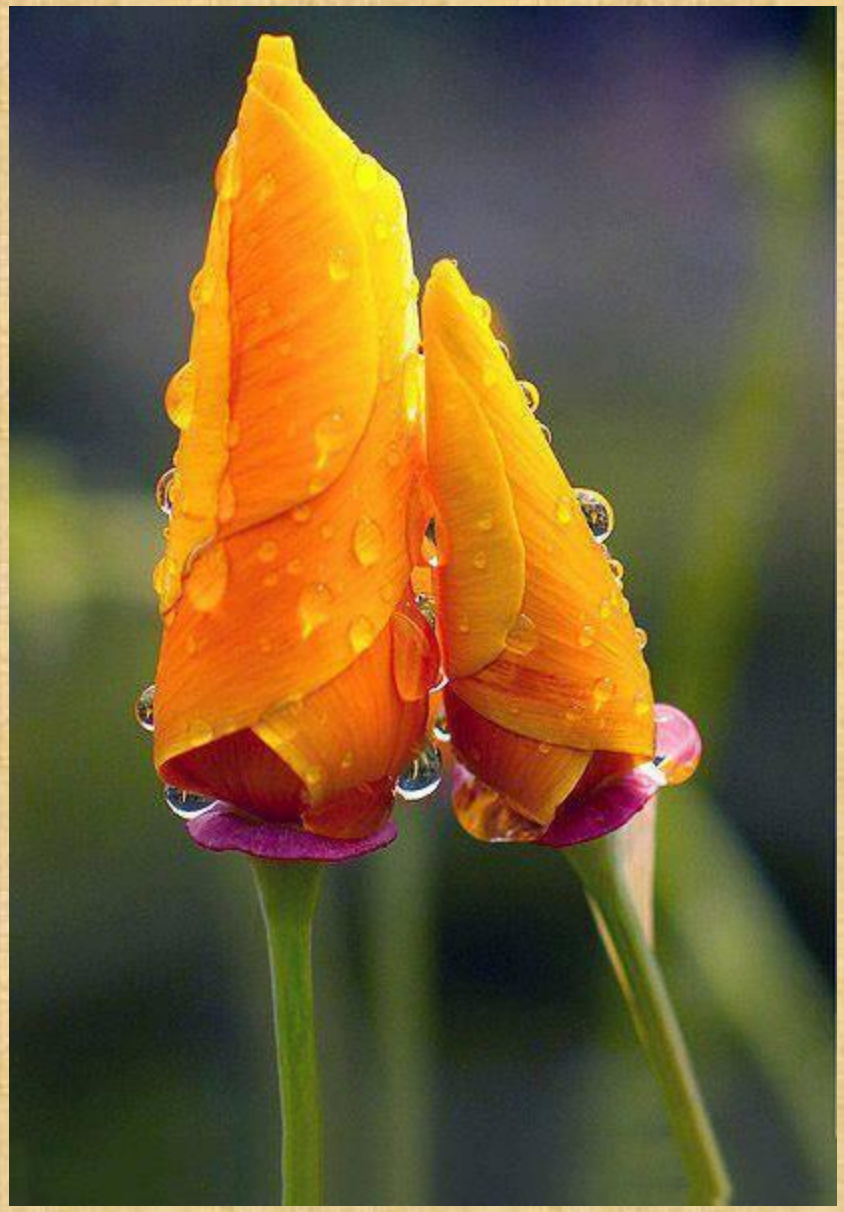

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Hypothesis

Mechanisms of Molecular Mimicry Involving the Microbiota in Neurodegeneration

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This paper describes the specific molecular pathways of these cross-seeding and neuroinflammatory processes.

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Keywords: Alzheimer's disease, amyloid, bacterial amyloid, metagenome, microbiota, neurodegenerative diseases, neuroinflammation, oxidative stress, Parkinson's disease

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Aquaporin 4 Molecular Mimicry and Implications for Neuromyelitis Optica

Radhika A. Vaishnav[1,2], Ruolan Liu[1], Joab Chapman[6], Andrew M. Roberts[2], Hong Ye[3], Jovan D. Rebolledo-Mendez[4], Takeshi Tabira[7], Alicia H. Fitzpatrick[5], Anat Achiron[6], Mark

The spreading in the brain of misfolded Alpha Synuclein and tau appears to be along neuronal connections through axonal membranes utilizing a prion-like cell-to-cell spread with neuronal connectivity, not proximity, being critical.

University, Tokyo, Japan

Abstract

Neuromyelitis Optica (NMO) is associated with antibodies to aquaporin 4 (AQP4). We hypothesized that antibodies to AQP4 can be triggered by exposure to environmental proteins. We compared human AQP4 to plant and bacterial proteins to investigate the occurrence of significantly similar structures and sequences. High similarity to a known epitope for NMO-IgG, AQP4(207-232), was observed for corn ZmTIP4-1. NMO and non-NMO serum was assessed for reactivity to AQP4(207-232) and the corn peptide. NMO patient serum showed reactivity to both peptides as well as to plant tissue. These findings warrant further investigation into the role of the environment in NMO etiology.

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Aquaporin 4 Molecular Mimicry and Implications for Neuromyelitis Optica

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Furthermore, myenteric neurons in the gut wall contain alpha synuclein deposits in PD. These findings suggest that the origin of protein misfolding in PD may reside in the gut.

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Abstract

Neuromyelitis Optica (NMO) is associated with antibodies to aquaporin 4 (AQP4). We hypothesized that antibodies to AQP4 can be triggered by exposure to environmental proteins. We compared human AQP4 to plant and bacterial proteins to investigate the occurrence of significantly similar structures and sequences. High similarity to a known epitope for NMO-IgG, AQP4(207-232), was observed for corn ZmTIP4-1. NMO and non-NMO serum was assessed for reactivity to AQP4(207-232) and the corn peptide. NMO patient serum showed reactivity to both peptides as well as to plant tissue. These findings warrant further investigation into the role of the environment in NMO etiology.

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Cellular and Molecular Life Sciences

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REVIEW

Voices from within: gut microbes and the CNS

Paul Forsythe · Wolfgang A. Kunze

There is now evidence that these central responses to intentional infection and inflammation may be modulated by commensal bacteria.

with the influence of pivotal species that induce specific responses, can modulate adult neural function, peripherally and centrally. Effects of commensal gut bacteria in adult animals include protection from the central effects of infection and inflammation as well as modulation of normal behavioral responses. There is now robust evidence that gut bacteria influence the enteric nervous system, an effect that may contribute to afferent signaling to the brain. The vagus nerve has also emerged as an important means of communicating signals from gut bacteria to the CNS. Further understanding of the mechanisms underlying

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Microbiota–gut–brain axis

It is now well established that the brain and the gut are engaged in constant bi-directional communication. Most individuals are made aware of such communication when alteration in gastrointestinal function is communicated to the brain bringing about the perception of visceral events such as nausea, satiety, and pain or when, in turn, stressful experiences lead to altered gastrointestinal secretions and motility [1].

The mechanisms underlying gut–brain axis communication involve neural pathways as well as immune and endocrine mechanisms. The gastrointestinal tract is a point of interaction between the body's largest concentration of immune cells, a vast network of 500 million neurons and the gut microbiota. With an estimated mass of 1–2 kg, the approximately 100 trillion bacteria that constitute the human gut microbiota consist of at least 1,800 genera and up to 40,000 species of bacteria [2] and together possess 100 times the number of genes in the human genome [3]. Given the scale of the metabolic and genetic coding capacity of this "virtual organ", it is not surprising that the gut microbiota impacts various aspects of host physiology [4–7]. It is now clear that these influences include modulation of gut–brain communication. Indeed, it is emerging

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Voices from within: gut microbes and the CNS

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Similarly, a number of studies have demonstrated that gut bacteria influence BDNF levels, particularly in the hippocampus.

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We are at the very early stages of understanding the complex communication systems between gut bacteria and the brain. However, there is already strong supporting evidence for what was, only a few years ago, a largely hypothetical relationship between the gut microbiota, mood, and behavior

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Premise #6

A GFD may contribute to dysbiosis

Detective Adrian Monk

British Journal of Nutrition (2009), 102, 1154–1160

Br J of Nutrition (2009), 102, 1154–1160

Effects of a gluten-free diet on gut microbiota and immune function in healthy adult human subjects

Giada De Palma, Inmaculada Nadal, Maria Carmen Collado and Yolanda Sanz*

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(Received 13 August 2008 – Revised 3 April 2009 – Accepted 6 April 2009 – First published online 18 May 2009)

Diet influences the composition of the gut microbiota and host's health, particularly in patients suffering from food-related diseases.

British Journal of Nutrition

Intestinal microbiota: Gluten-free diet: Coeliac disease: Immunity

Diet influences the composition and function of the gut microbiota and thereby the host's health, particularly in patients suffering from food-related diseases. Coeliac disease (CD) is an inflammatory disorder of the small intestine caused by a permanent intolerance to gluten proteins in predisposed individuals. In these patients, gluten peptides trigger an abnormal immune response that causes the typical CD tissue lesion characterised by villous atrophy, crypt hyperplasia, and increased numbers of intra-epithelial and lamina propria lymphocytes[1,2]. CD enteropathy is sustained by a T-helper (Th)1 immune response with production of pro-inflammatory cytokines (for example, interferon (IFN)-γ), as well as by an innate immune response mediated by IL-15 that activates intra-epithelial lymphocytes and epithelial cell killing[3]. Increased production of pro-inflammatory cytokines by cells of the innate immune system (monocytes, macrophages and dendritic cells) is also thought to mediate the recruitment of lymphocytes into the lamina propria and epithelium, thus contributing to the disease[4]. The treatment with a gluten-free diet (GFD) usually leads to normalisation of mucosal histology and remission of clinical symptoms. Nevertheless, compliance with this dietary therapy is very complex and patients often suffer from higher health risks and nutritional deficiencies[5,6]. The composition and metabolic activity of the intestinal microbiota is currently thought to be involved in a number of chronic inflammatory disorders. Most recent studies indicate that CD patients untreated and treated with a GFD have unbalanced microbiota that can play a pathogenic role or constitute a risk factor for this disorder[7,8]. Nevertheless, part of the detected microbial changes could be due not only to the underlying disease but also to the dietary intervention by a GFD in treated CD patients. A GFD has also been tested as dietary treatment for autism[9]. However, the possible effect of a GFD in the gut ecosystem remains largely unknown.

The objective of the present study was to analyse the impact of a GFD on the composition and immune function of the microbiota in healthy subjects to gain further insights on interactions between diet and gut microbes, as well as on

Abbreviations: CD, coeliac disease; FISH, fluorescence *in situ* hybridisation; GFD, gluten-free diet; IFN, interferon; IQR, interquartile range; PBMC, peripheral blood mononuclear cells; qPCR, quantitative PCR; Th, T-helper.

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In the present preliminary study, the effects of a GFD on the composition and immune function of the gut microbiota were analysed in ten <u>healthy</u> subjects (mean age 30·3 years) over 1 month.

British NS

Diet influences the composition and function of the gut microbiota and thereby the host's health, particularly in patients suffering from food-related diseases. Coeliac disease (CD) is an inflammatory disorder of the small intestine caused by a permanent intolerance to gluten proteins in predisposed individuals. In these patients, gluten peptides trigger an abnormal immune response that causes the typical CD tissue lesion characterised by villous atrophy, crypt hyperplasia, and increased numbers of intra-epithelial and lamina propria lymphocytes[1,2]. CD enteropathy is sustained by a T-helper (Th)1 immune response with production of pro-inflammatory cytokines (for example, interferon (IFN)-γ), as well as by an innate immune response mediated by IL-15 that activates intra-epithelial lymphocytes and epithelial cell killing[3]. Increased production of pro-inflammatory cytokines by cells of the innate immune system (monocytes, macrophages and dendritic cells) is also thought to mediate the recruitment of lymphocytes into the lamina propria and epithelium, thus contributing to the disease[4]. The treatment with a gluten-free diet (GFD) usually leads to normalisation of mucosal histology and remission of clinical symptoms. Nevertheless, compliance with this dietary therapy is very complex and patients often suffer from higher health risks and nutritional deficiencies[5,6]. The composition and metabolic activity of the intestinal microbiota is currently thought to be involved in a number of chronic inflammatory disorders. Most recent studies indicate that CD patients untreated and treated with a GFD have unbalanced microbiota that can play a pathogenic role or constitute a risk factor for this disorder[7,8]. Nevertheless, part of the detected microbial changes could be due not only to the underlying disease but also to the dietary intervention by a GFD in treated CD patients. A GFD has also been tested as dietary treatment for autism[9]. However, the possible effect of a GFD in the gut ecosystem remains largely unknown.

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Bifidobacterium, Clostridium lituseburense and Faecalibacterium prausnitzii proportions decreased as a result of the GFD analysed by FISH. Bifidobacterium, Lactobacillus and Bifidobacterium longum counts decreased, while Enterobacteriaceae and Escherichia coli counts increased after the GFD.

predisposed individuals. In these patients, gluten peptides trigger an abnormal immune response that causes the typical CD tissue lesion characterised by villous atrophy, crypt hyperplasia, and increased numbers of intra-epithelial and lamina propria lymphocytes[1,2]. CD enteropathy is sustained by a T-helper (Th)1 immune response with production of pro-inflammatory cytokines (for example, interferon (IFN)-γ), as well as by an innate immune response mediated by IL-15 that activates intra-epithelial lymphocytes and epithelial cell killing[3]. Increased production of pro-inflammatory cytokines by cells of the innate immune system (monocytes, macrophages and dendritic cells) is also thought to mediate the recruitment of lymphocytes into the lamina propria and epithelium, thus contributing to the disease[4]. The treatment with a gluten-free diet (GFD) usually leads

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TNF-a, interferon-g, IL-10 and IL-8 production was also reduced after the diet.

longus counts decreased ($P=0.020$, $P=0.001$ and $P=0.017$, respectively), while *Enterobacteriaceae* and *Escherichia coli* counts increased ($P=0.005$ and $P=0.003$) after the GFD assessed by qPCR. TNF-α, interferon-γ, IL-10 and IL-8 production by PBMC stimulated with faecal samples was also reduced ($P=0.021$, $P=0.037$, $P=0.002$ and $P=0.007$, respectively) after the diet. Therefore, the GFD led to reductions in beneficial gut bacteria populations and the ability of faecal samples to stimulate the host's immunity. Thus, the GFD may constitute an environmental variable to be considered in treated CD patients for its possible effects on gut health.

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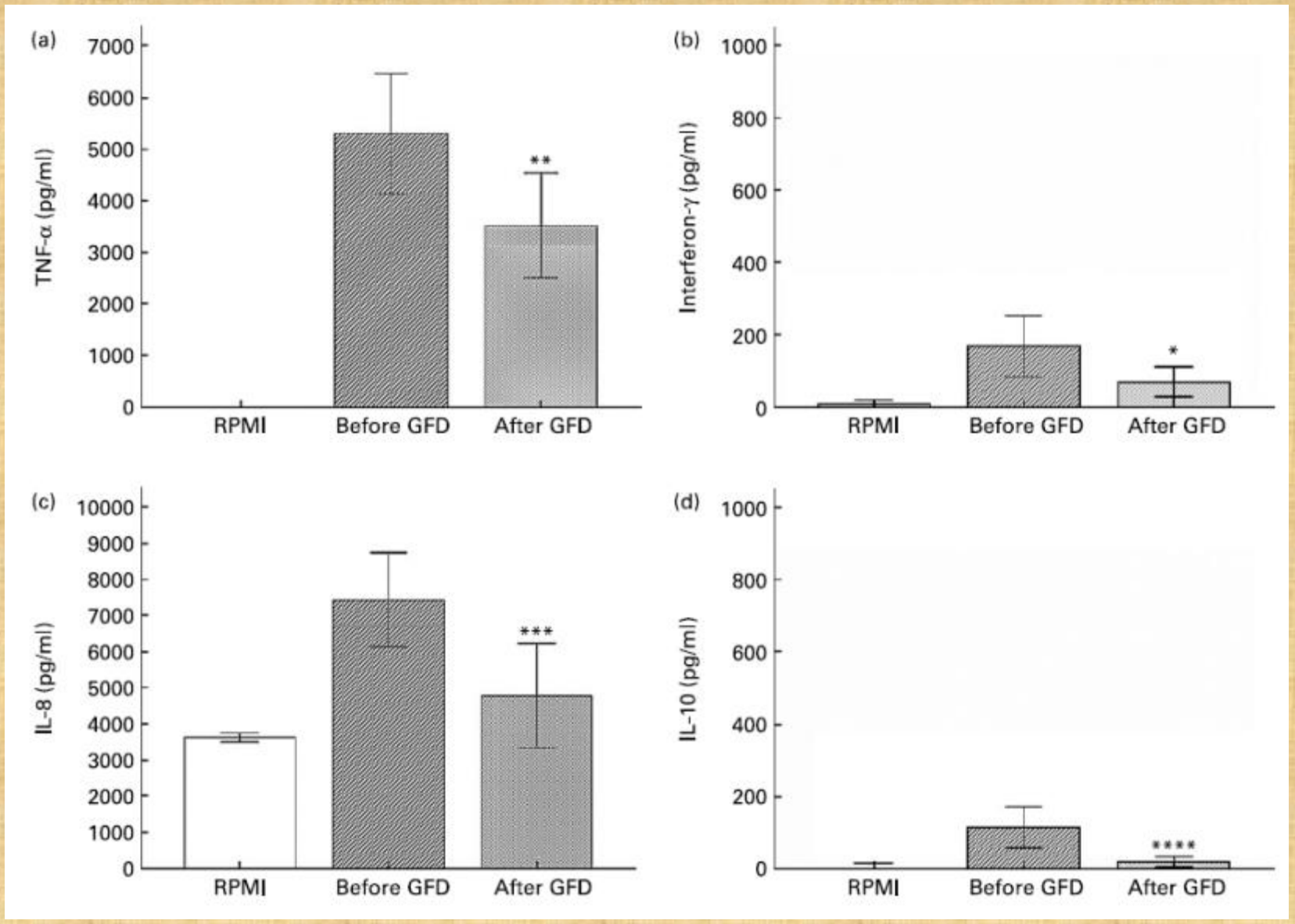

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CASE STUDY #3

a broad-based gait leaning to the right, dysmetria with right finger-to-nose, hyperreflexia, an upgoing right toe, right lower extremity weakness, and right foot drop.

146

CASE REPORT

White Matter Lesions Suggestive of Amyotrophic Lateral Sclerosis Attributed to Celiac Disease

K.J. Brown
V. Jewells
H. Herfarth
M. Castillo

SUMMARY: CD is an autoimmune-mediated disorder of the gastrointestinal tract. Initial symptom presentation is variable and can incl... athy, dizziness, epilepsy, and cortical ... management. We present a case of a ... imaging findings worrisome for ALS ... discovered, and CD was confirmed by upper gastrointestinal endoscopy with duodenal biopsies. MR imaging findings suggestive of ALS improved after gluten-free diet institution.

ABBREVIATIONS: ALS = amyotrophic lateral sclerosis; CD = celiac disease; FLAIR = fluid-attenuated inversion recovery; IgA = immunoglobulin A

Am J Neuroradiol. 2010 May;31(5):880-1

A 32-year-old man with a 1-year history of balance difficulties presented with 1 week of worsening symptoms, including hand tremors and gait disturbance.

Celiac disease is an inflammatory condition of the small intestine also called celiac sprue, nontropical sprue, and gluten-sensitive enteropathy. The most common presenting symptoms in...

right finger-to-nose, hyperreflexia, an upgoing right toe, right lower extremity weakness, and right foot drop. Sensation was normal. Laboratory studies revealed a slightly elevated phosphorus concentration (4.8 mg/dL), but findings were otherwise normal. Brain MR imaging showed abnormal increased signal intensity on T2 and FLAIR in the bilateral corona radiata, extending inferiorly into the corticospinal tracts without contrast enhancement (Fig 1).

Initial diagnostic considerations included ALS and Friedrich ataxia. Electromyelography findings of the right upper and lower extremities were normal. Total spine MR imaging and CT findings of the chest, abdomen, and pelvis were normal. CSF findings for herpes simplex virus, human herpesvirus 6 cytomegalovirus, varicella-zoster virus, Epstein-Barr virus, and Venereal Disease Research Laboratory test were negative, but +4 oligoclonal bands were noted. Findings were negative for paraneoplastic antibodies. Ataxia work-up included a positive antiendomysial antibody titer of 1:160. Duodenal biopsies yielded crypt hyperplastic villous atrophy with numerous intraepithelial lymphocytes, most consistent with gluten-sensitive enteropathy.

The patient started a strict gluten-free diet with improvement of symptoms during the next several months. Repeat brain MR imaging (23 months after initial presentation) revealed resolution of initial abnormalities (Fig 2). Continued physical therapy and a gluten-free diet have been prescribed.

viduals by ingestion of foods containing gluten, such as wheat, rye, and barley. Consumption of triggering foods leads to an autoimmune-mediated inflammatory response in the small intestine, resulting in villous atrophy and malabsorption.[3] The most common presenting symptoms include diarrhea, steatorrhea, weight loss, iron deficiency anemia, and abdominal distension.

The diagnosis is sometimes difficult to make given that not all patients present in the same manner and that symptoms overlap other gastrointestinal disorders. Half of patients have iron deficiency anemia or osteoporosis, without diarrhea. Diagnostic evaluation for CD consists of antibody testing and duodenal biopsy.[4] The most sensitive and specific antibodies for its confirmation are tissue transglutaminase IgA and endomysial IgA antibodies. Due to the low specificity compared with tissue transglutaminase and endomysium antibodies, gliadin antibodies should no longer be used in the diagnostic work-up for CD. Duodenal biopsies are still the criterion standard for tissue diagnosis and reveal villous atrophy[5] and increased intraepithelial lymphocytes.[6]

Neurologic findings associated with CD disease were initially reported in 1966 by Cooke and Smith.[7] Most common symptoms are ataxia and neuropathy, followed by epilepsy, ALS and multiple sclerosis-like symptoms, isolated motor neuron disorders, sensory ataxia, and dizziness. These complications may arise as consequences of vitamin and mineral deficiencies. Other authors discuss a potential pathophysiologic role of antigliadin antibodies in a neurotoxic autoimmune process.[8]

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DOI 10.3174/ajnr.A1926

CASE REPORT

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ABBREVIATIONS: ALS = amyotrophic lateral sclerosis; CD = celiac disease; FLAIR = fluid-attenuated inversion recovery; IgA = immunoglobulin A

Admission review of systems revealed a 60 pound (27.22 kg) weight loss during the past year, which he attributed to diarrhea consisting of 3–4 loose stools per day.

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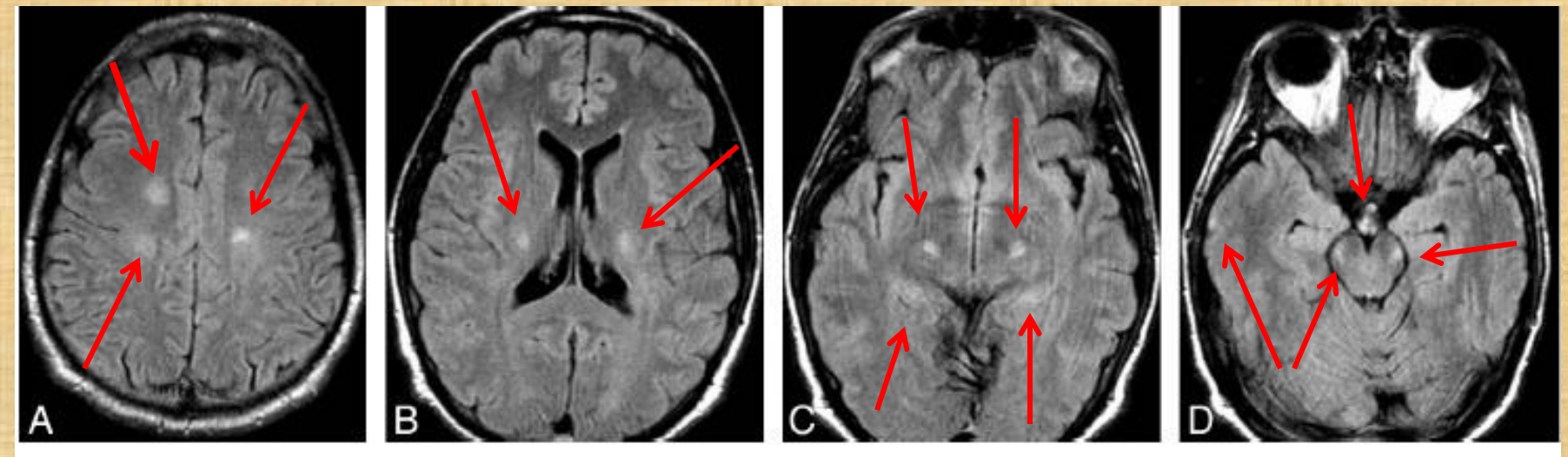

Fig 1. FLAIR images from initial brain MR imaging demonstrate abnormal increased signal intensity in the white matter of the centra semiovale and bilateral corticospinal tracts.

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and gait disturbance. Admission review of systems revealed a 60-pound (27.22 kg) weight loss during the past year, which he attributed to diarrhea consisting of 3–4 loose stools per day. Physical examination showed a broad-based gait leaning to the right, dysmetria with right finger-to-nose, hyperreflexia, an upgoing right toe, right lower extremity weakness, and right foot drop. Sensation was normal. Laboratory studies revealed a slightly elevated phosphorus concentration (4.8 mg/dL), but findings were otherwise normal. Brain MR imaging showed abnormal increased signal intensity on T2 and FLAIR in the bilateral corona radiata, extending inferiorly into the corticospinal tracts without contrast enhancement (Fig 1).

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insulin-dependent diabetes mellitus, IgA deficiency, and rheumatoid arthritis.[1]

Symptoms are precipitated in genetically predisposed individuals by ingestion of foods containing gluten, such as wheat, rye, and barley. Consumption of triggering foods leads to an autoimmune-mediated inflammatory response in the small intestine, resulting in villous atrophy and malabsorption.[3] The most common presenting symptoms include diarrhea, steatorrhea, weight loss, iron deficiency anemia, and abdominal distension.

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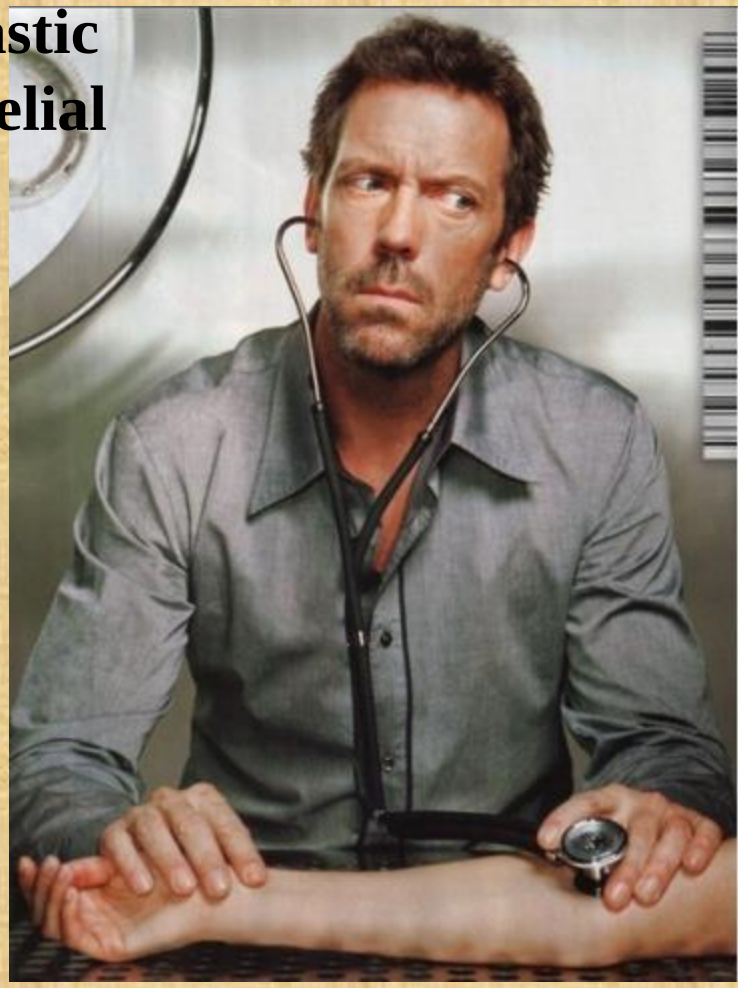

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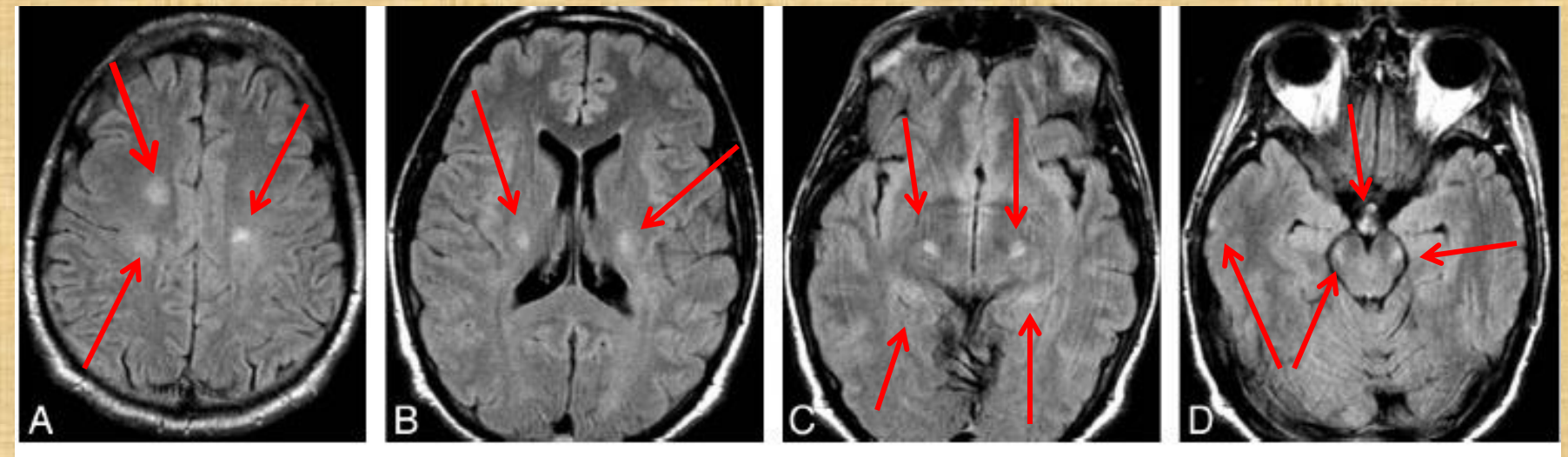

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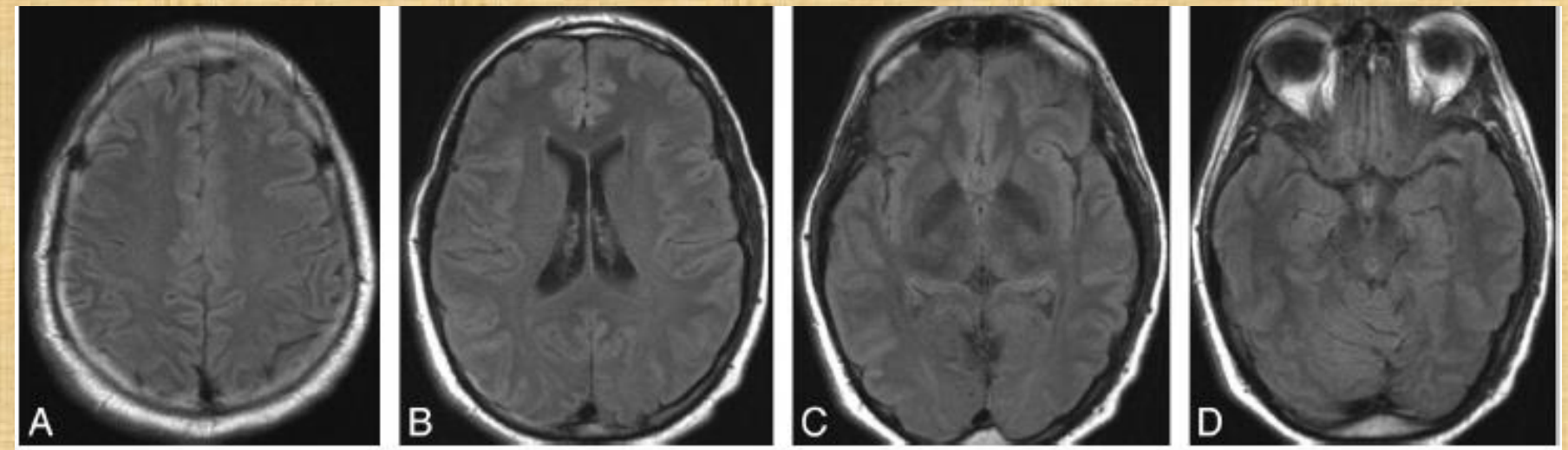

Fig 2. Follow-up FLAIR images after a gluten-free diet show complete resolution of signal-intensity abnormalities.

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"Because ALS is a progressive and untreatable disease while CD is easily treatable, considering the latter as a cause of neurologic disorders in patients with ALS-like symptoms may be indicated".

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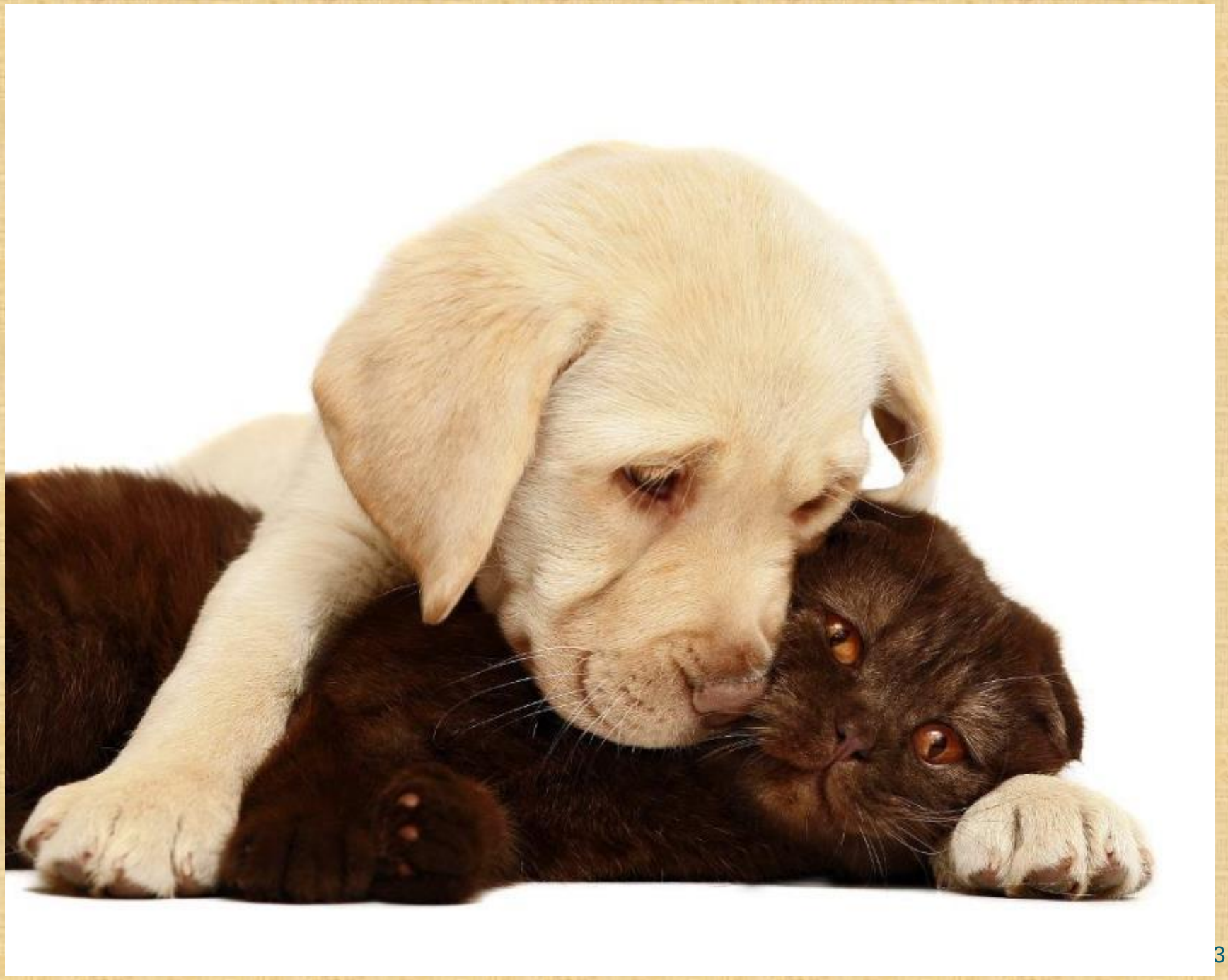
We M at a mic becom nal princ g cl

This is a Primary Contributor to the continued intestinal, then systemic Inflammation increasing Morbidity and Mortality

Premise #7

Every Office benefits from offering SUCCESSFUL, Comprehensive, Thorough Guidance for Patients to Transition into a Microbiome-balancing dietary lifestyle via a Well-Trained Nutritionist, Registered Dietician, or Staff Specialist



Dig Dis Sci
DOI 10.1007/s10620-007-0055-3

Dig Dis Sci. 2008 Jun;53(6):1573-81

ORIGINAL RESEARCH

Factors that Influence Adherence to a Gluten-Free Diet in Adults with Celiac Disease

Daniel A. Leffler · Jessica Edwards-George · Melinda Dennis · Detlef Schuppan · Francis Cook · Debra L. Franko · Jessica Blom-Hoffman · Ciaran P. Kelly

Many individuals were not content with the services provided by their health-care team to help them manage CD.

experienced nutritionist. Multivariate analysis was conducted to determine factors associated with adherence level. *Results* Thirteen factors hypothesized to contribute to gluten-free diet adherence were found to be significantly associated with improved adherence including: understanding of the gluten-free diet, membership of a celiac disease advocacy group, and perceived ability to maintain adherence despite travel or changes in mood or stress ($P < 0.001$). *Conclusions* This study identified specific factors correlated with gluten-free diet adherence. These results provide a foundation for the design of educational interventions to improve adherence.

D. A. Leffler (✉) · J. Edwards-George · M. Dennis · D. Schuppan · C. P. Kelly
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J. Edwards-George · D. L. Franko · J. Blom-Hoffman
Department of Psychology, Northeastern University, Boston, MA, USA

F. Cook
Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA

GFD Gluten-free diet
tTG Tissue transglutaminase

Introduction

There is rapidly rising clinical awareness of celiac disease (CD), which has resulted in increasing rates of diagnosis. These changes reflect recent advances in our understanding of the epidemiology and broad spectrum of clinical presentations of CD [1]. Accurate serological assays to identify untreated CD have resulted in a reevaluation of the population prevalence of CD in the United States and Europe. Multiple studies report the prevalence of CD in populations of European decent to be between 1:67 and 1:250 [2–5]. Furthermore, a growing body of literature supports the notation that CD is a common disease in diverse populations across the globe, especially the Near and Far East, and North Africa [6].

There are important ramifications for an individual who receives a diagnosis of CD. CD is a systemic, immunological disorder in which the sentinel lesion is an enteropathy triggered by polypeptides derived primarily from the prolamine proteins found in wheat, rye, and barley. Ingestion of the offending proteins leads to inflammation and intestinal mucosal damage, which may

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Fortnightly review

Coeliac disease

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Coeliac disease is an inflammatory disease of the upper small intestine and results from gluten ingestion in genetically susceptible individuals.[1,2] Inflammation may lead to the malabsorption of several important nutrients. Clinical and mucosal recovery after institution of a gluten free diet is objective evidence that the enteropathy is gluten induced. In 1950, Dicke observed the central role of gluten in the pathogenesis of coeliac disease.[3] Coeliac disease is closely related to dermatitis herpetiformis.[4] In dermatitis herpetiformis, skin rash

Summary points

In coeliac disease, dietary gluten causes inflammation of the small intestine, which may affect absorption of important nutrients including iron, folic acid, calcium, and fat soluble vitamins

Studies show coeliac disease to be a common disorder possibly affecting 1 in 200 of the general

Treatment consists of permanent withdrawal of gluten from the diet, which results in complete remission

The complex manufacture of modern processed food means that the <u>ongoing</u> advice of a <u>trained</u> Dietician (or Nutritionist) is required.

into intestinal features and those caused by malabsorption [1,2,9] (box 1). It should be emphasised, however, that many patients—especially those presenting in adulthood—have minimal or atypical symptoms.[10,11]

In infants less than 2 years of age, a more fulminant presentation of coeliac disease is likely, and chronic diarrhoea, failure to thrive, abdominal distension, and vomiting may occur.[12] This clinical presentation is now uncommon, and as paediatric patients tend to present at a later age (median 4 years), features such as loss of appetite and short stature may predominate.[13]

Intestinal symptoms may be absent in adults with coeliac disease, but in many clinically overt cases oral ulceration, dyspepsia, abdominal bloating, and diarrhoea may be present.[1,2,9] In some patients manifestations caused by malabsorption such as anaemia or osteoporosis may be found, whereas in others the predominant features may be of a disorder associated with coeliac disease—dermatitis herpetiformis is the classic example, with a typical pruritic vesicular rash.[4]

Epidemiology

A decade ago coeliac disease was considered a comparatively uncommon disorder, with prevalence rates of 1 in 1000 or lower quoted.[8,10] Several recent population studies, however, have shown a much higher prevalence, and it is now estimated that coeliac disease may affect 1 in 200 individuals.[14,15] The iceberg is a common model used to explain the epidemiology of coeliac disease (figure).[12] Accordingly, only a minority of individuals have clinically recognised disease, and this may explain the earlier inaccurately low prevalence figures. In contrast, the majority of patients have what is termed silent coeliac disease, which may remain undiagnosed because the condition has no symptoms.

The discovery that coeliac disease is a prevalent disorder can be attributed to the judicious use of serological screening tests, which measure antiendomysial and antigliadin antibodies.[14,15] Of these, the endomysial antibody test has advanced the diagnosis of coeliac disease owing to its specificity and sensitivity.[16,17] Further screening of populations should give information about the prevalence of coeliac disease worldwide.[11]

Invited Review

Nutr Clin Pract 2006; 21; 1

Gluten-Free Diet: The Medical and Nutrition Management of Celiac Disease

Jacalyn See, MS, RD, LD; and Joseph A. Murray, MD
Mayo Clinic College of Medicine, Rochester, Minnesota

ABSTRACT: Celiac disease (CD) is a chronic disease causing inflammation of the proximal small intestine that occurs in genetically predisposed individuals when they eat gluten, which is the storage protein in wheat, barley, and rye. The disease injury usually resolves when gluten

Close follow-up to assess for correction of nutrient deficiencies is advised.

suggested that it may be as common as 1 in 100 individuals from European countries or white populations. It can affect many ethnic groups. Though its occurrence in individuals from Southeast Asia is quite rare, it certainly can occur in individuals from

well understood, frequently goes undiagnosed, probably because of the nonspecific or vague nature of many of the symptoms that occur.

The cornerstone of treatment for CD is elimination of gluten from the diet. In most patients diagnosed with CD, a strict gluten-free diet (GFD) alone should result in complete symptomatic and histologic resolution of the disease and reduce risk of complications. Noncompliance with diet is the leading cause of failure to respond in patients with CD. For these reasons, thorough assessment and counseling at the time of diagnosis and ongoing care are crucial. In this article, we address briefly what is known about the pathogenesis and diagnosis of CD and address its treatment in detail.

Epidemiology

Celiac disease (CD), although it was considered a rare disease affecting as few as 1 in 2000 individuals, is now recognized as being much more common.[1–4] Population-based screening studies have

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Pathogenesis

CD affects the proximal small intestine, which sees the highest concentration of grain peptides. It is the partially digested peptides derived from the stored proteins of wheat, barley, and rye that induce a potent immune response in the proximal small intestine.[10] This immune response only occurs in individuals who carry a certain human leucocyte antigen (HLA) type, that is, DQ2 or, in some populations, DQ8.[11] The potent immune response to gluten consists of both adaptive and innate immune responses. Innate responses occur early, within hours of exposure to gluten, and consist of activation of the lymphocytes in the surface epithelium, changes or alterations in the epithelial cells themselves producing certain cytokines, particularly interleukin (IL)-15, that further condition the immune response to continued gluten exposure, and changes in permeability (Figure 1).[12,13] It is, however, the role of the adaptive immune response that is crucial in perpetuating the gluten sensitivity that results in loss of immune tolerance and the development of chronic inflammation within the small intestine. It is CD4-positive T-cells that are specifically reacting to gluten in a manner that is restricted by DQ2 or DQ8 that results in inflammation.

It has recently been discovered that some particularly immunogenic peptides from wheat glutens resist digestion in the human intestine.[14] These cells, once activated, produce a predominantly Th1-type immune response and are characterized predominantly by the production of interferon-γ and

Affective disorders and quality of life in adult coeliac disease patients on a gluten-free diet

Tiziana Fera[a], Barbara Cascio[a], Guiseppe Angelini[a], Silvia Martini[b] and Carla Sategna Guidetti[b]

Eur J of Gastro & Hep 2003, 15:1287–1292

Background Psychiatric symptoms, common
coeliac disease patients, may improve after gl
withdrawal.

Aims To estimate the incidence of psychiatric disorders in coeliac disease patients on gluten withdrawal and to evaluate: (1) the psychological weight of a chronic disease that involves a restrictive diet and a limited life style; (2) the acceptance of the disease; (3) the effects of both disease and diet on behaviour and quality of life.

Patients and methods Three groups of 100 patients (coeliac disease patients, diabetic patients and healthy controls, respectively) were assessed by means of a

Questionnaire showed a high psychological and somatic perception of illness in both coeliac and diabetic patients. Its subscale scores correlated significantly with anxiety and depression symptoms.

Conclusions In coeliac disease, affective disorders should be ascribed to difficulties in adjusting to the chronic nature of the disease rather than directly to the disease itself, thus giving an indication for preventive liaison psychiatric interventions. *Eur J Gastroenterol Hepatol* 15:1287–1292

A medical team willing to inform adequately and reassure patients, a strict follow-up in the early phases after diagnosis and, last but not least, contact with other patients and patient associations are indispensable features.

functional digestive disease were found to suffer from a major depressive disorder [1–3], the treatment of which may reduce or remove the altered health perception.

Coeliac disease is an autoimmune disorder induced by gluten intake in genetically susceptible individuals. Although its most crucial target organ is the small bowel mucosa, it is by no means solely an intestinal disorder as gluten sensitivity extends beyond the damage of jejunal mucosa and can include the central nervous system [4]. Psychiatric symptoms are common in untreated adult coeliac disease but they are also present in children and occasionally may mimic psychiatric disturbances, the most frequent findings being

prevention of late nutritional complications and malignancies [12]. The improvement of psychiatric status in children after gluten withdrawal has also been described [13,14].

In this study, our foremost aim was to estimate the incidence of affective disorders (i.e. anxiety and depression) in coeliac disease patients on gluten withdrawal for at least 1 year. This would provide insights into: the psychological weight of a chronic disease, such as coeliac disease, which involves a restrictive diet and a limited life style; how patients accept the disease; and the effects of disease and restrictive diet on patients' behaviour and quality of life.

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Alimentary Tract

Increased suicide risk in coeliac disease—A Swedish nationwide cohort study☆

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[e] Centre for Violence Prevention, Karolinska Institutet, Sweden

CD diagnosed in childhood was associated with a 40% increase in suicide risk.

Inflammation
Suicide

Results: The risk for suicide was higher in patients with coeliac disease compared to general population controls (HR = 1.55; 95%CI = 1.15–2.10; based on 54 completed suicides). Whilst suicide was also more common amongst individuals with inflammation (HR = 1.96; 95%CI = 1.39–2.77), no such increase was seen amongst individuals with a normal mucosa but positive coeliac disease serology (HR = 1.06; 95%CI = 0.37–3.02).

Conclusions: We found a moderately increased risk of suicide amongst patients with coeliac disease. This merits increased attention amongst physicians treating these patients.

1. Introduction

Coeliac disease (CD) is an immune-mediated disorder triggered by exposure to gluten. CD occurs in some 1/100 individuals, and is associated with a number of other somatic disorders including endocrine disease [1], sepsis [2] and osteoporosis [3]; but there are also several studies suggesting a positive association between CD and depression [4–10]. The mechanism behind the association between CD and depression may include conditions of the central nervous system [11], somatic comorbidity [1–3], poor quality of life [12], and economic restraints caused by health care and adherence to a gluten-free diet [13] – or a combination of these. Some data also indicate that the association with depression does not abate with a gluten-free diet [4,7]. Since CD has been associated with psychiatric disorders, it is possible that patients with CD are at increased risk for suicide.

In a recent paper, we found a 39% increased risk of overall death in CD [14]; most individuals died from cardiovascular disorder, malignancy and respiratory disease. However, other causes of death were also more common in individuals with CD (Hazard ratio, HR = 1.65; 95%CI = 1.51–1.81)[14].

We know of no large-scale studies on CD and suicide. An earlier Swedish study indicated an increased risk of death from external causes in CD [15], but that study was restricted to inpatients, and did not specifically examine the risk of suicide. A British study suggested an increased risk of death from accidents, suicides and violence in *children*, but not in adults, with CD [16].

Since the association between CD and suicide remains uncertain, we conducted a retrospective cohort study to compare the risk of suicide amongst 29,000 individuals in Sweden with biopsy-verified CD (with villous atrophy, VA) during 1969–2007 with that amongst general population controls. For comparative reasons, we also estimated the risk of suicide in individuals with small intestinal inflammation but without VA, and those with normal mucosa but positive CD serology.

☆ *Disclaimer:* None of the funders had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. *Guarantor:* JFL had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Invited Review

Nutr Clin Pract 2006; 21; 1

Gluten-Free Diet: The Medical and Nutrition Management of Celiac Disease

Jacalyn See, MS, RD, LD; and Joseph A. Murray, MD
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ABSTRACT: Celiac disease (CD) is a chronic disease causing inflammation of the proximal small intestine that occurs in genetically predisposed individuals when they eat gluten, which is the storage protein in wheat, barley, disease and reduce risk of complications. Noncompliance with diet is the leading cause of failure to respond in patients with CD. For these reasons, thorough assessment and counseling at the time of diagnosis and ongoing care are crucial. In this article, we address briefly what is known about the pathogenesis and diagnosis of CD and address its treatment in detail.

Follow-up visits with the dietitian are essential to assess knowledge, competence, and compliance, as well as to provide reinforcement. If possible, a return visit should be scheduled within 1–3 months.

Epidemiology

Celiac disease (CD), although it was considered a rare disease affecting as few as 1 in 2000 individuals, is now recognized as being much more common.[1–4] Population-based screening studies have suggested that it may be as common as 1 in 100 individuals from European countries or white populations. It can affect many ethnic groups. Though its occurrence in individuals from Southeast Asia is

intestine.[10] This immune response only occurs in individuals who carry a certain human leucocyte antigen (HLA) type, that is, DQ2 or, in some populations, DQ8.[11] The potent immune response to gluten consists of both adaptive and innate immune responses. Innate responses occur early, within hours of exposure to gluten, and consist of activation of the lymphocytes in the surface epithelium, changes or alterations in the epithelial cells themselves producing certain cytokines, particularly interleukin (IL)-15, that further condition the immune response to continued gluten exposure, and changes in permeability (Figure 1).[12,13] It is, however, the role of the adaptive immune response that is crucial in perpetuating the gluten sensitivity that results in loss of immune tolerance and the development of chronic inflammation within the small intestine. It is CD4-positive T-cells that are specifically reacting to gluten in a manner that is restricted by DQ2 or DQ8 that results in inflammation.

It has recently been discovered that some particularly immunogenic peptides from wheat glutens resist digestion in the human intestine.[14] These cells, once activated, produce a predominantly Th1-type immune response and are characterized predominantly by the production of interferon-γ and

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If this is not possible, the patient should be encouraged to correspond *via* mail, e-mail, or telephone. Points to cover in the follow-up visits with the dietitian can be seen in Table 3.

Epidemiology

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Table 3
Summary of medical nutrition therapy for celiac disease

Nutr Clin Pract 2006; 21; 1

- Initial assessment
  - Weight, weight history
  - Diet history
  - 24-h recall
  - Supplements
  - Nutrient deficiencies
- Counseling
  - Importance of strict compliance
  - Sources of gluten: food and nonfood
  - GF alternatives
  - Where to purchase GF alternatives
  - Support groups
  - Label reading, shopping
  - Eating away from home
- Follow-up
  - Weight
  - Compliance
  - Comprehension
  - Dietary adequacy, variety
  - Coping skills
  - Exercise
  - Troubleshooting (for intentional or unintentional ingestion of gluten)

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suggested that it may be as common as 1 in 100 individuals from European countries or white populations. It can affect many ethnic groups. Though its occurrence in individuals from Southeast Asia is

As with any chronic condition, support groups are an invaluable resource. Not only are they a source of current and dependable information but patients who connect with other individuals with CD in a support group tend to manage their disease better than those without peer influence.

Epidemiology

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changes or alterations in the epithelial cells themselves producing certain cytokines, particularly interleukin (IL)-15, that further condition the immune response to continued gluten exposure, and changes in permeability (Figure 1).[12,13] It is, however, the role of the adaptive immune response that is crucial in perpetuating the gluten sensitivity that results in loss of immune tolerance and the development of chronic inflammation within the small intestine. It is CD4-positive T-cells that are specifically reacting to gluten in a manner that is restricted by DQ2 or DQ8 that results in inflammation.

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3 Case Reports

- Conjunctival Tumor diagnosed as Karposi's sarcoma
- Gluten Psychosis in a 14 year old
- Amyotrophic Lateral Sclerosis


7 Premises To Look At

Premise #1

Food Sensitivities may have a lasting, significant impact on CNS function

Detective Adrian Monk

Premise #2

Gluten Sensitivity is not yet recognized by Practitioners as a <u>Primary Presentation</u> in Their Offices

Detective Adrian Monk

Premise #3

Gluten Sensitivity with or without the enteropathy Celiac Disease is a systemic autoimmune disease

Journal of Alzheimer's Disease 45 (2015) 349–362

Detective Adrian Monk

Premise #4

Food selection has a direct impact on dysbiosis and may be an initiating factor in an autoimmune cascade

Detective Adrian Monk

Premise #5

Both Parkinson's and Alzheimer's diseases involve the formation of transmissible self-propagating prion-like proteins.

Journal of Alzheimer's Disease 45 (2015) 349–362

Detective Adrian Monk

Premise #6

A GFD may contribute to dysbiosis

Detective Adrian Monk

Premise #7

Every Office benefits from offering SUCCESSFUL, Comprehensive, Thorough Guidance for Patients to Transition into a Microbiome-balancing dietary lifestyle via a Well-Trained Nutritionist, Registered Dietician, or Staff Specialist

Mechanisms identified in this Presentation

- Cross-reactivity with purkinje cells
- Anti-gliadin Abs strongly react with blood vessel structures in the brain
- 1 exposure of gluten per month in sensitive individuals increases the SMR to 6:1
- Diet changes explained 57% of the total structural variation in gut microbiota, whereas genetic mutation accounted for no more than 12%.
- GFD may lead to reductions in beneficial gut bacteria populations and the ability of faecal samples to stimulate the host's immunity
- gut microbiota influence the GABAergic, glutaminergic, serotonergic, dopaminergic, histaminergic, and adrenergic systems

All 29 studies are available to you for free at www.theDr.com/Shine
15 of the 29 are the full articles

Take Care of Yourself

Make Sure to Tell those Important to You How Much You Love them


“Thank You for Your Kind Attention”