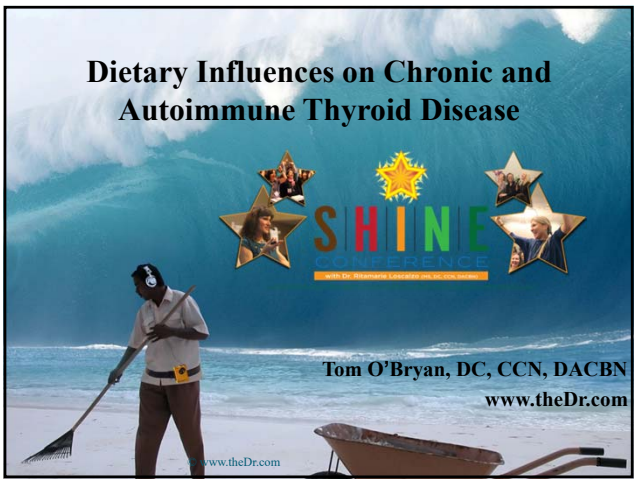

Tom O'Bryan, DC, CCN, DACBN

- 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

 4

OBJECTIVES

-Attendees will be able to identify 6 mechanisms by which gluten may impact on brain function
-Attendees will recognize the potential impact of the microbiota on brain function
-Attendees will learn the role of barrier integrity in the development of brain diseases such as Alzheimer's Disease.
-Attendees will learn the clinical applications of treatment for gluten-related neurological disorders

 5


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What's Coming Your Way in the next 90 minutes?
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7 Premises To Consider
8


3 Case Reports
Conjunctival Tumor diagnosed as Karposi's sarcoma
Gluten Psychosis in a 14 year old
Amyotrophic Lateral Sclerosis
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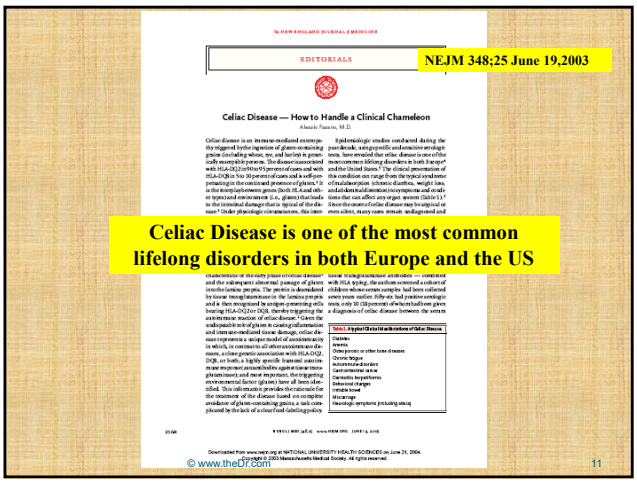
Premise #1

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

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

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

J Neurol Neurosurg Psychiatry 2012;83:1216–1221

Neuro-inflammation

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.

J Neurol Neurosurg Psychiatry 2012;83:1216–1221

Neuro-inflammation

RESEARCH PAPER

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

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

UK
[1]Department of Neurology, Royal Hallamshire Hospital, Sheffield, UK
[2]Department of Gastroenterology, Royal Hallamshire Hospital, Sheffield, UK

Correspondence to
Dr M Hadjivassiliou, Department of Neurology, Royal Hallamshire Hospital, Sheffield S10 2JF, UK;
m.hadjivassiliou@sheffield.ac.uk

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

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

J Neurol Neurosurg Psychiatry 2012;83:1216–1221

Neuro-inflammation

RESEARCH PAPER

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

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.

UK
[1]Department of Neurology, Royal Hallamshire Hospital, Sheffield, UK
[2]Department of Gastroenterology, Royal Hallamshire Hospital, Sheffield, UK

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Dr M Hadjivassiliou, Department of Neurology, Royal Hallamshire Hospital, Sheffield S10 2JF, UK;
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J Neurol Neurosurg Psychiatry 2012;83:1216–1221

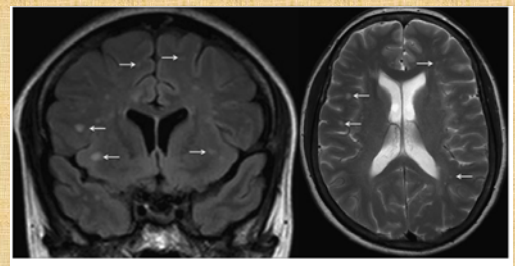
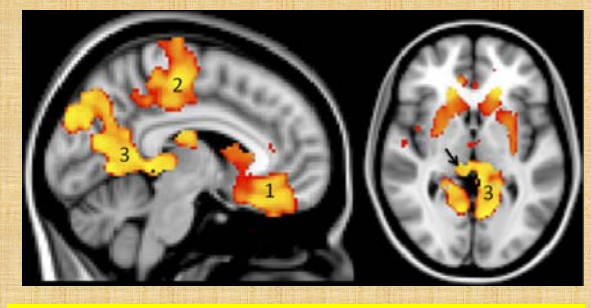
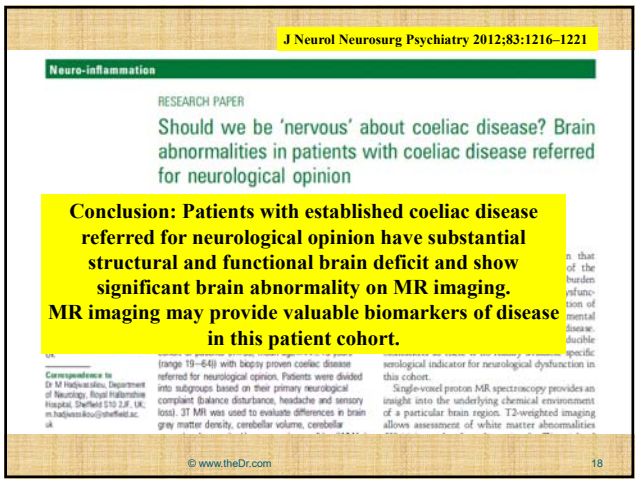


Figure 3 Typical example of white matter abnormalities found in the patient group. Coronal fluid attenuated inversion recovery (FLAIR) (left) and axial T2-weighted (right) images of a 57-year-old woman with coeliac disease who complained of recurrent headaches. Predominantly frontal subcortical white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

J Neurol Neurosurg Psychiatry 2012;83:1216–1221



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,


J Neurol Neurosurg Psychiatry 2012;83:1216–1221
Neuro-inflammation
RESEARCH PAPER
Should we be 'nervous' about coeliac disease? Brain abnormalities in patients with coeliac disease referred for neurological opinion
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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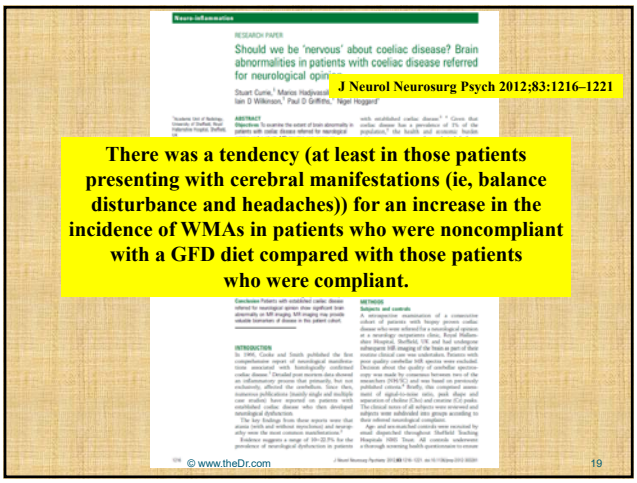
J Neurol Neurosurg Psych 2012;83:1216–1221
There was a tendency (at least in those patients presenting with cerebral manifestations (ie, balance disturbance and headaches)) for an increase in the incidence of WMAs in patients who were noncompliant with a GFD diet compared with those patients who were compliant.
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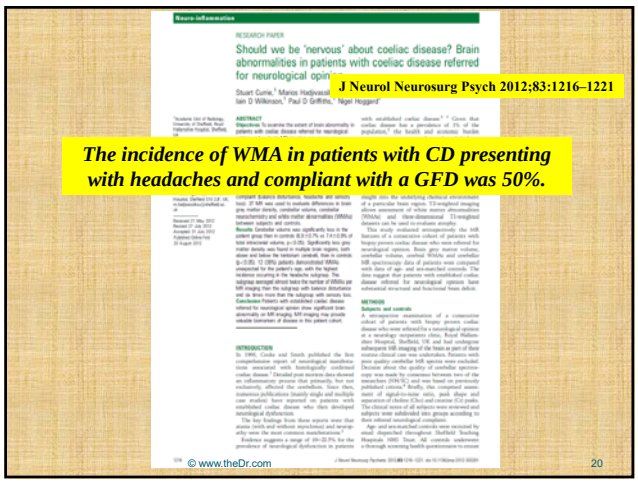
J Neurol Neurosurg Psych 2012;83:1216–1221
The incidence of WMA in patients with CD presenting with headaches and compliant with a GFD was 50%.
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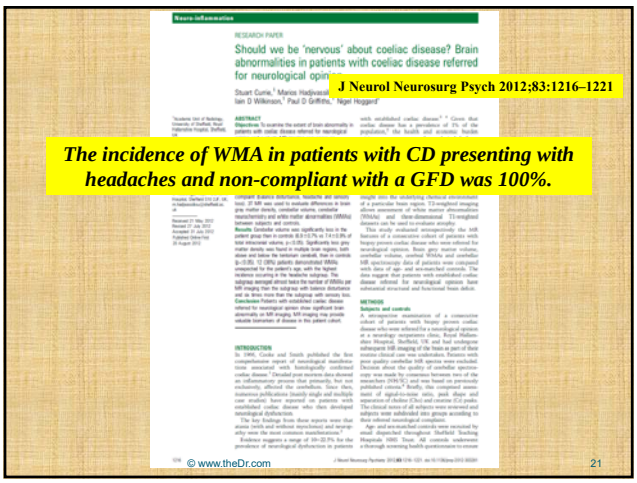
J Neurol Neurosurg Psych 2012;83:1216–1221
The incidence of WMA in patients with CD presenting with headaches and non-compliant with a GFD was 100%.
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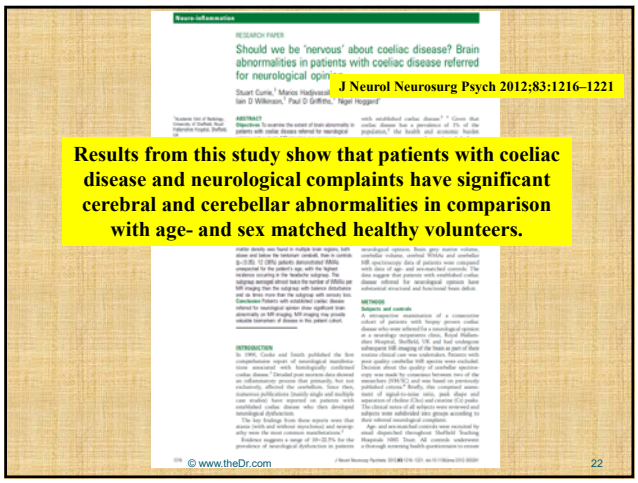
Neuro-inflammation
RESEARCH PAPER
Should we be 'nervous' about coeliac disease? Brain abnormalities in patients with coeliac disease referred for neurological opin
J Neurol Neurosurg Psych 2012;83:1216–1221
Results from this study show that patients with coeliac disease and neurological complaints have significant cerebral and cerebellar abnormalities in comparison with age- and sex matched healthy volunteers.
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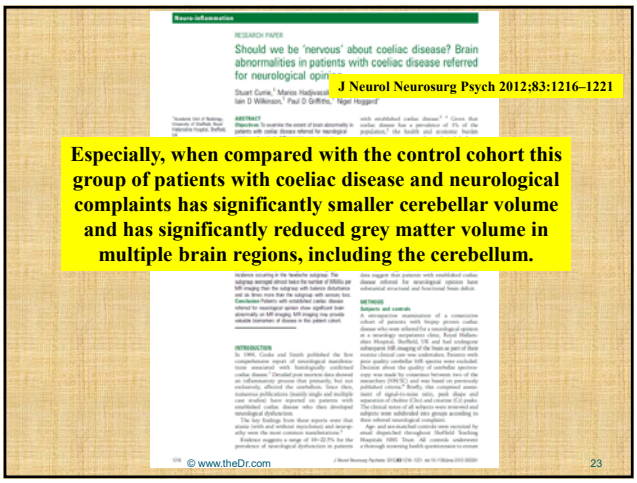
Neuro-inflammation
RESEARCH PAPER
Should we be 'nervous' about coeliac disease? Brain abnormalities in patients with coeliac disease referred for neurological opin
J Neurol Neurosurg Psych 2012;83:1216–1221
Especially, when compared with the control cohort this group of patients with coeliac disease 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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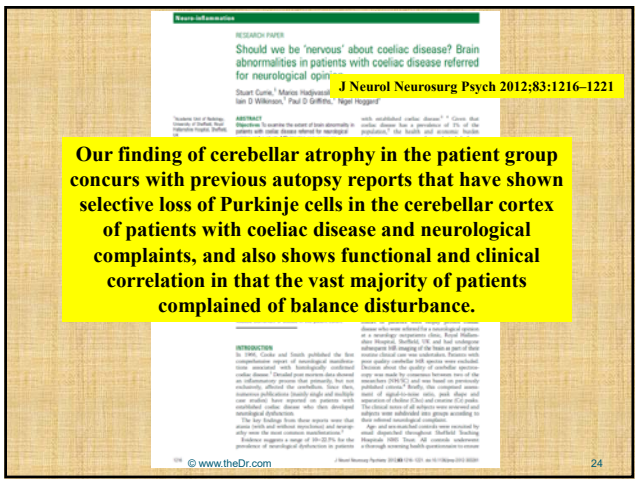
Neuro-inflammation
RESEARCH PAPER
Should we be 'nervous' about coeliac disease? Brain abnormalities in patients with coeliac disease referred for neurological opin
J Neurol Neurosurg Psych 2012;83:1216–1221
Our finding of cerebellar atrophy in the patient group concurs with previous autopsy reports that 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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Neuro-inflammation
RESEARCH PAPER
Should we be 'nervous' about coeliac disease? Brain abnormalities in patients with coeliac disease referred for neurological opin
J Neurol Neurosurg Psych 2012;83:1216–1221
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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Nutritional Neuroscience, Volume 7 Number 3 (June 2004), pp. 151–161

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Nutritional Neuroscience, Volume 7 Number 3 (June 2004), pp. 151–161

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.*,

Nutritional Neuroscience, Volume 7 Number 3 (June 2004), pp. 151–161

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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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Nutritional Neuroscience, Volume 7 Number 3 (June 2004), pp. 151–161

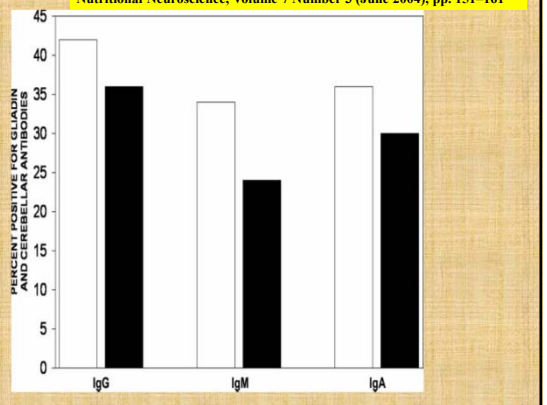
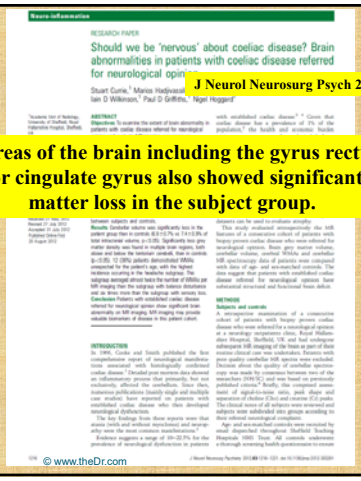


FIGURE 3 Percent positive sera from patients with Autism for IgG, IgM, and IgA antibodies against gliadin □ and cerebellar peptides ■.



Neuro-inflammation

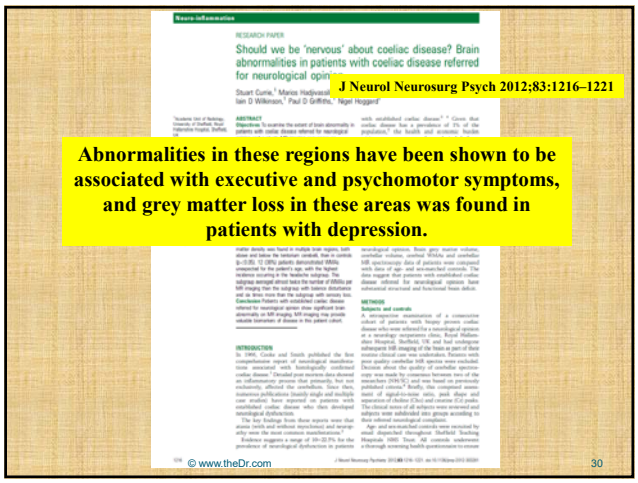
RESEARCH PAPER

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

Stuart Currie, Marios Hadjivassiliou, Ian D Wilkinson, Paul D Griffiths, Nigel Hoggard

J Neurol Neurosurg Psych 2012;83:1216–1221

Other areas of the brain including the gyrus rectus and anterior cingulate gyrus also showed significant grey matter loss in the subject group.


Neuro-inflammation
RESEARCH PAPER
Should we be 'nervous' about coeliac disease? Brain abnormalities in patients with coeliac disease referred for neurological opin
J Neurol Neurosurg Psych 2012;83:1216–1221
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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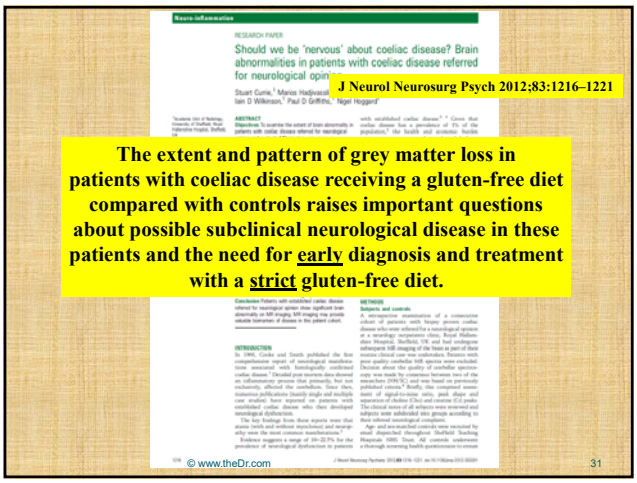
Neuro-inflammation
RESEARCH PAPER
Should we be 'nervous' about coeliac disease? Brain abnormalities in patients with coeliac disease referred for neurological opin
J Neurol Neurosurg Psych 2012;83:1216–1221
The extent and pattern of grey matter loss in patients with coeliac disease receiving a gluten-free diet compared with controls raises important questions about possible subclinical neurological disease in these patients and the need for early diagnosis and treatment with a strict gluten-free diet.
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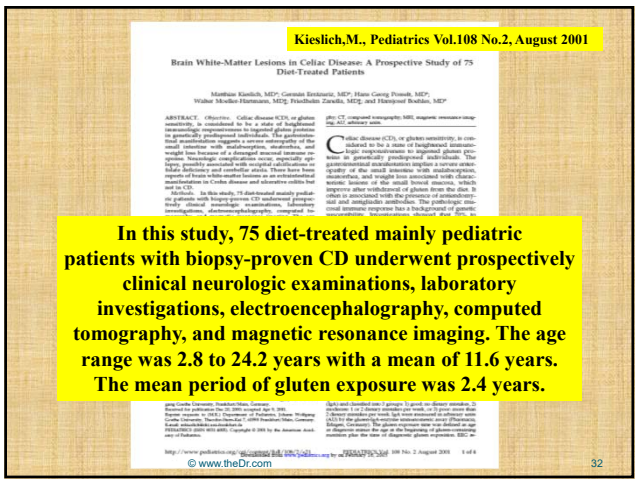
Kieslich,M., Pediatrics Vol.108 No.2, August 2001
Brain White-Matter Lesions in Celiac Disease: A Prospective Study of 75 Diet-Treated Patients
In this study, 75 diet-treated mainly pediatric patients with biopsy-proven CD underwent prospectively clinical neurologic examinations, laboratory investigations, 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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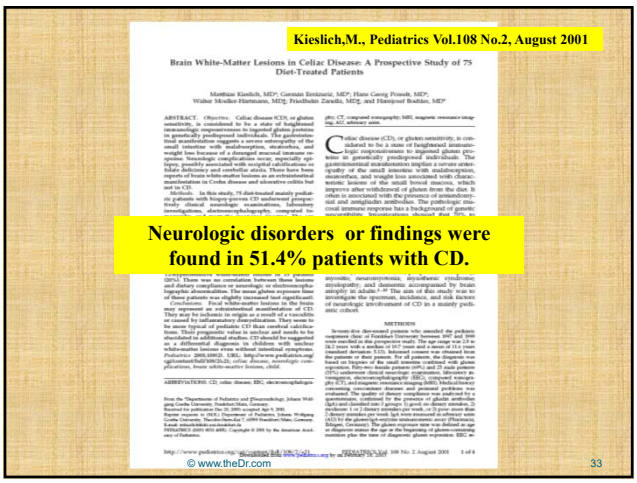
Kieslich,M., Pediatrics Vol.108 No.2, August 2001
Brain White-Matter Lesions in Celiac Disease: A Prospective Study of 75 Diet-Treated Patients
Neurologic disorders or findings were found in 51.4% patients with CD.
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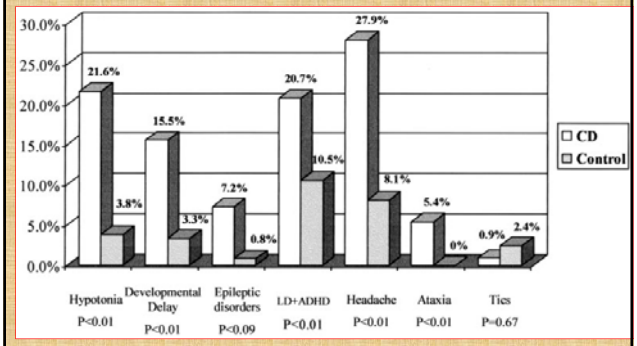
Pediatrics,Vol.113.No.6 June 2004



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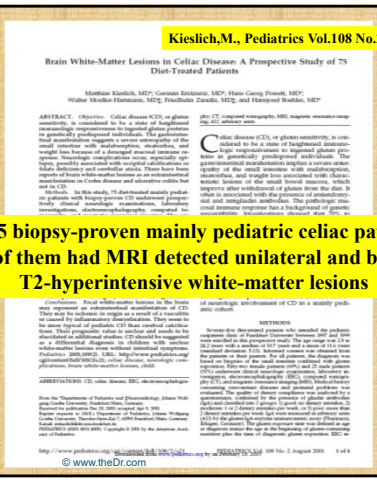
Kieslich,M., Pediatrics Vol.108 No.2, August 2001


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

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

 35

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

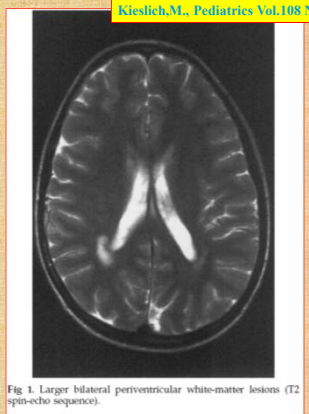


Fig. 1. Larger bilateral periventricular white-matter lesions (T2 spin-echo sequence).

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CASE STUDY #1

Conjunctival Tumor diagnosed as Kaposi's Sarcoma

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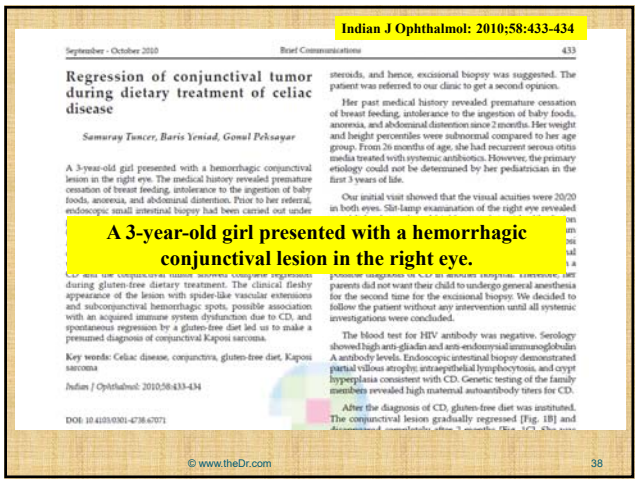
Indian J Ophthalmol: 2010;58:433-434
September - October 2010
Brief Communications
433
Regression of conjunctival tumor during dietary treatment of celiac disease
Samuray Tuncer, Baris Yeniad, Gonul Peksayar
A 3-year-old girl presented with a hemorrhagic conjunctival lesion in the right eye. The medical 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
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.
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
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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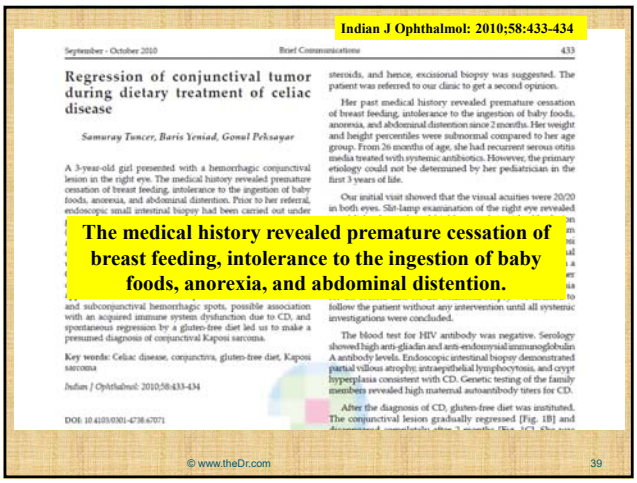
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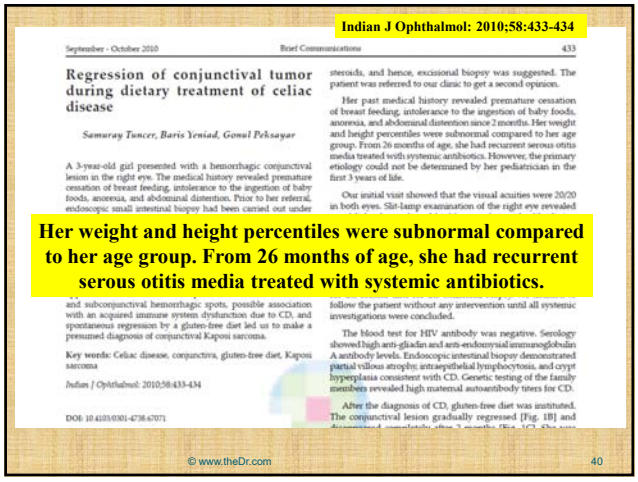
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Key words: Celiac disease, conjunctiva, gluten-free diet, Kaposi sarcoma
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DOI: 10.4103/0301-4738.67071
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After the diagnosis of CD, gluten-free diet was instituted. The conjunctival lesion gradually regressed [Fig. 1B] and
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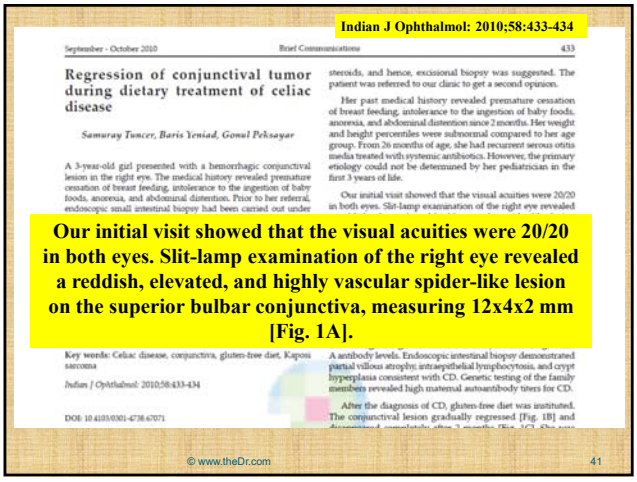
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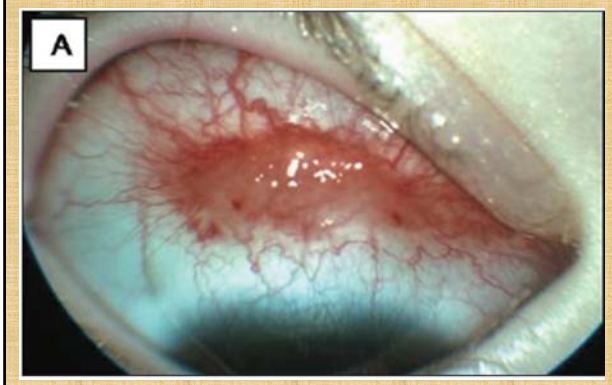

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Our initial visit showed that the visual acuities were 20/20

The differential diagnoses of such a conjunctival lesion includes KS, subconjunctival hemorrhage, malignant melanoma, squamous cell carcinoma, pyogenic granuloma, cavernous hemangioma, lymphoma, caroticocavernous fistula, foreign body granuloma, and lymphangioma

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

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Our presumed diagnosis was conjunctival Kaposi sarcoma (KS).

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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.

the visual acuities were 20/20 ...sion of the right eye revealed ...y vascular spider-like lesion ...ctiva, measuring 12×8×2 mm ...osis was conjunctival Kaposi ...al, endoscopic small intestinal ...der general anesthesia with a 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.

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The blood test for HIV antibody was negative.

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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.

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

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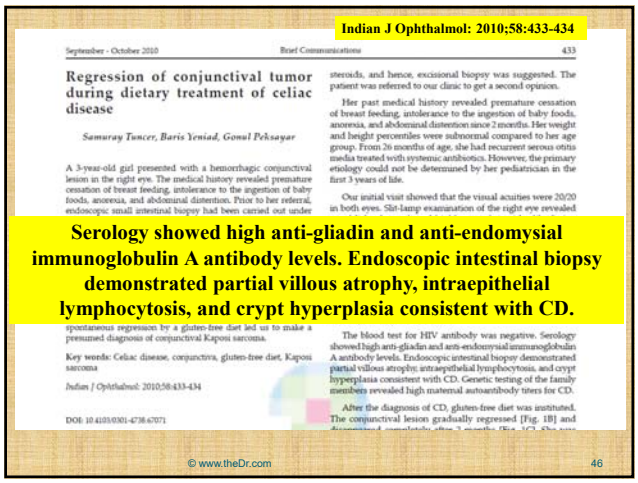
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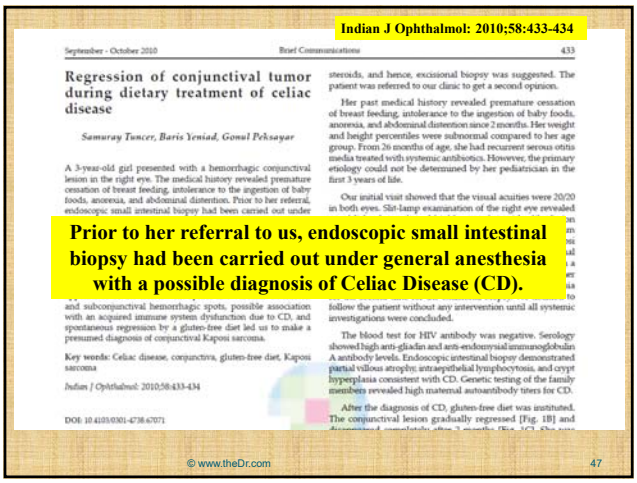
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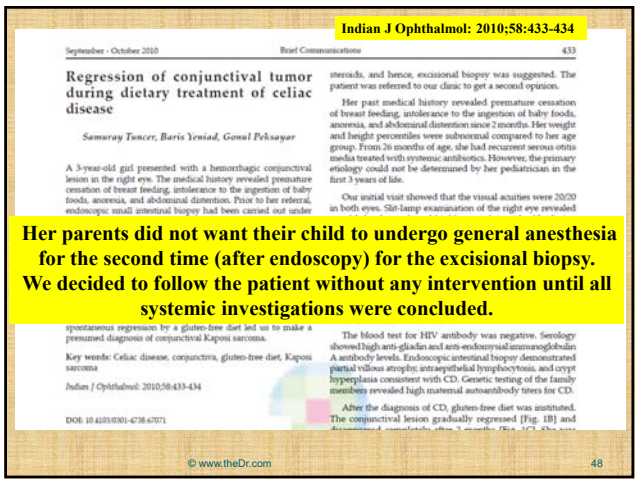
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Her parents did not want their child to undergo general anesthesia for the second time (after endoscopy) for the excisional biopsy. We decided to follow the patient without any intervention until all systemic investigations were concluded.
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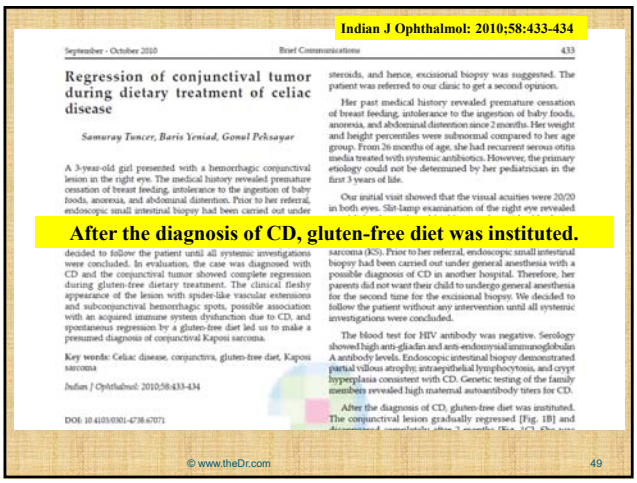
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Our initial visit showed that the visual acuities were 20/20 in both eyes. Slit-lamp examination of the right eye revealed

The conjunctival lesion gradually regressed [Fig. 1B] and disappeared completely after 2 months [Fig. 1C].

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.

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1 week of GFD 2 months of GFD

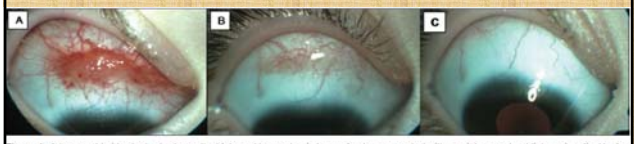

Figure 1: A 3-year-old girl, who had a 3-months history of hemorrhagic tear episodes, presented with a painless and reddish conjunctival lesion in the right eye. (A) Anterior segment photograph of the right eye showing reddish, fleshy, and highly vascular spider-like lesion on the superior bulbar conjunctiva. (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.

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.

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In conclusion, we present a very unusual conjunctival tumor in a patient with CD that showed complete regression by a gluten-free diet. The precise pathological nature of this conjunctival lesion remains unknown due to the lack of histopathological confirmation. However, prompt regression of the conjunctival lesion during gluten-free diet suggests a possible relationship to CD and an autoimmune process.

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

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Premise #2

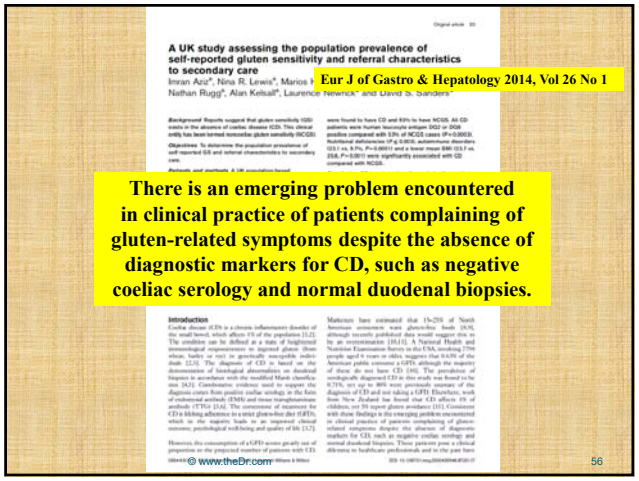
Gluten Sensitivity is not yet recognized by Practitioners as a <u>Primary Presentation</u> in Their Offices

Detective Adrian Monk

 54

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

 55

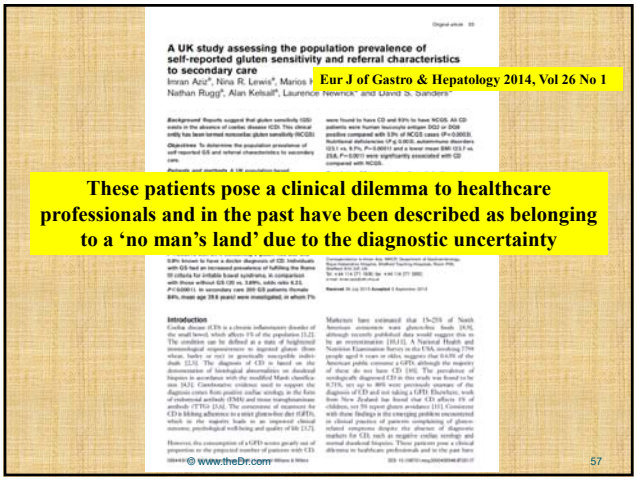


A UK study assessing the population prevalence of self-reported gluten sensitivity and referral characteristics to secondary care

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

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.

 56

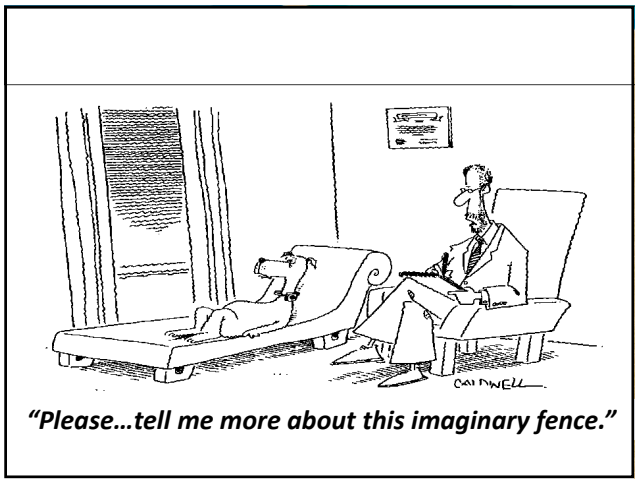


A UK study assessing the population prevalence of self-reported gluten sensitivity and referral characteristics to secondary care

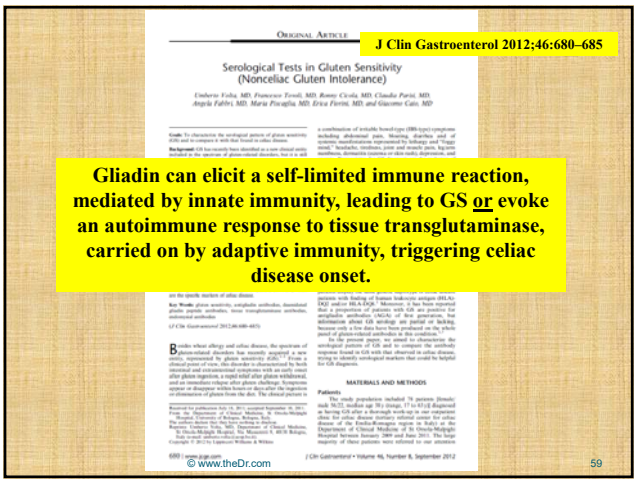
Eur J of Gastro & Hepatology 2014, Vol 26 No 1

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

 57



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



ORIGINAL ARTICLE

J Clin Gastroenterol 2012;46:680–685

Serological Tests in Gluten Sensitivity (Nonceliac Gluten Intolerance)

Gliadin can elicit a self-limited immune reaction, mediated by innate immunity, leading to GS or evoke an autoimmune response to tissue transglutaminase, carried on by adaptive immunity, triggering celiac disease onset.

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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?

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

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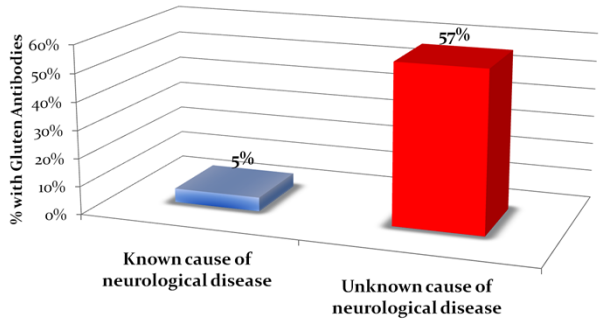
560 *J Neurol Neurosurg Psychiatry* 2002 72: 560-563



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?

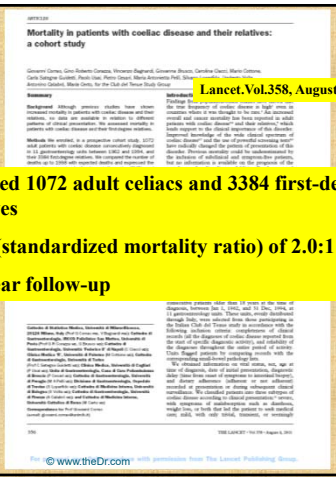
And How many Know or Suspect that IF you have an inadverdent exposure to Gluten, it seems to affect your Brain?

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

 63

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

 64



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

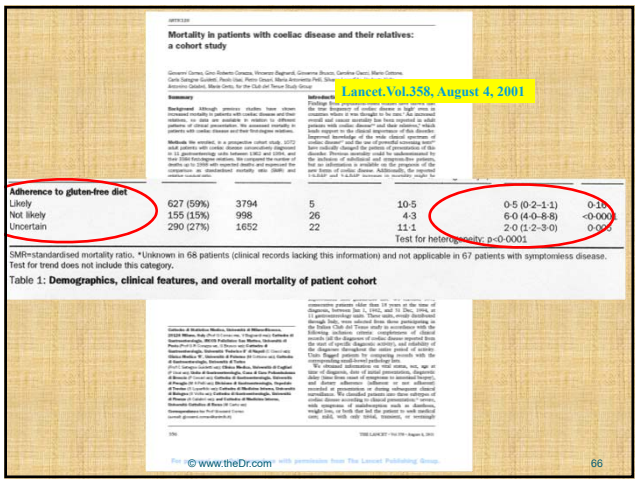
Lancet.Vol.358, August 4, 2001

Enrolled 1072 adult celiacs and 3384 first-degree relatives

SMR (standardized mortality ratio) of 2.0:1

20+ year follow-up

 65


Mortality in patients with coeliac disease and their relatives:
a cohort study
Lancet.Vol.358, August 4, 2001
Adherence to gluten-free diet
Likely
Not likely
Uncertain
627 (59%) 3794 5 10·5 0·5 (0·2–1·1) 0·16
155 (15%) 998 26 4·3 6·0 (4·0–8·8) <0·0001
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
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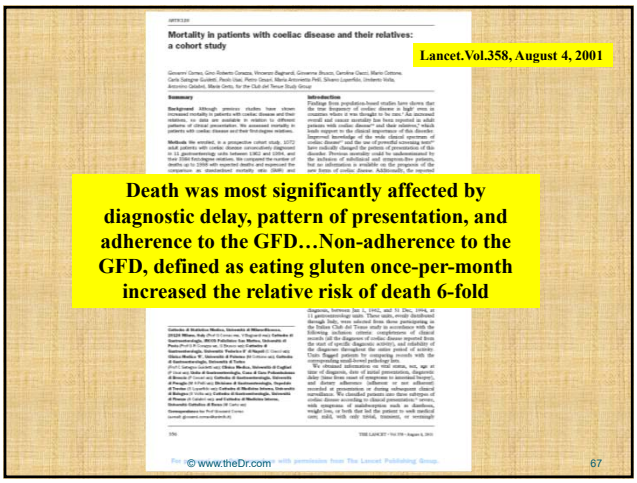
Mortality in patients with coeliac disease and their relatives:
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Death was most significantly affected by diagnostic delay, pattern of presentation, and adherence to the GFD…Non-adherence to the GFD, defined as eating gluten once-per-month increased the relative risk of death 6-fold
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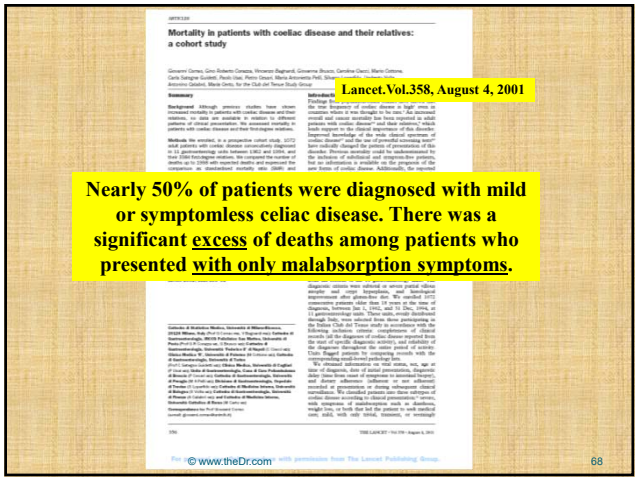
67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a cohort study
Lancet.Vol.358, August 4, 2001
Nearly 50% of patients were diagnosed with mild or symptomless celiac disease. There was a significant excess of deaths among patients who presented with only malabsorption symptoms.
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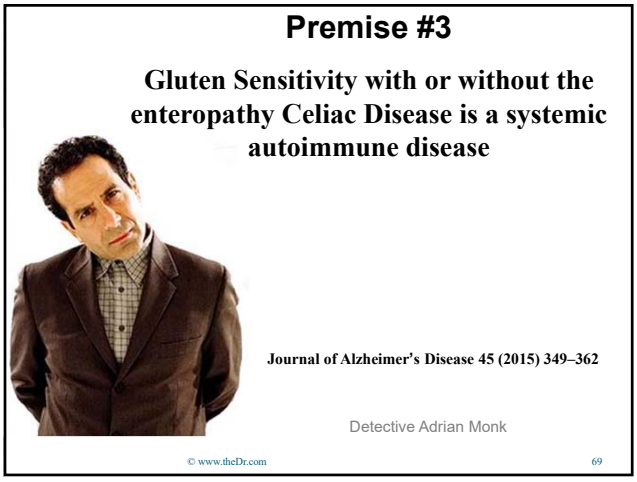
68


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
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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

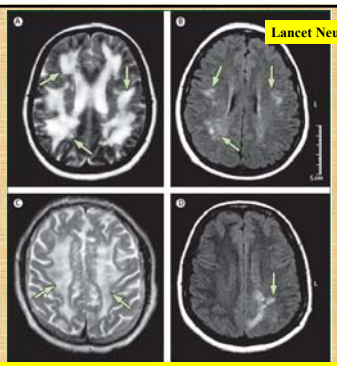
Lancet Neurol 2010; 9: 318–30

Gluten sensitivity is a systemic autoimmune disease with diverse manifestations. This disorder is characterised by

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.

was transcribed to coeliac. The study of coeliac disease was renewed by Gee[1] 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

neurological dysfunction continued to be published.[9,10] 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



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

Gluten sensitivity: from gut to brain

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Lancet Neurol 2010; 9: 318–30

Gluten sensitivity is a systemic autoimmune disease with diverse manifestations. This disorder is characterised by

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

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

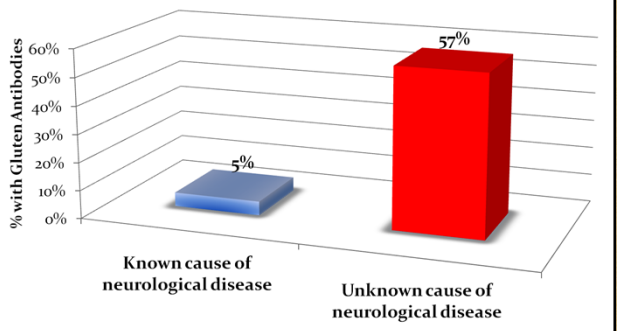
involved other parts of the CNS and peripheral nervous system. This finding favoured an immune-mediated pathogenesis.

Single and multiple case reports of patients with established coeliac disease who then developed neurological dysfunction continued to be published.[9,10] 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

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

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

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



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%.

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]

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

Brain (2003), 126, 685±691

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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]

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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Case Report

Gluten Psychosis: Confirmation of a New Clinical Entity

Non-celiac gluten sensitivity (NCGS) is a syndrome diagnosed in patients with symptoms that respond to removal of gluten from the diet, after celiac disease and wheat allergy have been excluded. NCGS has been related to neuro-psychiatric disorders, such as autism, schizophrenia and depression.

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The "classical" presentation of NCGS is, indeed, a combination of gastro-intestinal symptoms including abdominal pain, bloating, bowel habit abnormalities (either diarrhea or constipation), and systemic manifestations including disorders of the neuropsychiatric area such as "foggy mind", depression, headache, fatigue, and leg or arm numbness

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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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Gluten Psychosis: Confirmation of a New Clinical Entity

The proposed mechanism is a CD-unrelated, primary alteration of the small intestinal barrier (leaky gut) leading to abnormal absorption of gluten peptides that can eventually reach the central nervous system stimulating the brain opioid receptors and/or causing neuro-inflammation.

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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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Pediatric Neuro-Psychiatric Unit, G. Gaslini Institute, Via Gerolamo Gaslini 5, 16147 Genova, Italy;
E-Mail: margheritamancardi@ospedale-gaslini.ge.it
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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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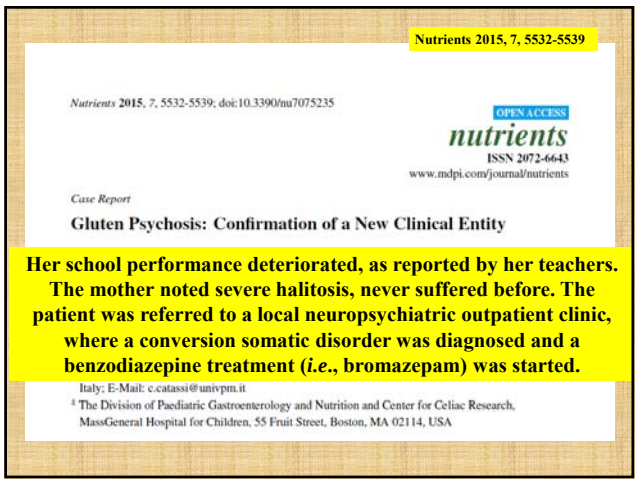
MassGeneral Hospital for Children, 55 Fruit Street, Boston, MA 02114, USA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Case Report
Gluten Psychosis: Confirmation of a New Clinical Entity
Her school performance deteriorated, as reported by her teachers. The mother noted severe halitosis, never 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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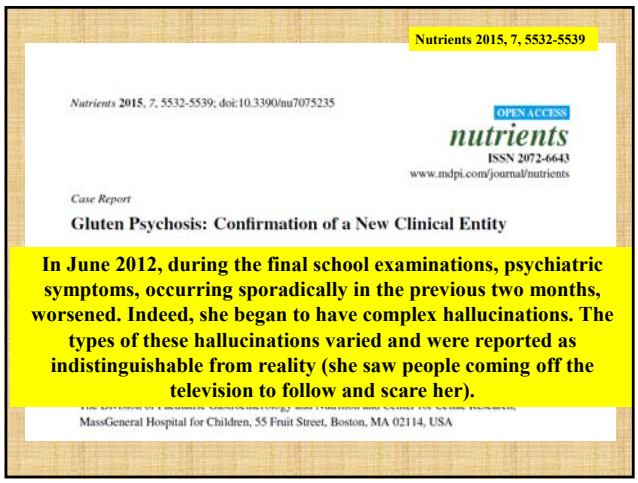
MassGeneral Hospital for Children, 55 Fruit Street, Boston, MA 02114, USA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Case Report
Gluten Psychosis: Confirmation of a New Clinical Entity
In June 2012, during the final school examinations, psychiatric symptoms, occurring sporadically in the previous 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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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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In order to exclude an organic neuropsychiatric cause of psychosis, the following tests were done: rheumatoid factor, streptococcal antibody tests, autoimmunity profile (including anti-nuclear, anti-double-stranded DNA, anti-neutrophil cytoplasmic, anti-Saccharomyces, anti-phospholipid, anti-mitochondrial, anti-SSA/Ro, anti-SSB/La, anti-transglutaminase IgA (tTG), anti-endomysium (EMA), and anti-gliadin IgA (AGA) antibodies), and screening for infectious and metabolic diseases, but they resulted all within the normal range. The only abnormal parameters were anti-thyroglobulin and thyroperoxidase antibodies.

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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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The steroid led to partial clinical improvement, with persistence of negative symptoms, such as emotional apathy, poverty of speech, social withdrawal and self-neglect. Her mother recalled that she did not return a "normal girl".

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[2] Pediatric Neuro-Psychiatric Unit, G. Gaslini Institute, Via Gerolamo Gaslini 5, 16147 Genova, Italy; E-Mail: margheritamancardi@ospedale-gaslini.ge.it

[3] Department of Pediatrics, Marche Polytechnic University, Ancona, Via Corridoni, 11, 60123 Ancona, Italy; E-Mail: c.catassi@univpm.it

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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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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.

[1] The Division of Paediatric Gastroenterology and Nutrition and Center for Celiac Research, MassGeneral Hospital for Children, 55 Fruit Street, Boston, MA 02114, USA

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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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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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Despite her efforts, she occasionally experienced inadvertent gluten exposures, which triggered the recurrence of her psychotic symptoms within about four hours. Symptoms took two to three days to subside again.

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Then, in April 2014 (two years after the onset of symptoms), she was admitted to our pediatric gastroenterology outpatient for suspected NCGS. Previous examinations excluded a diagnosis of CD because serology for CD was negative (*i.e.*, EMA, and tTG). A wheat allergy was excluded due to negativity of specific IgE to wheat, prick test, prick by prick and patch test for wheat resulted negative.

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Case Report

Therefore, we decided to perform a double-blind challenge test with wheat flour and rice flour (one pill containing 4 g of wheat flour or rice flour for the first day, following two pills in the second day and 4 pills from the third day to 15 days, with seven days of wash-out between the two challenges). During the administration of rice flour, symptoms were absent.

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During the second day of wheat flour intake, the girl presented headache, halitosis, abdominal distension, mood disorders, fatigue, and poor concentration, and three episodes of severe hallucinations. After the challenge, she tested negative for: (1) CD serology (EMA and tTG); (2) food specific IgE; (3) skin prick test to wheat (extract and fresh food); (4) atopy patch test to wheat; and (5) duodenal biopsy. Only serum anti-native gliadine antibodies of IgG class and stool calprotectin were elevated.

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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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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.

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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.

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Interestingly, in our case, we observed an elevation of fecal calprotectin that resolved during gluten-free diet, suggesting that a certain degree of gut inflammation may be found in NCGS. The role of stool calprotectin as a biomarker of NCGS requires further evaluation.

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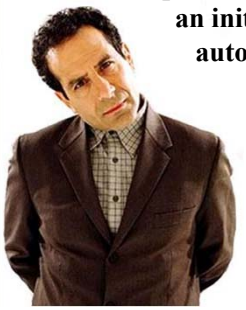
Premise #4

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



Detective Adrian Monk

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The ISME Journal (2010) 4, 232–241

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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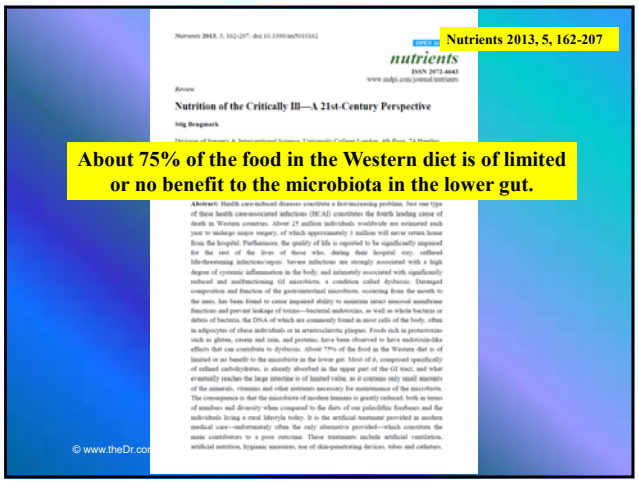
The ISME Journal (2010) 4, 232–241; doi:10.1038/ismej.2009.112; published online 29 October 2009

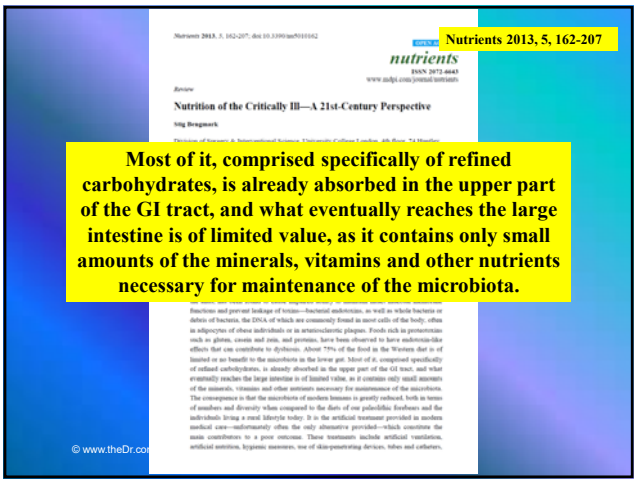
Nutrients 2013, 5, 162-207

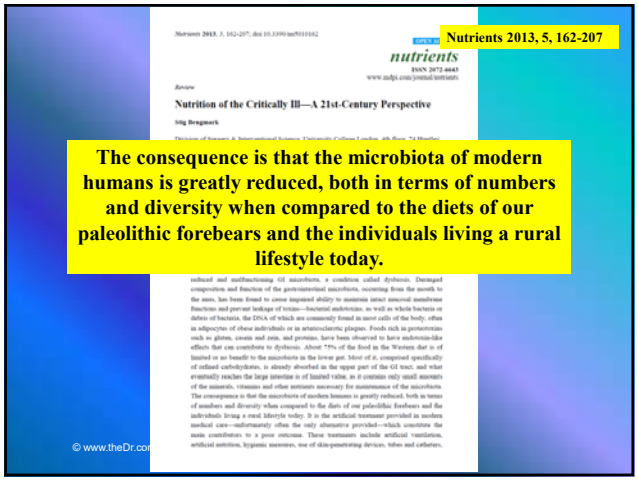
nutrients

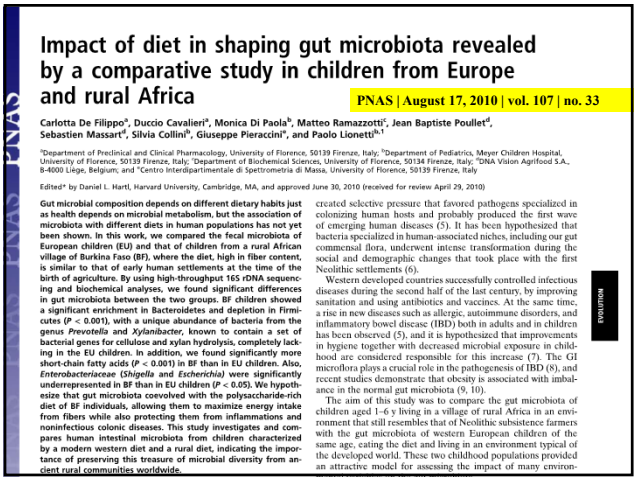
Nutrition of the Critically Ill—A 21st-Century Perspective

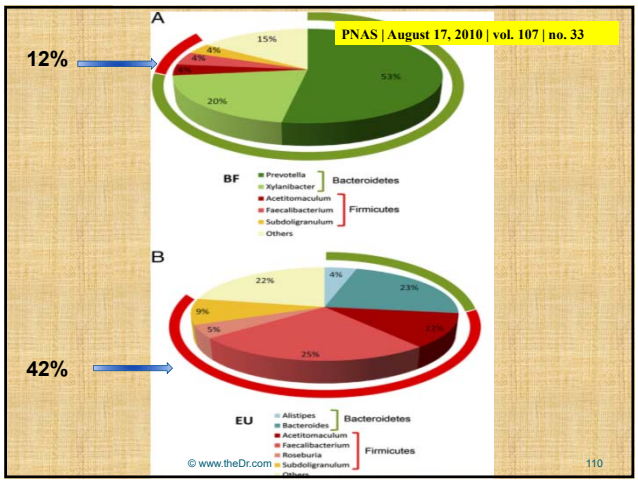
Foods rich in proteotoxins such as gluten, casein, zein, and proteins, have been observed to have endotoxin-like effects that can contribute to dysbiosis


Nutrients 2013, 5, 162-207
nutrients
Nutrition of the Critically Ill—A 21st-Century Perspective
About 75% of the food in the Western diet is of limited or no benefit to the microbiota in the lower gut.


Nutrients 2013, 5, 162-207
nutrients
Nutrition of the Critically Ill—A 21st-Century Perspective
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.


Nutrients 2013, 5, 162-207
nutrients
Nutrition of the Critically Ill—A 21st-Century Perspective
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.


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, Duccio Cavalieri, Monica Di Paola, Matteo Ramazzotti, Jean Baptiste Poullet, Sebastien Massart, Silvia Collini, Giuseppe Pieraccini, and Paolo Lionetti
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.
EVOLUTION


PNAS | August 17, 2010 | vol. 107 | no. 33
12%
42%
A
B
BF
Prevotella
Xylanibacter
Acetitomaculum
Faecalibacterium
Subdoligranulum
Others
Bacteroidetes
Firmicutes
EU
Alistipes
Bacteroides
Acetitomaculum
Faecalibacterium
Roseburia
Subdoligranulum
Others
Bacteroidetes
Firmicutes
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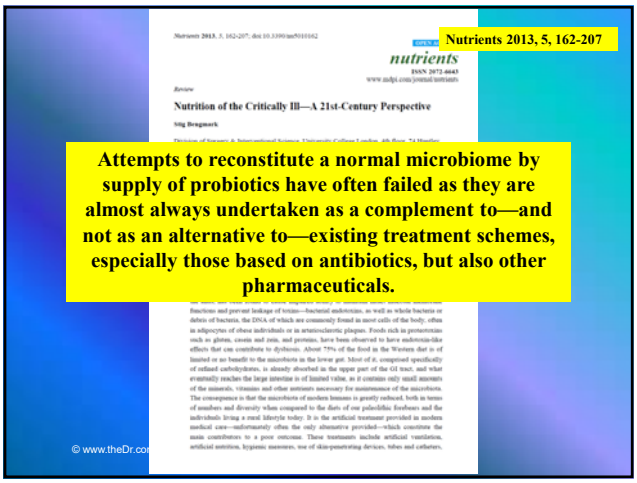
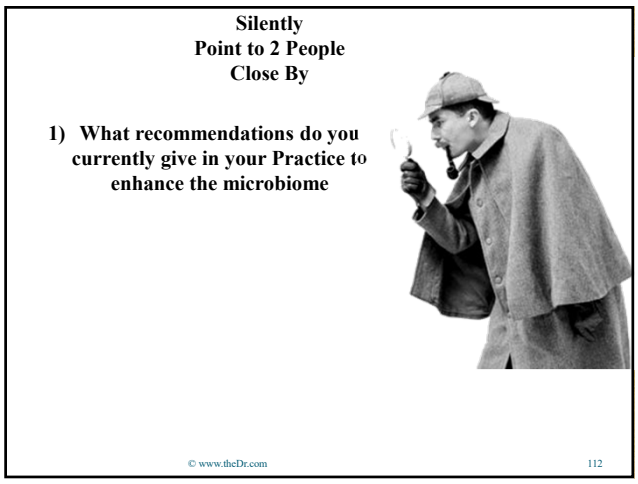
110


Nutrients 2013, 5, 162-207
nutrients
Nutrition of the Critically Ill—A 21st-Century Perspective
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.


Silently
Point to 2 People
Close By
1) What recommendations do you currently give in your Practice to enhance the microbiome
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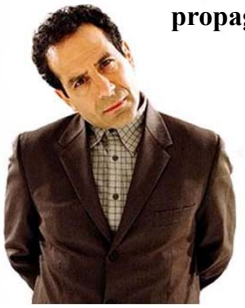
Premise #5

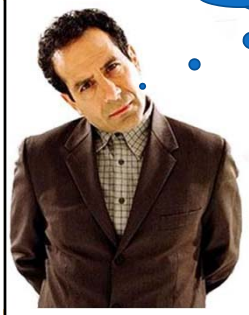
Both Parkinson's and Alzheimer's diseases involve the formation of <u>transmissible</u> self-propagating prion-like proteins.



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

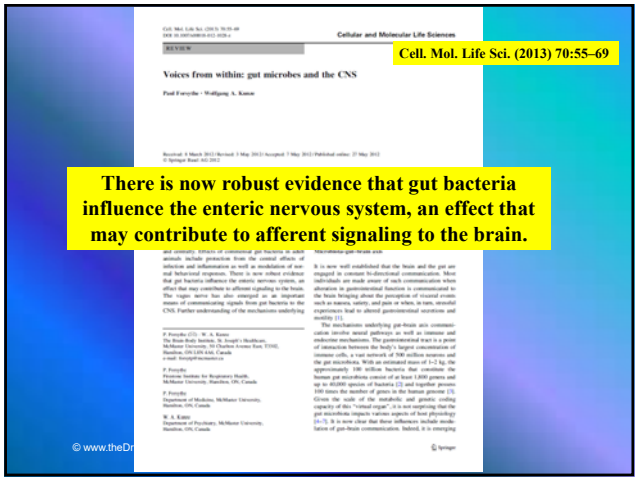
Detective Adrian Monk

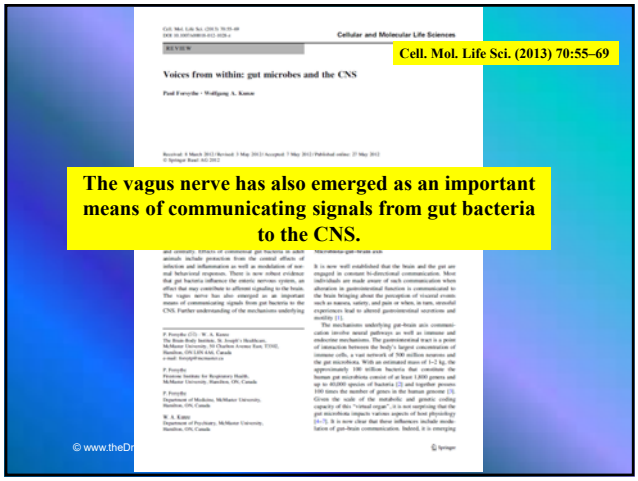
 114

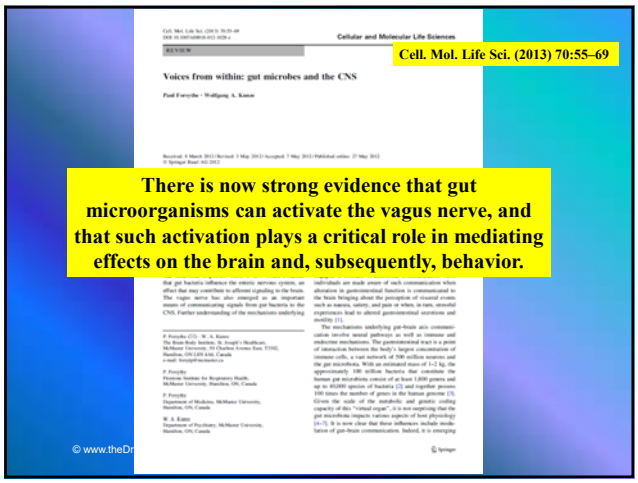


Detective Adrian Monk

 115






Cellular and Molecular Life Sciences
Cell. Mol. Life Sci. (2013) 70:55–69
Voices from within: gut microbes and the CNS
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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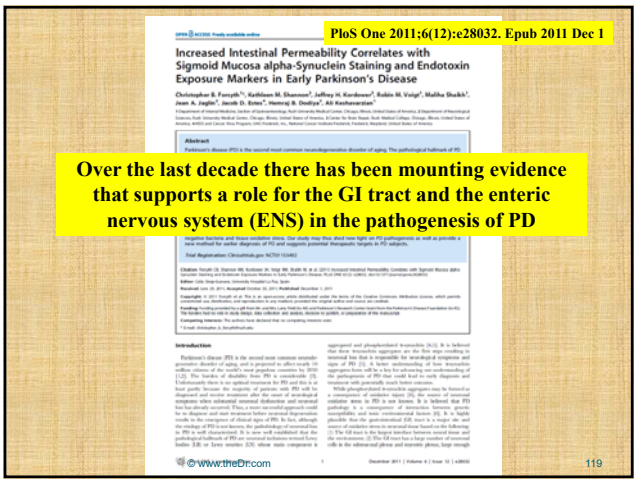
PloS One 2011;6(12):e28032. Epub 2011 Dec 1
Increased Intestinal Permeability Correlates with Sigmoid Mucosa alpha-Synuclein Staining and Endotoxin Exposure Markers in Early Parkinson's Disease
Over the last decade there has been mounting evidence that supports a role for the GI tract and the enteric nervous system (ENS) in the pathogenesis of PD
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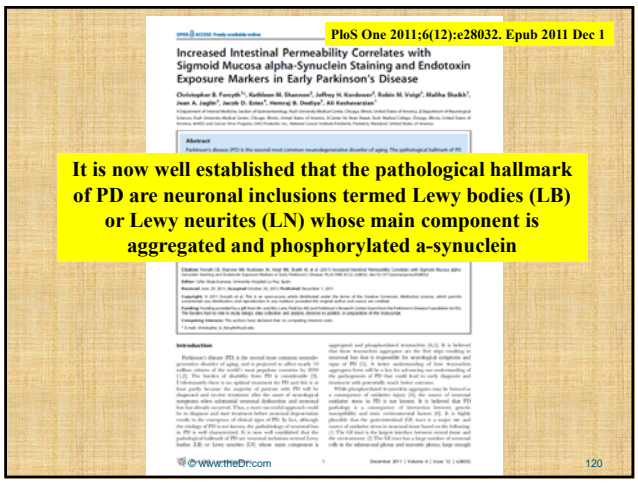
PloS One 2011;6(12):e28032. Epub 2011 Dec 1
Increased Intestinal Permeability Correlates with Sigmoid Mucosa alpha-Synuclein Staining and Endotoxin Exposure Markers in Early Parkinson's Disease
It is now well established that the pathological hallmark of PD are neuronal inclusions termed Lewy bodies (LB) or Lewy neurites (LN) whose main component is aggregated and phosphorylated a-synuclein
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PloS One 2011;6(12):e28032. Epub 2011 Dec 1
Increased Intestinal Permeability Correlates with Sigmoid Mucosa alpha-Synuclein Staining and Endotoxin Exposure Markers in Early Parkinson's Disease
It is believed that these a-synuclein aggregates are the first steps resulting in neuronal loss that is responsible for neurological symptoms and signs of PD
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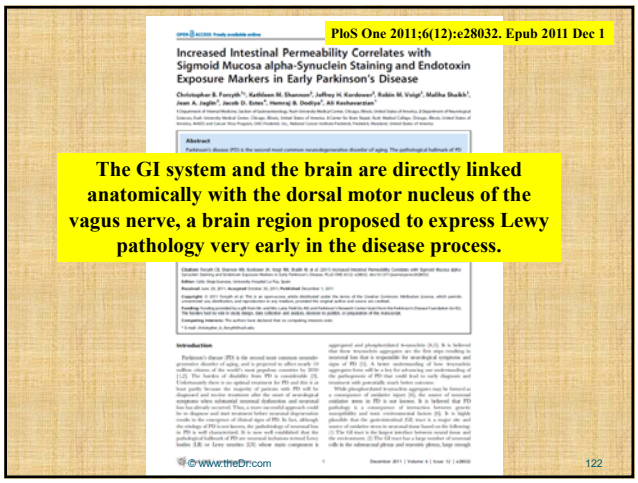
PloS One 2011;6(12):e28032. Epub 2011 Dec 1
Increased Intestinal Permeability Correlates with Sigmoid Mucosa alpha-Synuclein Staining and Endotoxin Exposure Markers in Early Parkinson's Disease
The GI system and the brain are directly linked anatomically with the dorsal motor nucleus of the vagus nerve, a brain region proposed to express Lewy pathology very early in the disease process.
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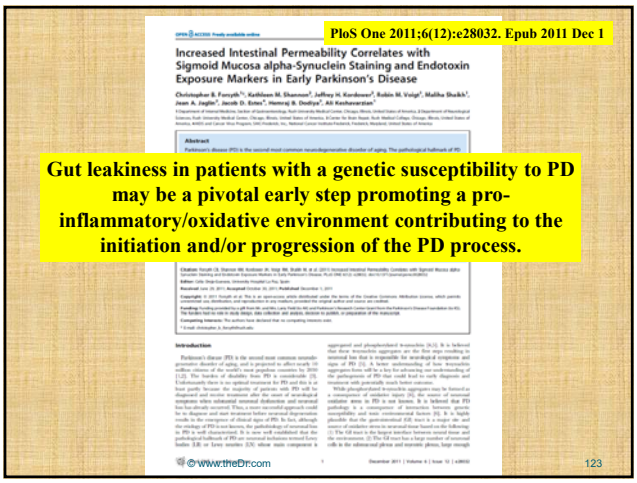
PloS One 2011;6(12):e28032. Epub 2011 Dec 1
Increased Intestinal Permeability Correlates with Sigmoid Mucosa alpha-Synuclein Staining and Endotoxin Exposure Markers in Early Parkinson's Disease
Gut leakiness in patients with a genetic susceptibility to PD may be a pivotal early step promoting a pro-inflammatory/oxidative environment contributing to the initiation and/or progression of the PD process.
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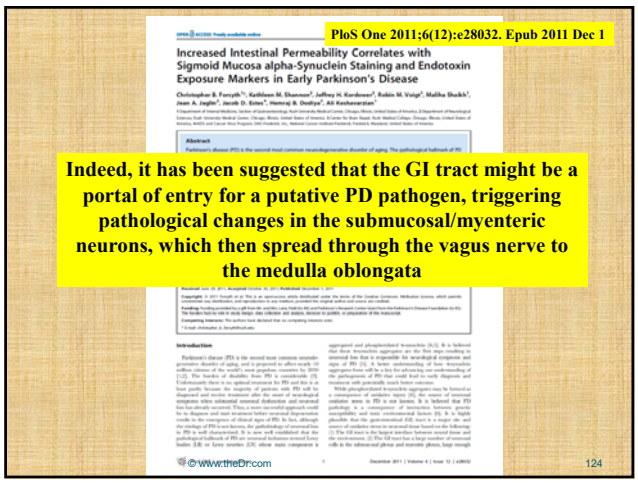
PloS One 2011;6(12):e28032. Epub 2011 Dec 1
Increased Intestinal Permeability Correlates with Sigmoid Mucosa alpha-Synuclein Staining and Endotoxin Exposure Markers in Early Parkinson's Disease
Indeed, it has been suggested that the GI tract might be a portal of entry for a putative PD pathogen, triggering pathological changes in the submucosal/myenteric neurons, which then spread through the vagus nerve to the medulla oblongata
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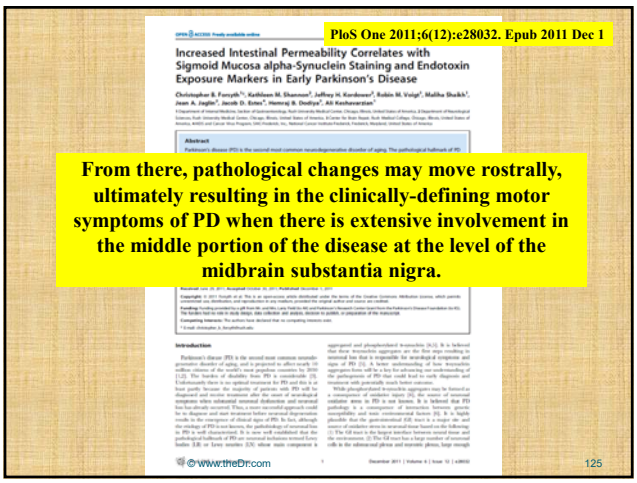
PloS One 2011;6(12):e28032. Epub 2011 Dec 1
Increased Intestinal Permeability Correlates with Sigmoid Mucosa alpha-Synuclein Staining and Endotoxin Exposure Markers in Early Parkinson's Disease
From there, pathological changes may move rostrally, ultimately resulting in the clinically-defining motor 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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Journal of Alzheimer's Disease 45 (2015) 349–362

Hypothesis

Mechanisms of Molecular Mimicry Involving the Microbiota in Neurodegeneration

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

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

Hypothesis

Mechanisms of Molecular Mimicry Involving the Microbiota in Neurodegeneration

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

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

Hypothesis

Mechanisms of Molecular Mimicry Involving

Bacterial proteins may elicit cross-seeded misfolding, inflammation and oxidative stress, and cellular toxicity in the neurodegenerative conformational disorders, initiating or otherwise influencing the development of Parkinson's disease (PD), Alzheimer's disease (AD), and related conditions.

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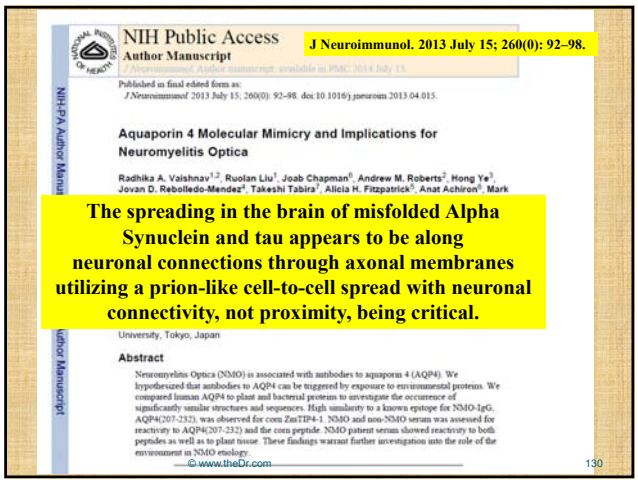
NIH Public Access
Author Manuscript
J Neuroimmunol. 2013 July 15; 260(0): 92–98.
Aquaporin 4 Molecular Mimicry and Implications for Neuromyelitis Optica
The spreading in the brain of misfolded Alpha Synuclein and tau appears to be along neuronal connections through axonal membranes utilizing a prion-like cell-to-cell spread with neuronal connectivity, not proximity, being critical.
Abstract
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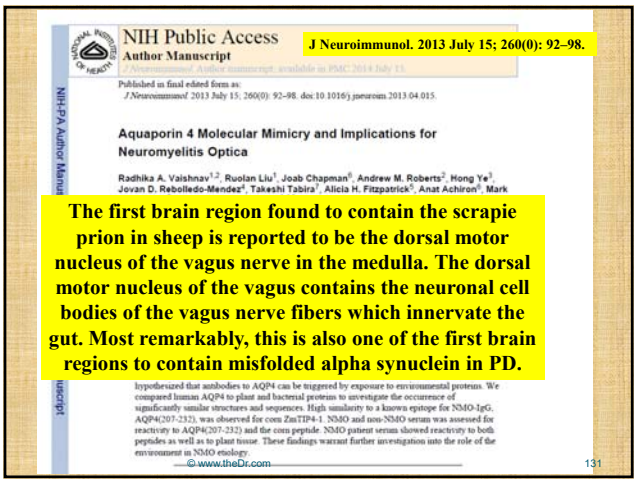
NIH Public Access
Author Manuscript
J Neuroimmunol. 2013 July 15; 260(0): 92–98.
Aquaporin 4 Molecular Mimicry and Implications for Neuromyelitis Optica
The first brain region found to contain the scrapie prion in sheep is reported to be the dorsal motor nucleus of the vagus nerve in the medulla. The dorsal motor nucleus of the vagus contains the neuronal cell bodies of the vagus nerve fibers which innervate the gut. Most remarkably, this is also one of the first brain regions to contain misfolded alpha synuclein in PD.
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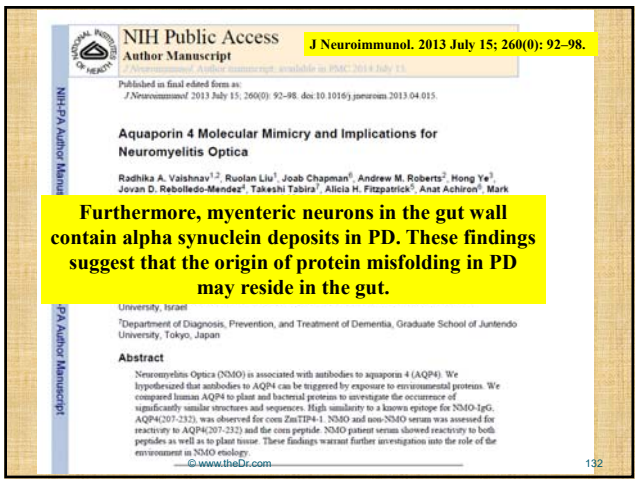
NIH Public Access
Author Manuscript
J Neuroimmunol. 2013 July 15; 260(0): 92–98.
Aquaporin 4 Molecular Mimicry and Implications for Neuromyelitis Optica
Furthermore, myenteric neurons in the gut wall contain alpha synuclein deposits in PD. These findings suggest that the origin of protein misfolding in PD may reside in the gut.
Abstract
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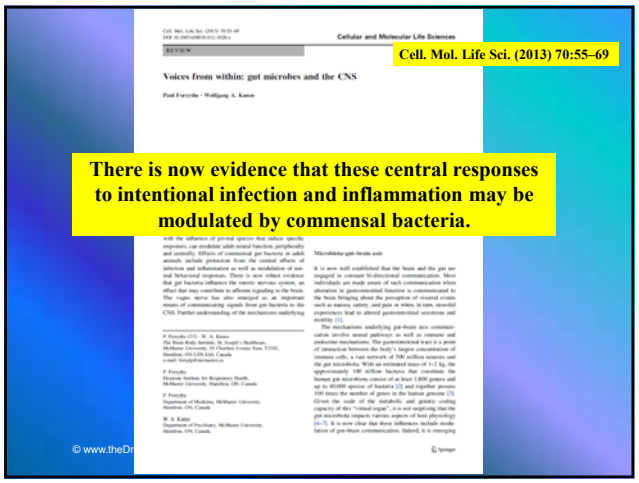
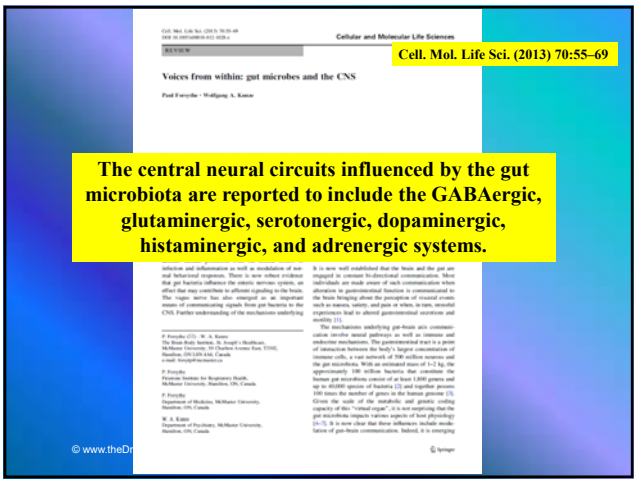
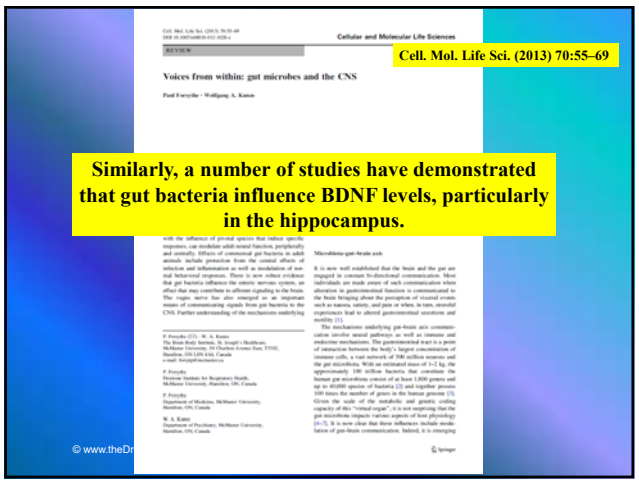
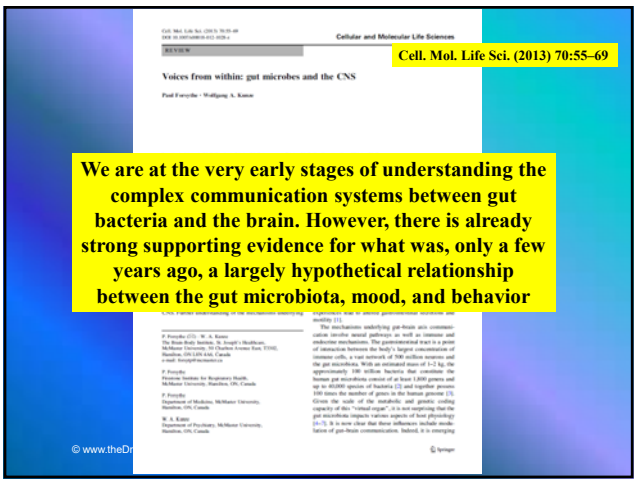

Cellular and Molecular Life Sciences
Cell. Mol. Life Sci. (2013) 70:55–69
Voices from within: gut microbes and the CNS
There is now evidence that these central responses to intentional infection and inflammation may be modulated by commensal bacteria.


Cellular and Molecular Life Sciences
Cell. Mol. Life Sci. (2013) 70:55–69
Voices from within: gut microbes and the CNS
The central neural circuits influenced by the gut microbiota are reported to include the GABAergic, glutaminergic, serotonergic, dopaminergic, histaminergic, and adrenergic systems.


Cellular and Molecular Life Sciences
Cell. Mol. Life Sci. (2013) 70:55–69
Voices from within: gut microbes and the CNS
Similarly, a number of studies have demonstrated that gut bacteria influence BDNF levels, particularly in the hippocampus.


Cellular and Molecular Life Sciences
Cell. Mol. Life Sci. (2013) 70:55–69
Voices from within: gut microbes and the CNS
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

Premise #6

A GFD may contribute to dysbiosis

Detective Adrian Monk

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

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

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

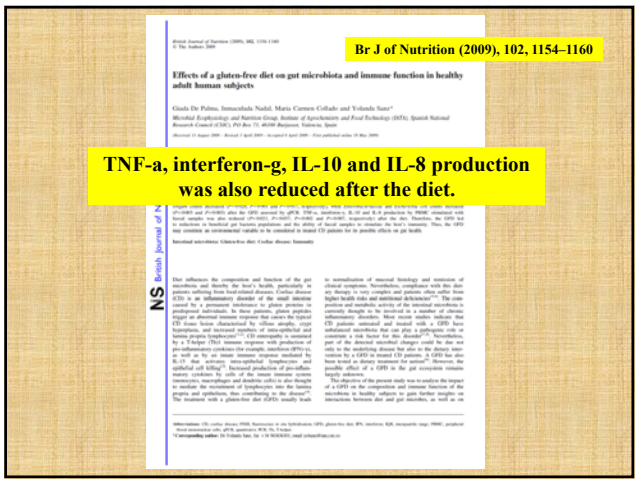
Effects of a gluten-free diet on gut microbiota and immune function in healthy adult human subjects

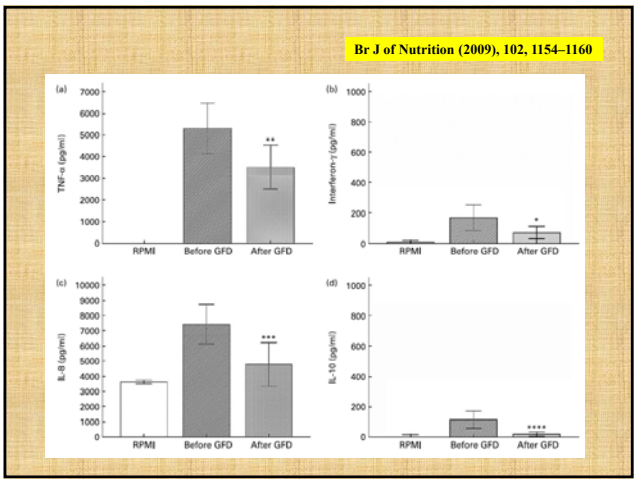
In the present preliminary study, the effects of a GFD on the composition and immune function of the gut microbiota were analysed in ten healthy subjects (mean age 30·3 years) over 1 month.

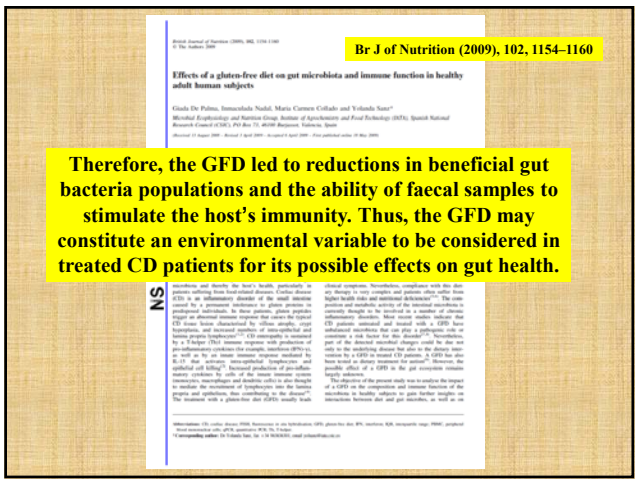
Br J of Nutrition (2009), 102, 1154–1160

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

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.


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

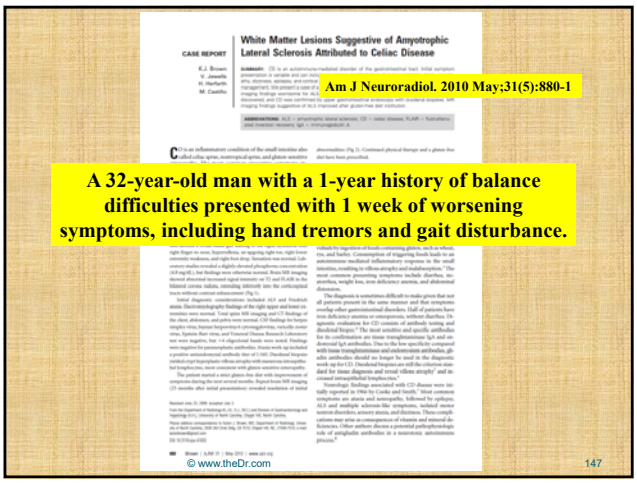

Br J of Nutrition (2009), 102, 1154–1160
RPMI
Before GFD
After GFD


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
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.

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



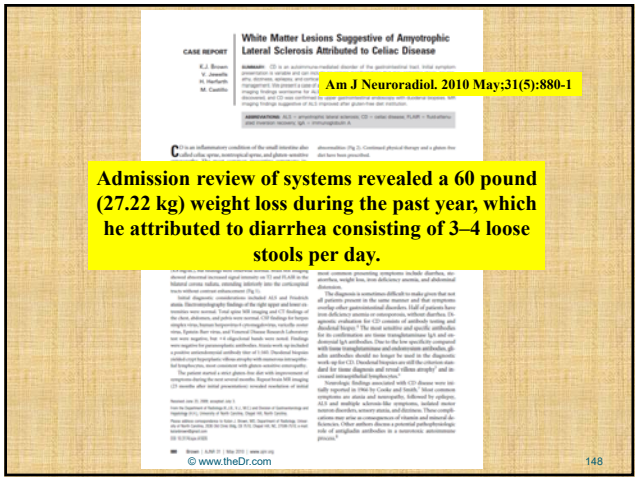
White Matter Lesions Suggestive of Amyotrophic Lateral Sclerosis Attributed to Celiac Disease

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

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.

147



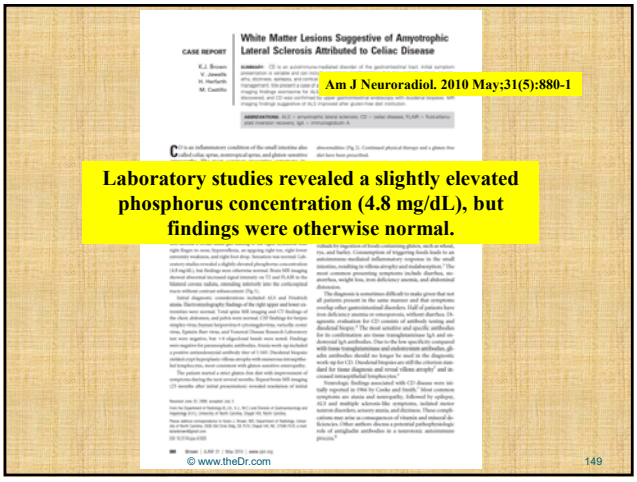
White Matter Lesions Suggestive of Amyotrophic Lateral Sclerosis Attributed to Celiac Disease

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

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

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.

148



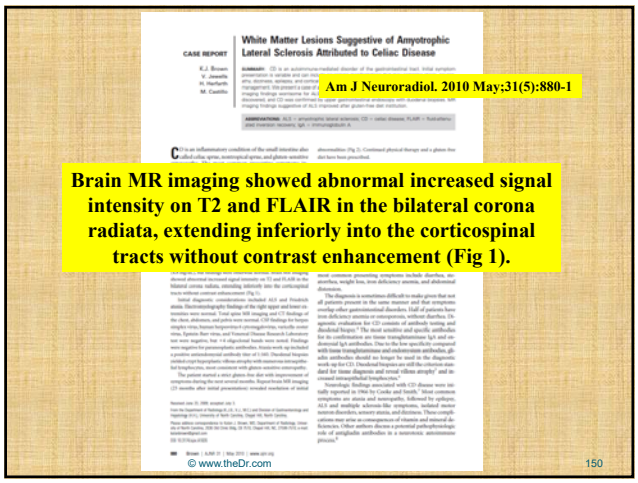
White Matter Lesions Suggestive of Amyotrophic Lateral Sclerosis Attributed to Celiac Disease

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

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

Laboratory studies revealed a slightly elevated phosphorus concentration (4.8 mg/dL), but findings were otherwise normal.

149


CASE REPORT
White Matter Lesions Suggestive of Amyotrophic Lateral Sclerosis Attributed to Celiac Disease
Am J Neuroradiol. 2010 May;31(5):880-1
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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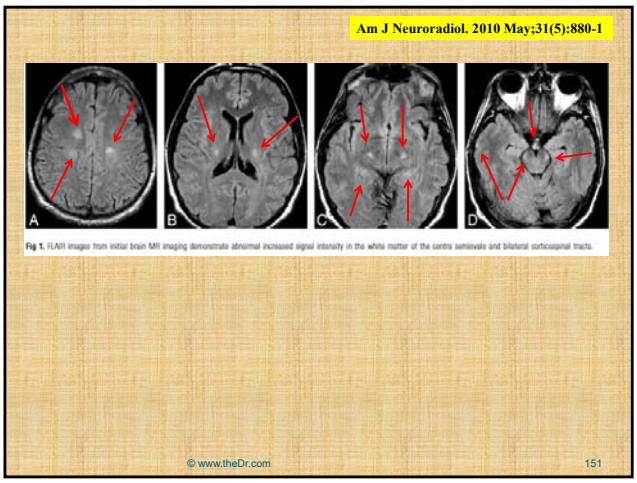
Am J Neuroradiol. 2010 May;31(5):880-1
A
B
C
D
Fig 1. FLAIR images from initial brain MR imaging demonstrate abnormal increased signal intensity in the white matter of the centra semiovale and bilateral corticospinal tracts.
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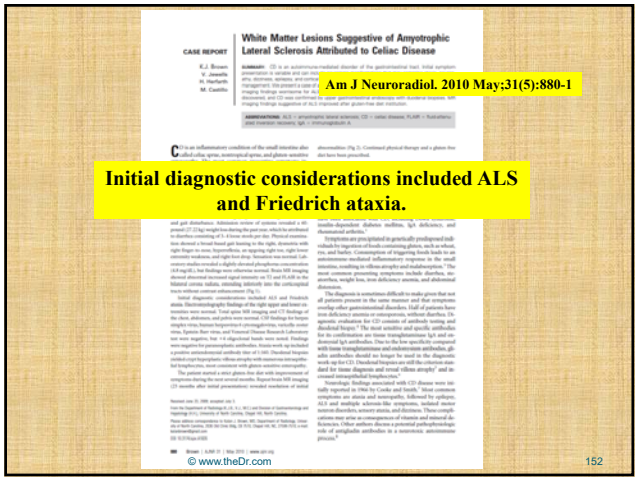
CASE REPORT
White Matter Lesions Suggestive of Amyotrophic Lateral Sclerosis Attributed to Celiac Disease
Am J Neuroradiol. 2010 May;31(5):880-1
Initial diagnostic considerations included ALS and Friedrich ataxia.
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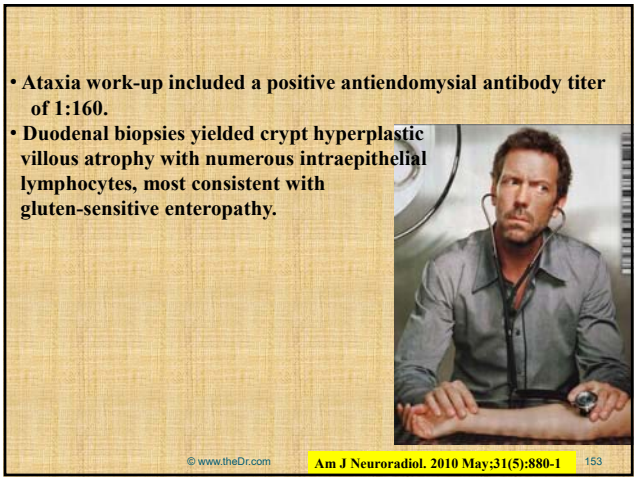
• Ataxia work-up included a positive antiendomysial antibody titer of 1:160.
• Duodenal biopsies yielded crypt hyperplastic villous atrophy with numerous intraepithelial lymphocytes, most consistent with gluten-sensitive enteropathy.
© www.theDr.com
Am J Neuroradiol. 2010 May;31(5):880-1
153


CASE REPORT
White Matter Lesions Suggestive of Amyotrophic Lateral Sclerosis Attributed to Celiac Disease
Am J Neuroradiol. 2010 May;31(5):880-1
The patient started a strict gluten-free diet with improvement of symptoms during the next several months.
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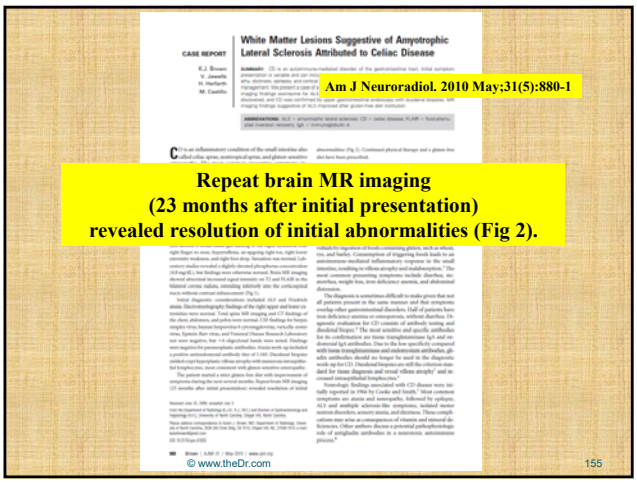
CASE REPORT
White Matter Lesions Suggestive of Amyotrophic Lateral Sclerosis Attributed to Celiac Disease
Am J Neuroradiol. 2010 May;31(5):880-1
Repeat brain MR imaging (23 months after initial presentation) revealed resolution of initial abnormalities (Fig 2).
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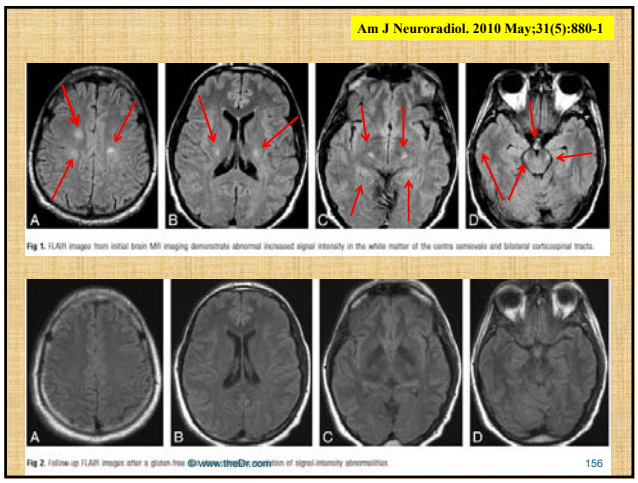
Am J Neuroradiol. 2010 May;31(5):880-1
A
B
C
D
Fig 1. FLAIR images from initial brain MR imaging demonstrate abnormal increased signal intensity in the white matter of the centra semiovals and bilateral corticospinal tracts.
A
B
C
D
© www.theDr.com
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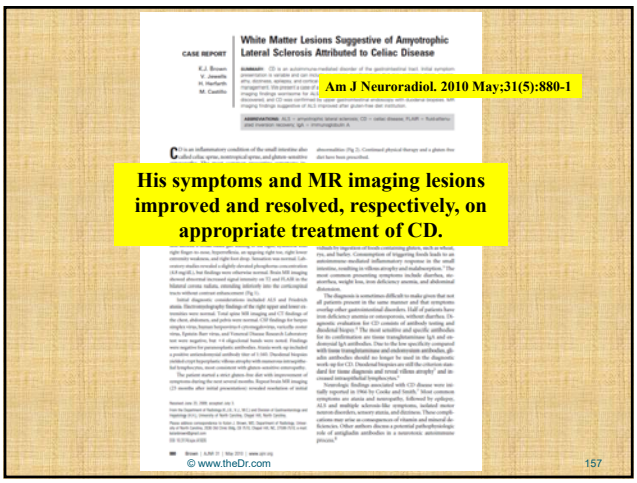
CASE REPORT
White Matter Lesions Suggestive of Amyotrophic Lateral Sclerosis Attributed to Celiac Disease
Am J Neuroradiol. 2010 May;31(5):880-1
His symptoms and MR imaging lesions improved and resolved, respectively, on appropriate treatment of CD.
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"Because 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".

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

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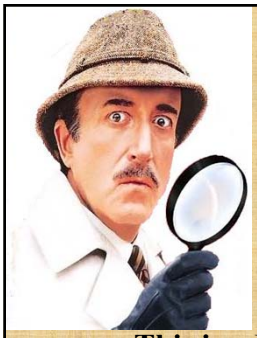
159

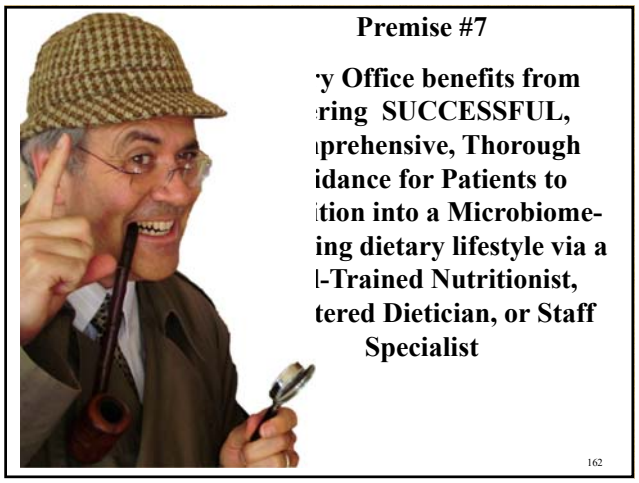


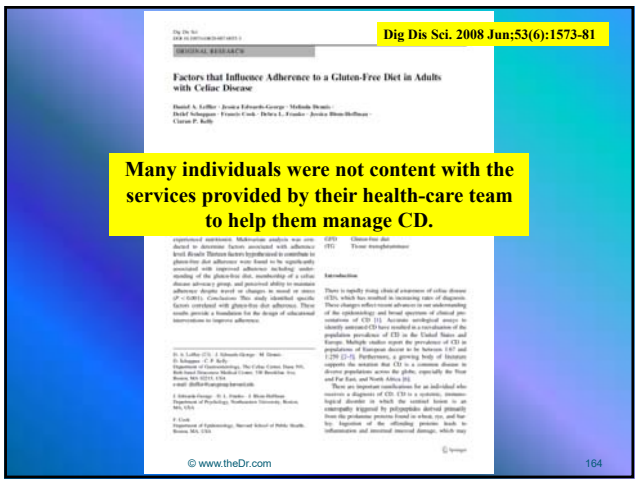
We M at a mi becom nal princ g c

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

160

161


Premise #7
y Office benefits from
ring SUCCESSFUL,
prehensive, Thorough
idance for Patients to
tion into a Microbiome-
ing dietary lifestyle via a
l-Trained Nutritionist,
tered Dietician, or Staff
Specialist
162


Dig Dis Sci. 2008 Jun;53(6):1573-81
Factors that Influence Adherence to a Gluten-Free Diet in Adults with Celiac Disease
Many individuals were not content with the services provided by their health-care team to help them manage CD.
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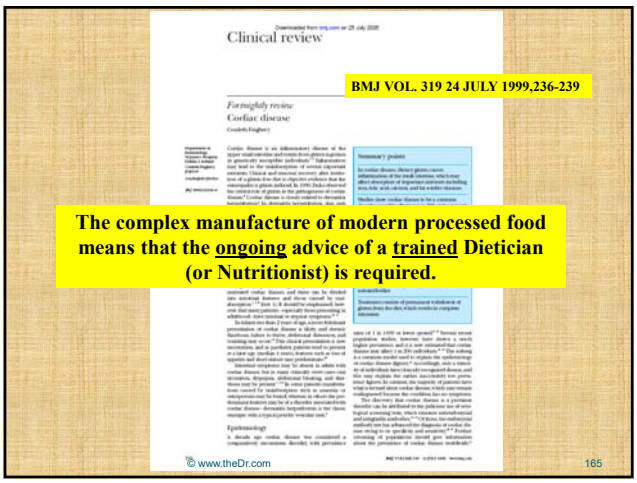
Clinical review
BMJ VOL. 319 24 JULY 1999,236-239
Coeliac disease
The complex manufacture of modern processed food means that the ongoing advice of a trained Dietician (or Nutritionist) is required.
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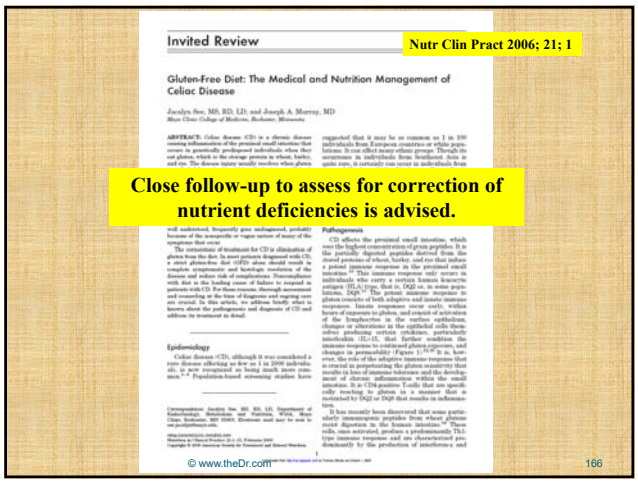
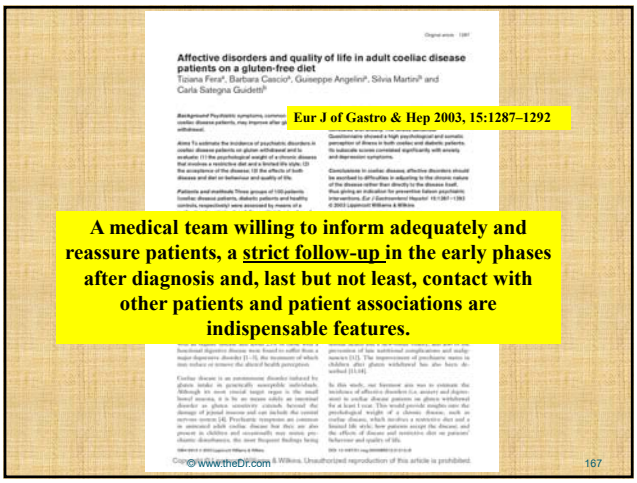

Invited Review

Nutr Clin Pract 2006; 21; 1

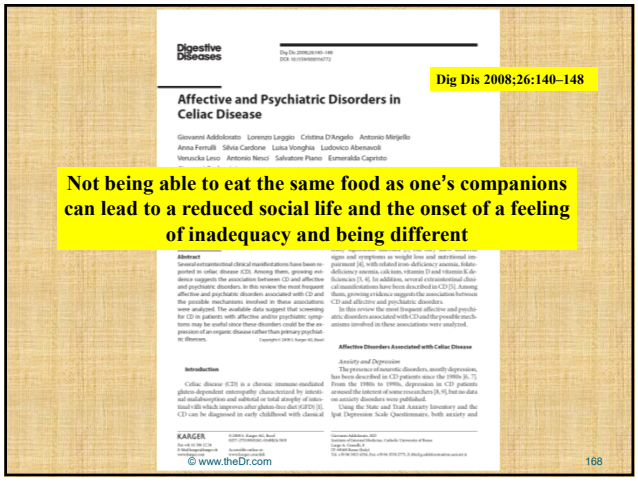
Gluten-Free Diet: The Medical and Nutrition Management of Celiac Disease

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


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

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

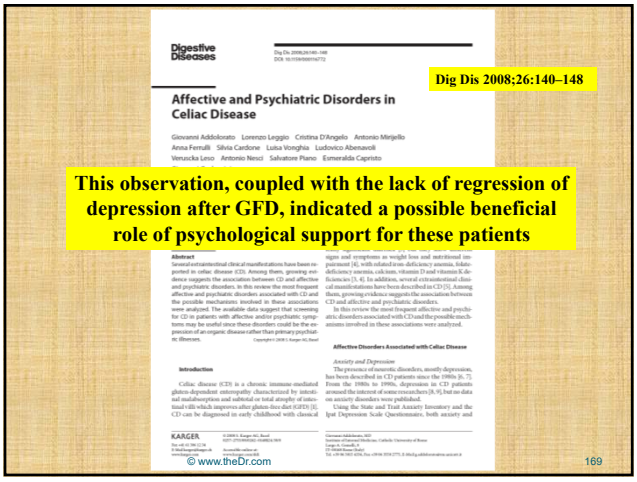
A medical team willing to inform adequately and reassure patients, a strict follow-up in the early phases after diagnosis and, last but not least, contact with other patients and patient associations are indispensable features.


Digestive Diseases

Dig Dis 2008;26:140–148

Affective and Psychiatric Disorders in Celiac Disease

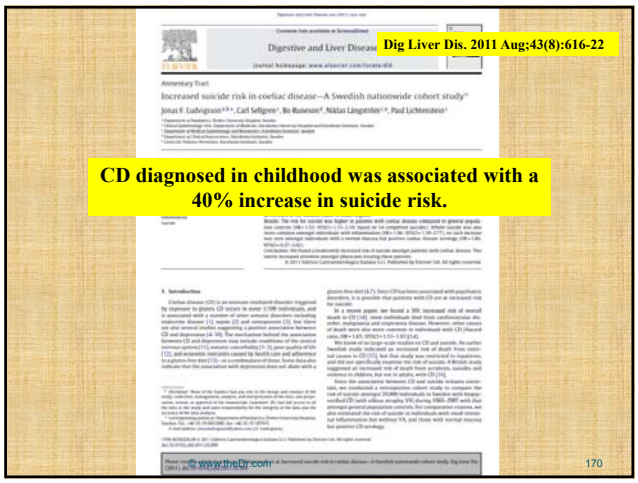
Not being able to eat the same food as one's companions can lead to a reduced social life and the onset of a feeling of inadequacy and being different


Digestive Diseases

Dig Dis 2008;26:140–148

Affective and Psychiatric Disorders in Celiac Disease

This observation, coupled with the lack of regression of depression after GFD, indicated a possible beneficial role of psychological support for these patients


Digestive and Liver Disease
Dig Liver Dis. 2011 Aug;43(8):616-22
Increased suicide risk in coeliac disease--A Swedish nationwide cohort study
CD diagnosed in childhood was associated with a 40% increase in suicide risk.
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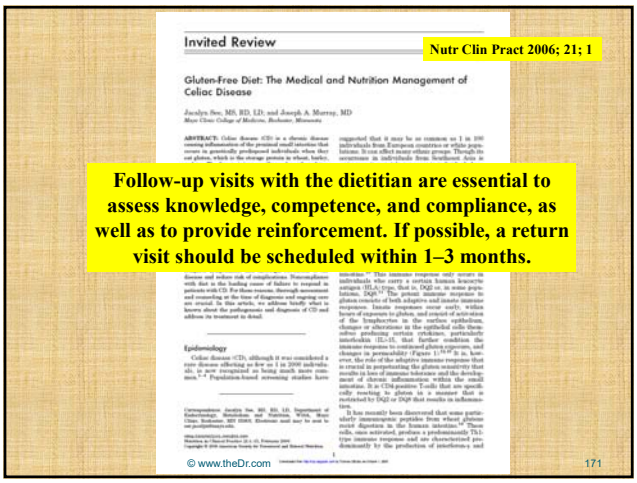
Invited Review
Nutr Clin Pract 2006; 21; 1
Gluten-Free Diet: The Medical and Nutrition Management of Celiac Disease
Follow-up visits with the dietitian are essential to assess knowledge, competence, and compliance, as well as to provide reinforcement. If possible, a return visit should be scheduled within 1–3 months.
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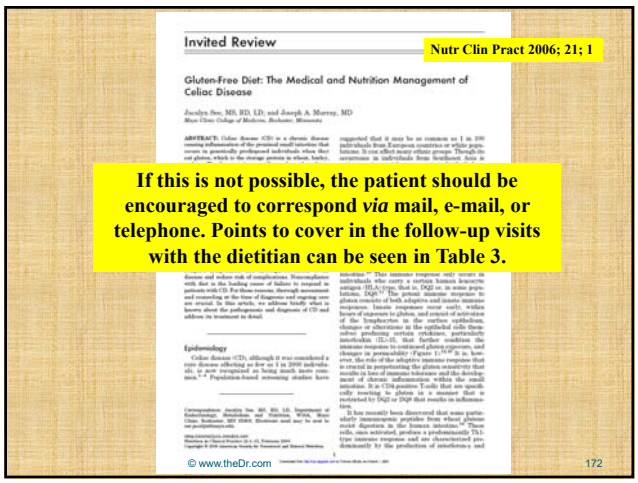
Invited Review
Nutr Clin Pract 2006; 21; 1
Gluten-Free Diet: The Medical and Nutrition Management of Celiac Disease
If this is not possible, the patient should be encouraged to correspond *via* mail, e-mail, or telephone. Points to cover in the follow-up visits with the dietitian can be seen in Table 3.
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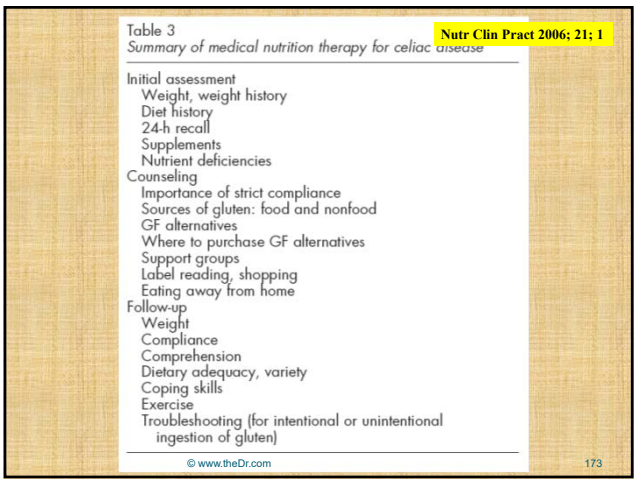
Table 3
Summary of medical nutrition therapy for celiac disease
Nutr Clin Pract 2006; 21; 1
Initial assessment
Weight, weight history
Diet history
24-h recall
Supplements
Nutrient deficiencies
Counseling
Importance of strict compliance
Sources of gluten: food and nonfood
GF alternatives
Where to purchase 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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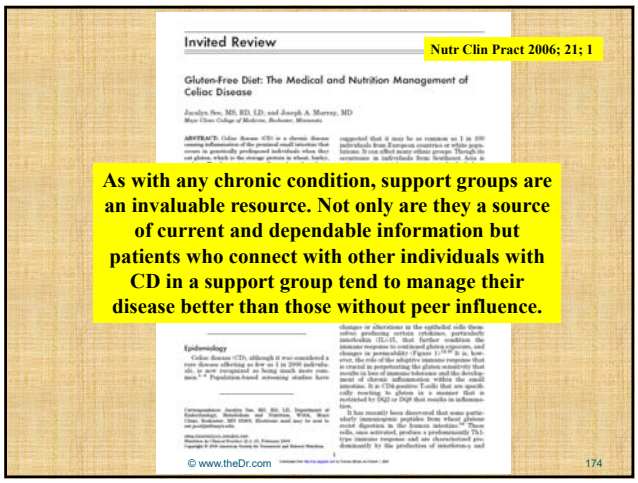
Invited Review
Nutr Clin Pract 2006; 21; 1
Gluten-Free Diet: The Medical and Nutrition Management of Celiac Disease
As with any chronic condition, support groups are an invaluable resource. Not only are they a source of current and dependable information but patients who connect with other individuals with CD in a support group tend to manage their disease better than those without peer influence.
Epidemiology
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3 Case Reports
1. Conjunctival Tumor diagnosed as Karposi's sarcoma
2. Gluten Psychosis in a 14 year old
3. Amyotrophic Lateral Sclerosis
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7 Premises To Look At

Premise #1

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

Detective Adrian Monk

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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

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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

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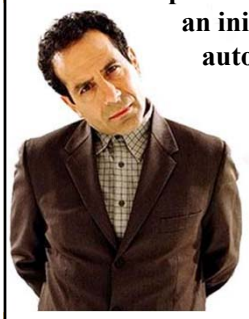
Premise #4

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



Detective Adrian Monk

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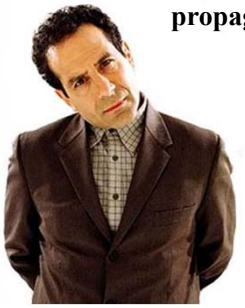
Premise #5

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



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

Detective Adrian Monk

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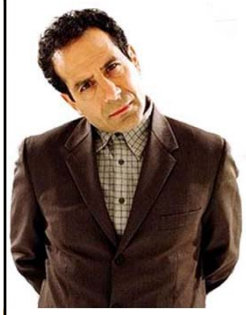
Premise #6

A GFD may contribute to dysbiosis



Detective Adrian Monk

 183

Premise #7

'y Office benefits from 'ring SUCCESSFUL, 'prehensive, Thorough idance for Patients to tion into a Microbiome-ing dietary lifestyle via a l-Trained Nutritionist, tered Dietician, or Staff Specialist

184

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**

 185

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

186

Take Care of Yourself

187

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

188

189


Wishing you Sunrises of Beauty throughout your life