WITH DR. THOMAS O'BRYAN

Canary in the Coalmine
Early Biomarkers of a Brain on Fire

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- ***Adjunct Faculty - The Institute for Functional Medicine***
- ***Adjunct Faculty - The National University of Health Sciences***
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- ***Clinical Consultant on Functional Medicine - NuMedica, Inc.***
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- ***Editorial Review Board - Alternative Therapies in Health and Medicine***
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Premise #1

What is the Most Prevalent Pathology at the Root of Practically All Disease

Detective Adrian Monk

HHS Public Access
Author manuscript
Nat Med. Author manuscript; available in PMC 2020 April 10.

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Chronic inflammation in the etiology of disease across the life span

David Furman[1,2,3,4,*], **Judith Campisi**[1,5], **Eric Verdin**[1], **Pedro Carrera-Bastos**[6], **Sasha Targ**[4,7], **Claudio Franceschi**[8,9], **Luigi Ferrucci**[10], **Derek W. Gilroy**[11], **Alessio Fasano**[12], **Gary W. Miller**[13], **Andrew H. Miller**[14], **Alberto Mantovani**[15,16,17], **Cornelia M. Weyand**[18], **Nir Barzilai**[19], **Jorg J. Goronzy**[20], **Thomas A. Rando**[20,21,22], **Rita B. Effros**[23], **Alejandro Lucia**[24,25], **Nicole Kleinstreuer**[26,27], **George M. Slavich**[28]

One of the most important medical discoveries of the past two decades has been that the immune system and inflammatory processes are involved in not just a few select disorders, but a wide variety of mental and physical health problems that dominate present-day morbidity and mortality worldwide

[9]Department of Applied Mathematics and Laboratory of Systems Biology of Aging, Lobachevsky University, Nizhny Novgorod, Russia.

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[11]Centre for Clinical Pharmacology and Therapeutics, Division of Medicine, University College London, London, UK.

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Peer review information Hannah Stower was the primary editor on this article and managed its editorial process and peer review in collaboration with the rest of the editorial team.

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Indeed, chronic inflammatory diseases have been recognized as the most significant cause of death in the world today,

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Understanding inflammation, its regulation, and relevance for health: A top scientific and public priority

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One of the most important scientific discoveries in health research in recent years has involved the realization that inflammation plays a role in not just a few disorders, but many disease conditions that cause substantial morbidity and contribute to early mortality (Couzin-Frankel, 2010). Included in this list are several psychiatric conditions, such as anxiety, unipolar and bipolar depression, schizophrenia, and post-traumatic stress disorder, as well as numerous physical disease conditions including asthma, rheumatoid arthritis,

All told, inflammation is involved in at least 8 of the top 10 leading causes of death in the United States today

Although it is easy to characterize inflammation as bad, the story is complicated and several issues remain unresolved. The first issue involves *time course*. Time-limited increases in inflammation are important for promoting wound healing and recovery and for limiting the spread of communicable infections. Inflammation, therefore, is certainly not always bad and rather can be absolutely critical for survival, especially during times of injury and infection. Presently, however, we have only a limited understanding of when elevated levels of inflammatory activity are helpful versus harmful. The second issue involves *location*. Although classic theories conceptualized inflammation as a localized process, novel assays for detecting different inflammatory mediators have ushered in new ideas about "systemic inflammation". At the same time, these advancements have shown that inflammatory activity occurring in different places, including in peripheral tissues, different organs, oral fluids, and the central nervous system, are usually not highly correlated and likely have different effects on health. Therefore, although it is convenient to characterize individuals as having "high" versus "low" levels of inflammation, these descriptions are overly crude and highlight a need to talk about "elevated inflammation" in more precise terms. A third issue concerns *conditional effects*. Although inflammation is a core feature of some diseases, in

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Conflicts of interest
The author declares that he has no conflicts of interest with respect to the authorship or publication of this article.

National Vital Statistics Reports

Volume 64, Number 7 July 27, 2015

Table C. Deaths and percentage of total deaths for the 10 leading causes of death: United States, 2010–2011

[An asterisk (*) preceding a cause-of-death code indicates that the code is not included in the *International Classification of Diseases, 10th Revision* (ICD–10); see Technical Notes]

Cause of death (based on ICD–10)	Rank[1]	2011 Deaths	2011 Percent of total deaths	2010 Deaths	2010 Percent of total deaths
All causes	. . .	2,515,458	100.0	2,468,435	100.0
Diseases of heart . . . . . (I00–I09,I11,I13,I20–I51)	1	596,577	23.7	597,689	24.2
Malignant neoplasms . . . . . (C00–C97)	2	576,691	22.9	574,743	23.3
Chronic lower respiratory diseases . . . . . (J40–J47)	3	142,943	5.7	138,080	5.6
Cerebrovascular diseases . . . . . (I60–I69)	4	128,932	5.1	129,476	5.2
Accidents (unintentional injuries) . . . . . (V01–X59,Y85–Y86)	5	126,438	5.0	120,859	4.9
Alzheimer's disease . . . . . (G30)	6	84,974	3.4	83,494	3.4
Diabetes mellitus . . . . . (E10–E14)[2]	7	73,831	2.9	69,071	2.8
Influenza and pneumonia . . . . . (J09–J18)	8	53,826	2.1	50,097	2.0
Nephritis, nephrotic syndrome and nephrosis . . . . (N00–N07,N17–N19,N25–N27)[3]	9	45,591	1.8	50,476	2.0
Intentional self-harm (suicide) . . . . . (*U03,X60–X84,Y87.0)	10	39,518	1.6	38,364	1.6

. . . Category not applicable

[1]Based on number of deaths.

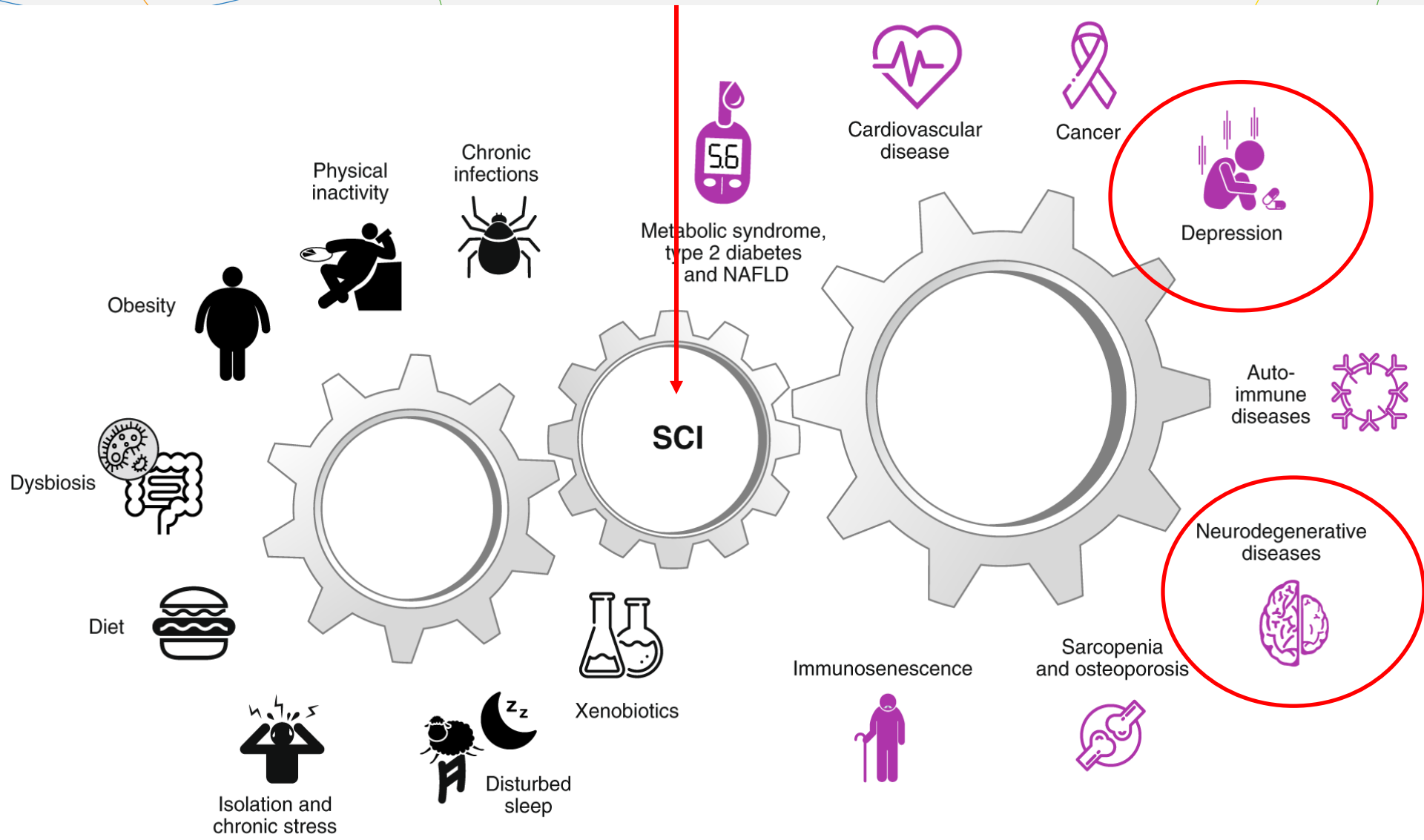
[2]Because of coding-rule changes in data year 2011, the increase in number of deaths from Diabetes mellitus should be interpreted with caution; see Technical Notes.

[3]Because of coding-rule changes in data year 2011, the decrease in number of deaths and rank order for Nephritis, nephrotic syndrome and nephrosis should be interpreted with caution; see Technical Notes.

It is also important to note that rankings do not necessarily denote the causes of death of greatest public health importance. Some causes of death of public health significance are excluded from the ranking

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
National Center for Health Statistics
National Vital Statistics System

Systemic Chronic Inflammation



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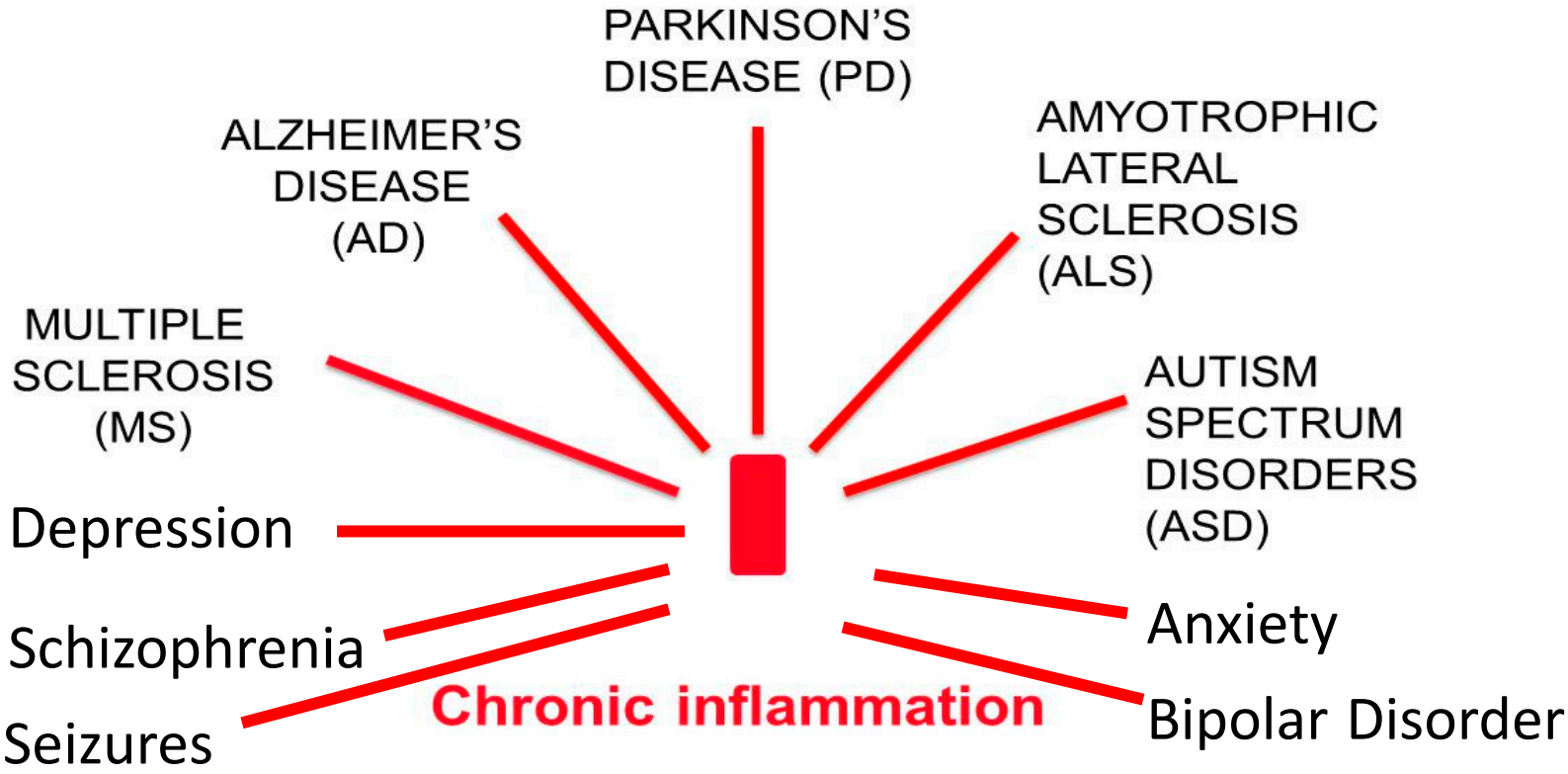

Figure 1. Chronic neurodegenerative diseases have a chronic inflammatory basis in common.

Nutrients. 2019 Nov 9;11(11):2714 + Modifications

nutrients

MDPI

Review

Undigested Food and Gut Microbiota May Cooperate in the Pathogenesis of Neuroinflammatory Diseases: A Matter of Barriers and a Proposal on the Origin of Organ Specificity

Paolo Riccio and Rocco Rossano *

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* Correspondence: rocco.rossano@unibas.it

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check for updates

As for neuroinflammatory diseases, in most cases, the neuroinflammatory state does not originate in the central nervous system (CNS), but is thought to come from a chronic systemic inflammation (CSI)

setting up of adequate experimental models of disease and develop targeted dietary interventions.

Keywords: diet; gut microbiota; inflammation; intestinal barrier; blood-brain barrier; Alzheimer's disease; Parkinson's disease; multiple sclerosis; autism spectrum disorders; amyotrophic lateral sclerosis

1. Chronic Neurodegenerative Diseases are Associated with Low-Grade Chronic Inflammation

Despite having different etiology and different pathogenic mechanisms, chronic neurodegenerative diseases, such as multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and autism spectrum disorder (ASD), all have an inflammatory nature in common [1] (Figure 1).

Fighting the inflammatory processes that underlie these diseases may reduce their progression and their severity. Inflammation is an innate, non-specific defense process [2,3]. It occurs in response to the presence of foreign material (*non-self*), or as a consequence of tissue damage caused by physical, chemical or biological agents, or by abnormalities such as the failure to eliminate waste or digest nutrients. If the cause of inflammation persists, the inflammation also persists, usually with low intensity, and is called low-grade chronic inflammation. As for the chronic neuroinflammatory diseases, in most cases, the neuroinflammatory state does not originate in the central nervous system (CNS), but is thought to come from a chronic systemic inflammation (CSI) [4–6]. Recent evidence suggests that CSI may in turn result from a persistent intestinal inflammation spreading through the intestinal

Nutrients. 2019 Nov 9;11(11):2714

Triggers and Mediators of Systemic Inflammation

- **What Neurological Presenting Complaints in Your Practice are NOT Inflammatory?**

Premise #1

The Brain is Your
'Yellow Canary in the Coal Mine'

Detective Adrian Monk

Funct Neurol Rehabil Ergon 2013;3(2-3):173-181 ISSN: 2156-941X

BRAIN-REACTIVE ANTIBODIES IN TRAUMATIC BRAIN INJURY

*Aristo Vojdani**
Immunosciences Lab., Inc., Los Angeles, CA USA

ABSTRACT

It is estimated that the human brain contains more than ten billion capillaries, which translates into one vessel for each neuron. The total length of the capillaries in the human brain is about 400 miles.

Keywords: Autoimmune, traumatic brain injury, autoantigens, S100 B antibodies

INTRODUCTION

Autoimmune diseases affect about 7% of the world's population. In these disorders, pathogenic T_H1 cells, autoreactive T_H17 cells, antibodies and associated molecules attack antigens of various tissues, including brain tissue. Brain-reactive antibodies are detected in about 3% of the general population but do not contribute to brain pathology unless they cross the blood-brain barrier (BBB) [1].

The BBB is composed of highly specialized brain endothelial cells which are fully differentiated to the neurovascular system. It is estimated that the human brain contains more than ten billion capillaries, which translates into one vessel for each neuron. The total length of the capillaries in the human brain is about 400 miles. In conjunction with microglia, astrocytic foot processes and pericytes, the BBB separates the neurons from various components of the circulating blood [2]. The endothelial tight junctions, together with astrocytic foot processes, prevent the passage of all soluble

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What are the current numbers of frequency of brain dysfunction at both ends of life?

The Prevalence of Parent-Reported Autism Spectrum Disorder Among US Children

Michael D. Kogan, PhD,[a] Catherine J. Vladutiu, PhD, MPH,[a] Laura A. Schieve, PhD,[b] Reem M. Ghandour, DrPH,[a] Stephen J. Blumberg, PhD,[c] Benjamin Zablotsky, PhD,[c] James M. Perrin, MD,[d] Paul Shattuck, PhD,[e] Karen A. Kuhlthau, PhD,[d] Robin L. Harwood, PhD,[a] Michael C. Lu, MD, MPH[f]

abstract

OBJECTIVES: To estimate the national prevalence of parent-reported autism spectrum disorder (ASD) diagnosis among US children aged 3 to 17 years as well as their treatment and health care experiences using the 2016 National Survey of Children's Health (NSCH).

METHODS: The 2016 NSCH is a nationally representative survey of 50 212 children focused on the health and well-being of children aged 0 to 17 years. The NSCH collected parent-

characteristics and co-occurring conditions.

CONCLUSIONS: The estimated prevalence of US children with a parent-reported ASD diagnosis is now 1 in 40, with rates of ASD-specific treatment usage varying by children's sociodemographic and co-occurring conditions.

WHAT THIS STUDY ADDS:

The estimated prevalence of US children with parent-reported diagnosis of ASD is now 1 in 40.

[a]Health Resources and Services Administration, Maternal and Child Health Bureau, Rockville, Maryland; [b]National Center on Birth Defects and Developmental Disabilities and [c]National Center for Health Statistics, Centers for Disease Control and Prevention, Hyattsville, Maryland; [d]Department of Pediatrics, Harvard Medical School, Harvard University and MassGeneral Hospital for Children, Boston, Massachusetts; [e]AJ Drexel Autism Institute, School of Public Health, Drexel University, Philadelphia, Pennsylvania; and [f]Office of the Dean, Milken Institute School of Public Health, George Washington University, Washington, District of Columbia

Dr Kogan conceptualized and designed the study and drafted most of the initial manuscript; Dr Vladutiu conducted the data analyses and assisted with drafting of the initial manuscript; Dr Schieve assisted with drafting of the initial manuscript and provided critical review of subsequent manuscript drafts; Drs Ghandour, Blumberg, Zablotsky, Perrin, Shattuck, Kuhlthau, Harwood, and Lu provided critical reviews on all manuscript drafts; and all authors approved the final manuscript as submitted.

WHAT'S KNOWN ON THIS SUBJECT: Previous studies over the last 20 years have shown an increasing prevalence of autism spectrum disorder (ASD) among US children. Moreover, families of children with ASD have reported greater health care needs and challenges compared with children with other emotional or behavioral conditions.

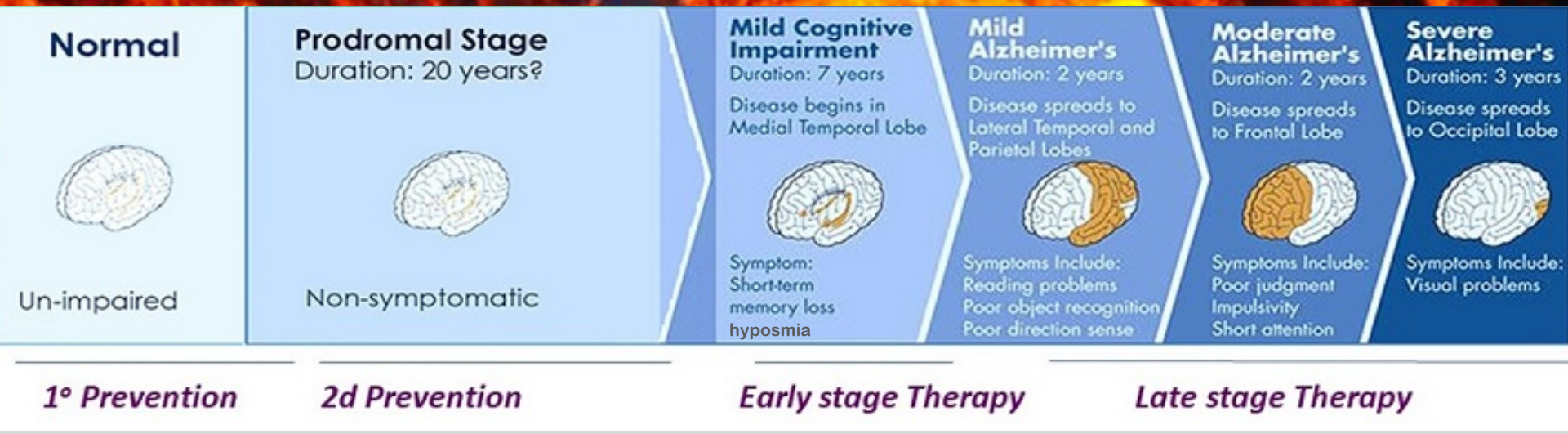
WHAT THIS STUDY ADDS: In this study, we present new nationally representative data on the prevalence of ASD, reported health care challenges, and estimates on ASD-specific behavioral and medication treatments. The estimated prevalence of US children with parent-reported diagnosis of ASD is now 1 in 40.

To cite: Kogan MD, Vladutiu CJ, Schieve LA, et al. The Prevalence of Parent-Reported Autism Spectrum Disorder Among US Children. *Pediatrics.* 2018;142(6):e20174161

Pediatrics. 2018;142(6):e20174161

MORTALITY AND MORBIDITY

Normal levels of brain antibodies (cellular regeneration, apoptosis, autophagy)



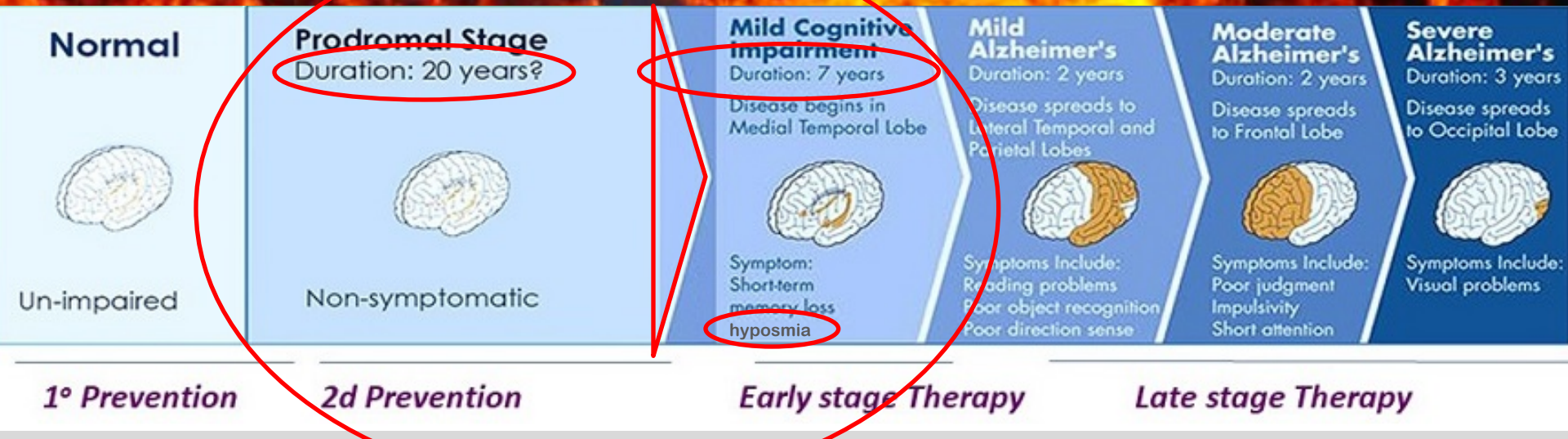
Food sensitivities (loss of oral tolerance)
Infections (bacterial, viral, LPS, … loss of tolerance)
Environmental exposure loss of tolerance
Electromagnetic pollution loss of tolerance
Emotional stress loss of tolerance
Structural loss of tolerance

https://aspe.hhs.gov/advisory-council-july-2019-meeting-presentation-adrd-therapeutic-approaches

Elevated levels of antibodies - brain+

(molecular mimicry, self-antigen modification, bystander activation, and immune reactivity modulation)

Creates a Breach of the Blood Brain Barrier(B4)



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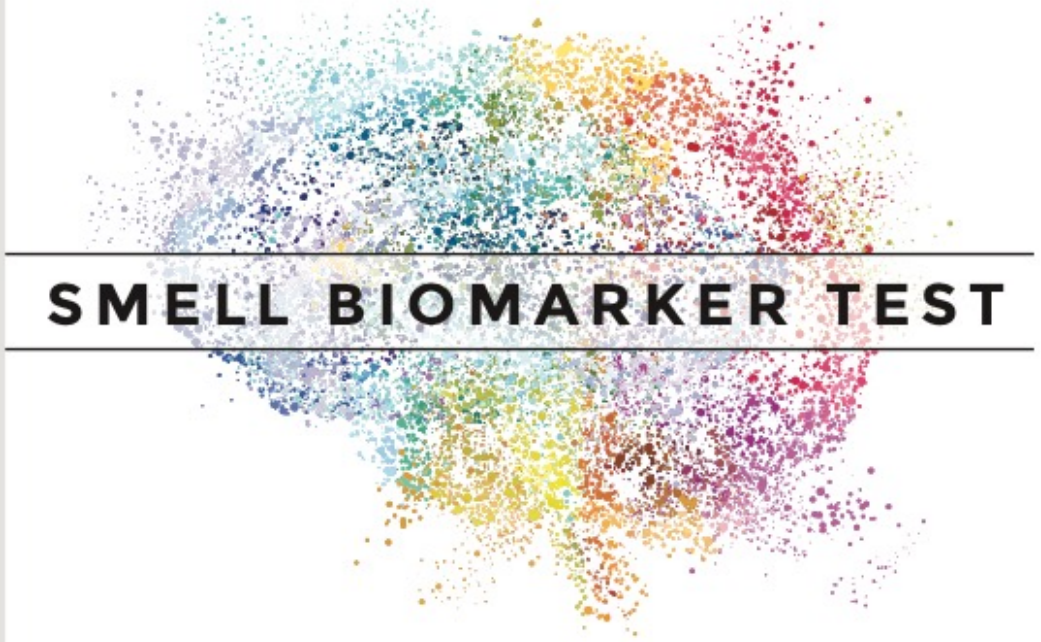
SMELL IDENTIFICATION TEST (UPSIT)



www.theDr.com/smell
www.theDr.com/smelltest10

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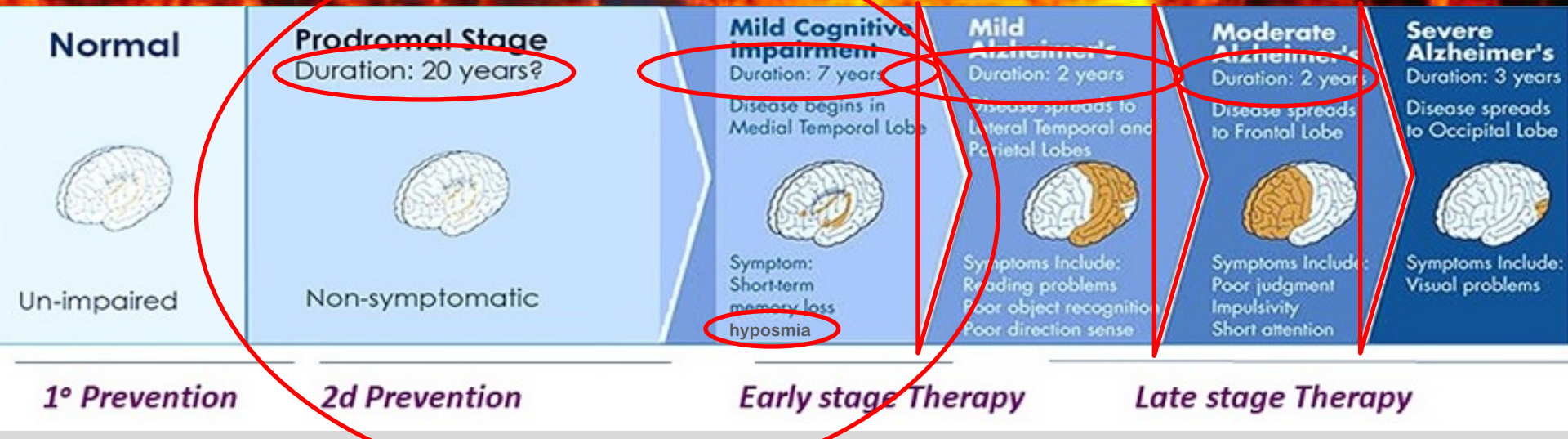

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4 YEARS!

EARLY-ONSET DEMENTIA
AND ALZHEIMER'S RATES GROW

EXHIBIT 1:

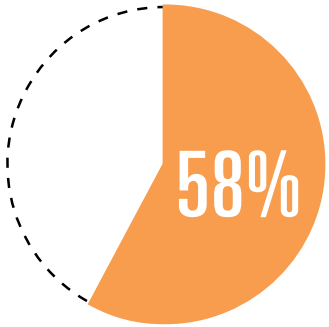
	2013	2017	
Early-onset dementia and Alzheimer's disease combined diagnosis rates for adults ages 30 to 64	4.2 per 10,000 adults	12.6 per 10,000 adults	↑ 200%

AVERAGE AGE

49

PERSON LIVING WITH EITHER FORM OF DEMENTIA

MORE COMMON IN WOMEN



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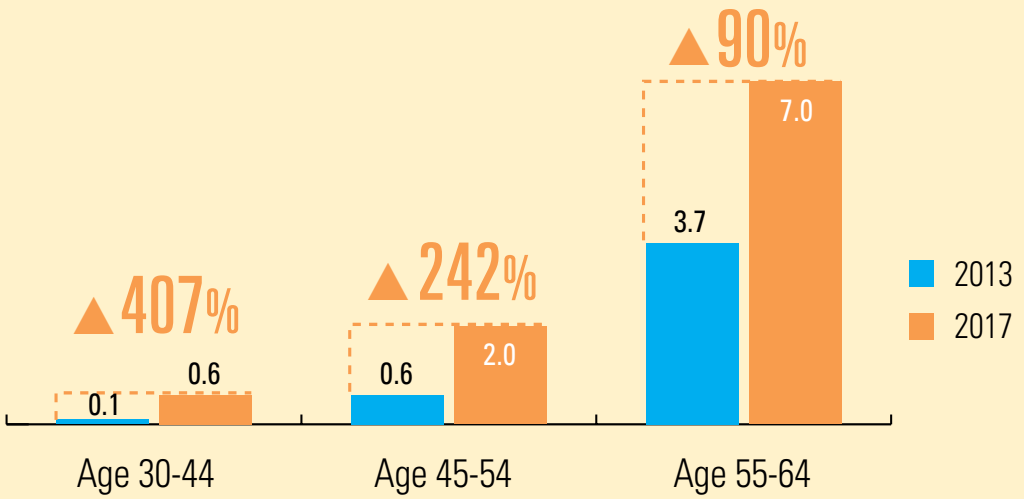
https://www.bcbs.com/the-health-of-america/reports/early-onset-dementia-alzheimers-disease-affecting-younger-american-adults

Overall diagnosis of the condition is small, but from 2013 to 2017, there were large increases in early-onset Alzheimer's disease among people ages 30 to 54. (See Exhibit 5.)

EXHIBIT 5: DIAGNOSIS RATES OF EARLY-ONSET ALZHEIMER'S DISEASE BY AGE, PER 10,000 PEOPLE (2013 vs. 2017)



https://www.bcbs.com/the-health-of-america/reports/early-onset-dementia-alzheimers-disease-affecting-younger-american-adults

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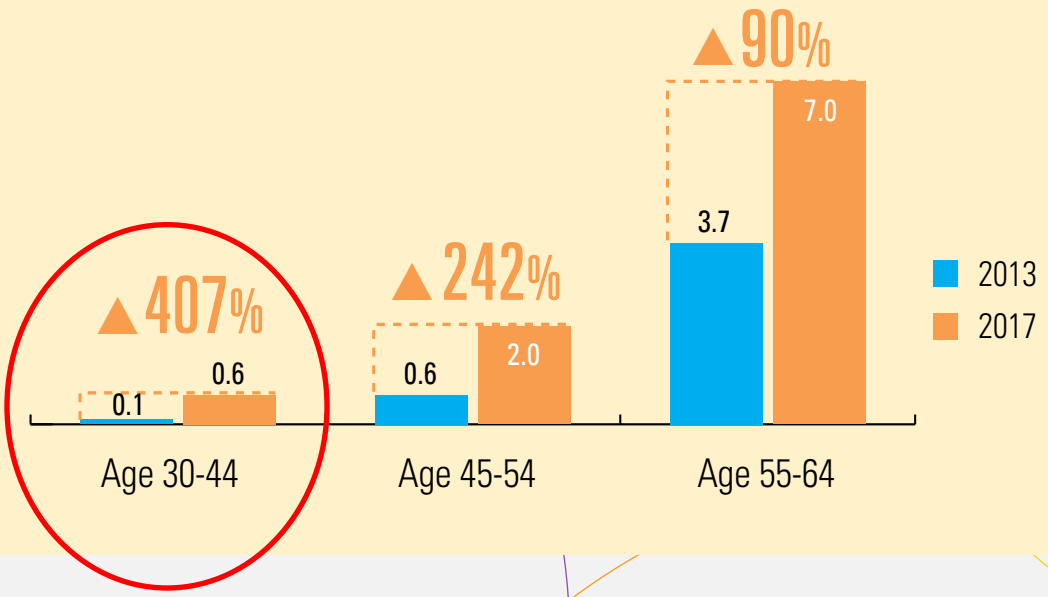
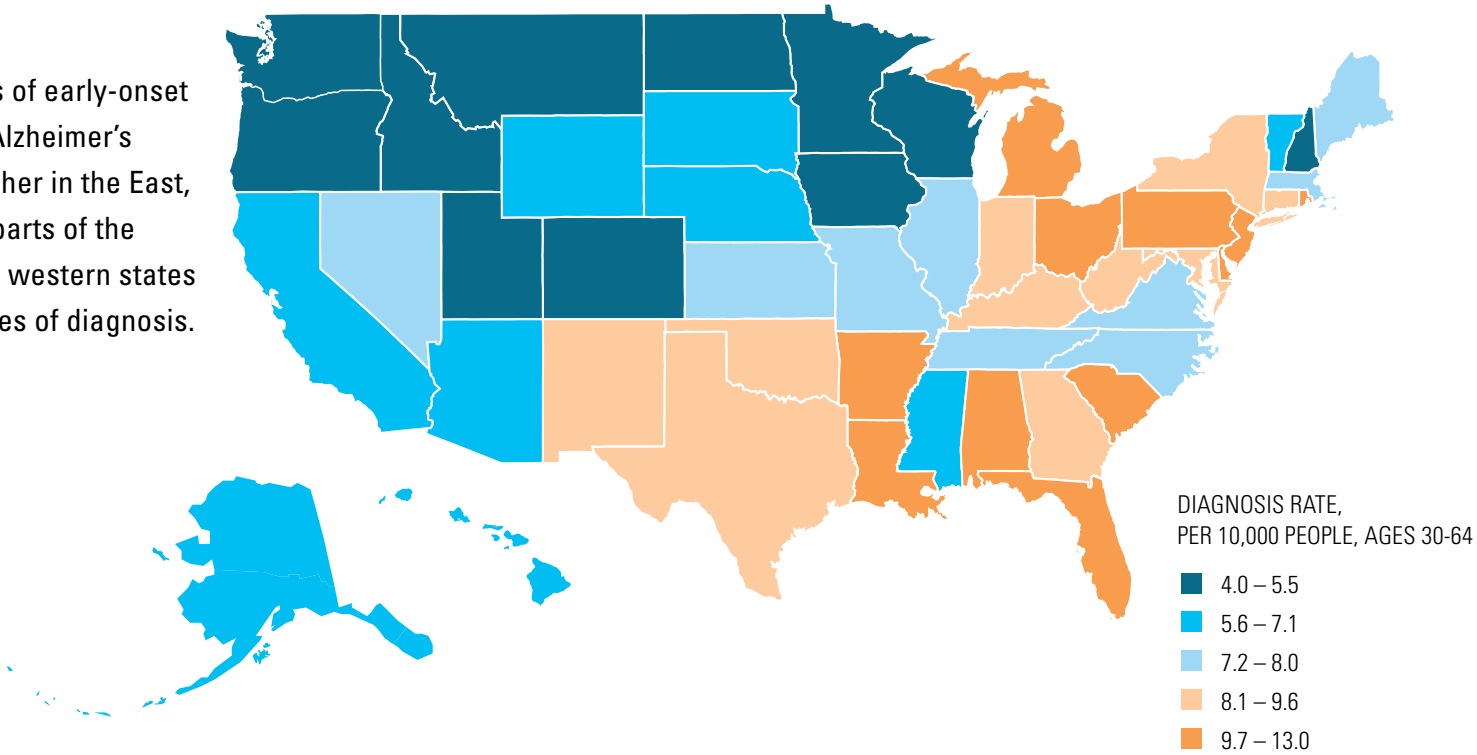


https://www.bcbs.com/the-health-of-america/reports/early-onset-dementia-alzheimers-disease-affecting-younger-american-adults

EXHIBIT 3: DIAGNOSIS RATE OF EARLY-ONSET DEMENTIA AND ALZHEIMER'S, BY STATE (2013-2017)

Diagnosis rates of early-onset dementia and Alzheimer's disease are higher in the East, the South and parts of the Midwest, while western states show lower rates of diagnosis. (See Exhibit 3.)



https://www.bcbs.com/the-health-of-america/reports/early-onset-dementia-alzheimers-disease-affecting-younger-american-adults

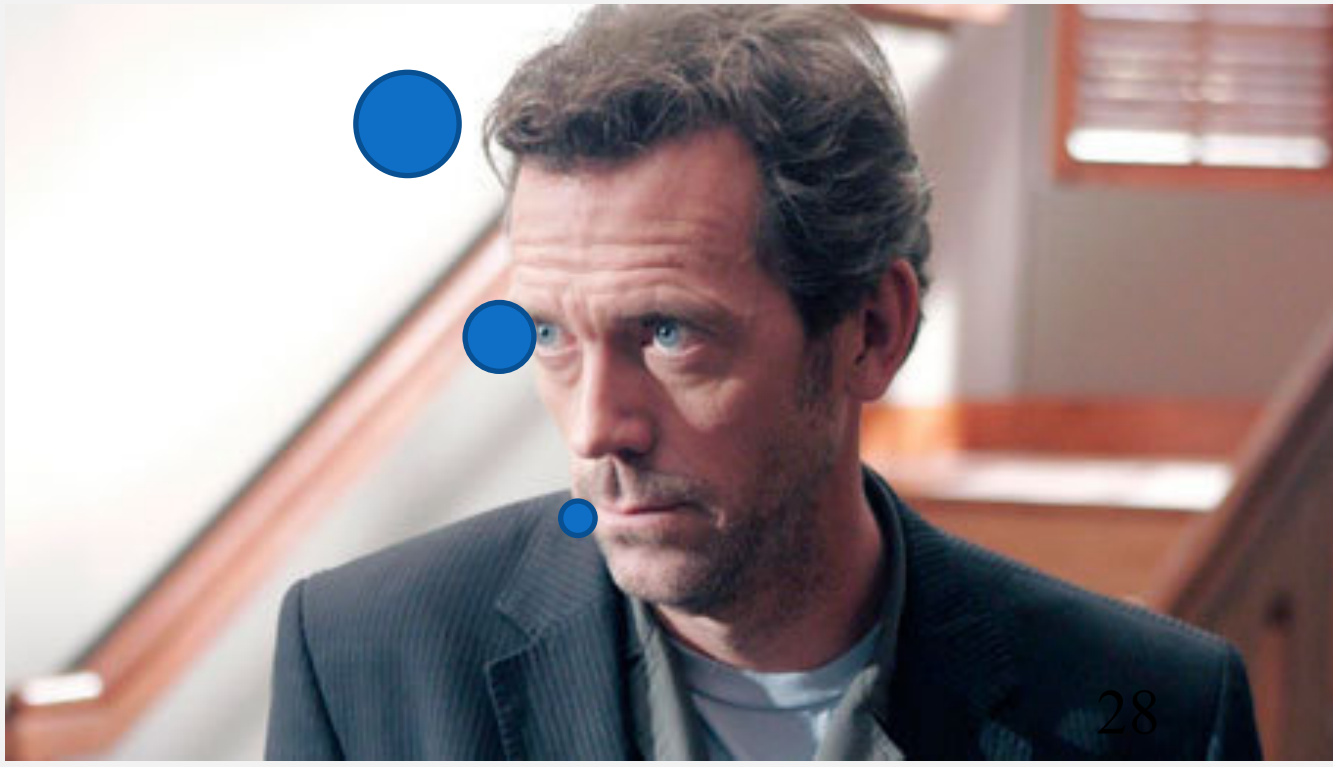
So what is the takeaway from these startling statistics as to what is happening to our Brains?

The Brain, our *'yellow canary in the coal mine'*, is under constant assault from conception to elderly

and We're Losing the Battle

How Do We [illegible] Where This

First and foremost is the understanding that Alzheimer's is a decades-long process of ongoing inflammation causing brain cell destruction



Although there are dozens of environmental triggers that have contributed to an individuals' specific inflammatory state, what's the *'Big Kahuna'*?

Check for updates

REVIEW

All disease begins in the (leaky) gut: role of zonulin-mediated gut permeability in the pathogenesis of some chronic inflammatory diseases [version 1; peer review: 3 approved]

Alessio Fasano [1,2]

[1]Mucosal Immunology and Biology Research Center, Center for Celiac Research and Treatment and Division of Pediatric Gastroenterology and Nutrition, Massachusetts General Hospital for Children, Boston, Massachusetts, USA
[2]European Biomedical Research Institute of Salerno, Salerno, Italy

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Latest published: 31 Jan 2020, **9**(F1000 Faculty Rev):69 (https://doi.org/10.12688/f1000research.20510.1)

Abstract

Improved hygiene leading to reduced exposure to microorganisms has been implicated as one possible cause for the recent "epidemic" of chronic [illegible] and the composition of gut microbiome and its epigenetic influence on the host genomic expression have been identified as three additional elements in causing CIDs. During the past decade, a growing number of publications have focused on human genetics, the gut microbiome, and proteomics, suggesting that loss of mucosal barrier function, particularly in the gastrointestinal tract, may substantially affect antigen trafficking, ultimately influencing the close bidirectional interaction between gut microbiome and our immune system. This cross-talk is highly influential in shaping the host gut immune system function and ultimately shifting genetic predisposition to clinical outcome. This observation led to a re-visitation of the possible causes of CIDs epidemics, suggesting a key pathogenic role of gut permeability. Pre-clinical and clinical studies have shown that the zonulin family, a group of proteins modulating gut permeability, is implicated in a variety of CIDs, including autoimmune, infective, metabolic, and tumoral diseases. These data offer novel therapeutic targets for a variety of CIDs in which the zonulin pathway is implicated in their pathogenesis.

Keywords

Chronic inflammatory diseases, Gut permeability, microbiome, zonulin

The activation of the zonulin pathway may represent a defensive mechanism that "flushes out" microorganisms.

Open Peer Review

Reviewer Status ✓ ✓ ✓

	Invited Reviewers		
	1	**2**	**3**

commissioned and are peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

1 **Xin M. Luo**, Virginia Tech, Blacksburg, USA

2 **Michael Maes**, Chulalongkorn University, Bangkok, Thailand

3 **Arul Jayaraman**, Texas A&M Health Science Center, Bryan, USA

Any comments on the article can be found at the end of the article.

https://f1000research.com/articles/9-69/v1

REVIEW

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[2]European Biomedical Research Institute of Salerno, Salerno, Italy

v1 **First published:** 31 Jan 2020, **9**(F1000 Faculty Rev):69 (https://doi.org/10.12688/f1000research.20510.1)
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Among the several potential intestinal luminal stimuli that can stimulate zonulin release (thus Intestinal Permeability), small exposure to large amounts of bacteria (and its exhaust LPS) and gluten, have been identified as the two most powerful triggers

suggesting that loss of mucosal barrier function, particularly in the gastrointestinal tract, may substantially affect antigen trafficking, ultimately influencing the close bidirectional interaction between gut microbiome and our immune system. This cross-talk is highly influential in shaping the host gut immune system function and ultimately shifting genetic predisposition to clinical outcome. This observation led to a re-visitation of the possible causes of CIDs epidemics, suggesting a key pathogenic role of gut permeability. Pre-clinical and clinical studies have shown that the zonulin family, a group of proteins modulating gut permeability, is implicated in a variety of CIDs, including autoimmune, infective, metabolic, and tumoral diseases. These data offer novel therapeutic targets for a variety of CIDs in which the zonulin pathway is implicated in their pathogenesis.

Keywords
Chronic inflammatory diseases, Gut permeability, microbiome, zonulin

Open Peer Review

Reviewer Status ✓ ✓ ✓

names and affiliations.

1 **Xin M. Luo**, Virginia Tech, Blacksburg, USA

2 **Michael Maes**, Chulalongkorn University, Bangkok, Thailand

3 **Arul Jayaraman**, Texas A&M Health Science Center, Bryan, USA

Any comments on the article can be found at the end of the article.

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REVIEW

All disease begins in the (leaky) gut: role of zonulin-mediated gut permeability in the pathogenesis of some chronic inflammatory diseases [version 1; peer review: 3 approved]

Alessio Fasano [1,2]

[1]Mucosal Immunology and Biology Research Center, Center for Celiac Research and Treatment and Division of Pediatric Gastroenterology and Nutrition, Massachusetts General Hospital for Children, Boston, Massachusetts, USA
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Abstract

Improved hygiene leading to reduced exposure to microorganisms has been implicated as one possible cause for the recent "epidemic" of chronic inflammatory diseases (CIDs) in industrialized countries. That is the

and the composition of gut microbiome and its epigenetic influence on the host genomic expression have been identified as three additional elements in causing CIDs. During the past decade, a growing number of publications have focused on human genetics, the gut microbiome, and proteomics, suggesting that loss of mucosal barrier function, particularly in the gastrointestinal tract, may substantially affect antigen trafficking, ultimately influencing the close bidirectional interaction between gut microbiome and our immune system. This cross-talk is highly influential in shaping the host gut immune system function and ultimately shifting genetic predisposition to clinical outcome. This observation led to a re-visitation of the possible causes of CIDs epidemics, suggesting a key pathogenic role of gut permeability. Pre-clinical and clinical studies have shown that the zonulin family, a group of proteins modulating gut permeability, is implicated in a variety of CIDs, including autoimmune, infective, metabolic, and tumoral diseases. These data offer novel therapeutic targets for a variety of CIDs in which the zonulin pathway is implicated in their pathogenesis.

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	Invited Reviewers		
	1	**2**	**3**
version 1	✓	✓	✓

publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

1 **Xin M. Luo**, Virginia Tech, Blacksburg, USA

2 **Michael Maes**, Chulalongkorn University, Bangkok, Thailand

3 **Arul Jayaraman**, Texas A&M Health Science Center, Bryan, USA

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Gluten is misinterpreted by the zonulin pathway as a potential harmful component of a microorganism.

https://f1000research.com/articles/9-69/v1

Clinical Review & Education

JAMA | Review

Celiac Disease and Nonceliac Gluten Sensitivity
A Review

Maureen M. Leonard, MD, MMSc; Anna Sapone, MD, PhD; Carlo Catassi, MD, MPH; Alessio Fasano, MD

IMPORTANCE The prevalence of gluten-related disorders is rising, and increasing numbers of individuals are empirically trying a gluten-free diet for a variety of signs and symptoms. This review aims to present current evidence regarding screening, diagnosis, and treatment for celiac disease and nonceliac gluten sensitivity.

OBSERVATIONS Celiac disease is a gluten-induced immune-mediated enteropathy characterized by a specific genetic genotype (*HLA-DQ2* and *HLA-DQ8* genes) and autoantibodies (antitissue transglutaminase and antiendomysial). Although the inflammatory process specifically targets the intestinal mucosa, patients may present with gastrointestinal signs or symptoms, extraintestinal signs or symptoms, or both, suggesting that celiac disease is a systemic disease. Nonceliac gluten sensitivity is diagnosed in individuals who do not have celiac disease or wheat allergy but who have intestinal symptoms, extraintestinal symptoms, or both, related to ingestion of gluten-containing grains, with symptomatic improvement on their withdrawal. The

and the development of possible comorbidities.

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CME Quiz at jamanetwork.com/learning

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Section Editors: Edward Livingston, MD, Deputy Editor, and Mary McGrae McDermott, MD, Senior Editor.

Previous studies have shown that gliadin (in wheat) can cause an immediate and transient increase in gut permeability. This process takes place in all individuals who ingest gluten.

Celiac disease is a chronic, small-intestinal immune-mediated enteropathy initiated by exposure to dietary gluten in genetically predisposed individuals and characterized by specific autoantibodies against tissue transglutaminase 2 (anti-tTG2), endomysium, and/or deamidated gliadin peptide.[1] Although up to 40% of the population carries the genotype *HLA-DQ2* or *HLA-DQ8*, which is required for the development of celiac disease, only 2% to 3% of *HLA-DQ2* or *HLA-DQ8* carriers subsequently develop celiac disease.[2] Celiac disease, once considered a relatively rare gastrointestinal condition affecting almost exclusively young white children, can develop at any age and can affect almost any race. Celiac disease was first described by Samuel Gee in 1887. Wheat was hypothesized as the possible offending agent by William Dicke in 1941.[3]

The epidemiology, clinical presentation, pathophysiology, and management of the disease have changed since its initial description. There is strong evidence that celiac disease is an autoimmune disease triggered by the ingestion of gluten present in wheat, barley, and rye in genetically predisposed individuals. The prevalence of celiac disease in the general population is 1%, with regional differences (**Table 1**).[4] Celiac disease can affect any human organ or tissue (Table 1 and **Table 2**).[6]

Nonceliac gluten sensitivity is a term used to describe individuals who have intestinal signs or symptoms, extraintestinal signs or symptoms, or both, related to ingestion of gluten-containing grains (Table 2), with improvement when these are removed from a patient's diet. The frequency of nonceliac gluten sensitivity is unknown owing to the lack of validated biomarkers, but it is thought to be more common than celiac disease. Wheat allergy, the third gluten-related disorder, which will not be addressed in this review, is defined as an adverse type-2 helper T-cell immunologic reaction to wheat proteins and typically presents soon after wheat

ORIGINAL PAPERS

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Increased Expression of TLR4 and TLR7 but Not Prolactin mRNA by Peripheral Blood Monocytes in Active Celiac Disease*

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation;

Gliadin fragments have been identified to activate the innate immune system *via* TLR4

clinical signs and symptoms of CD improve after the introduction of a gluten-free diet (GFD). The focus was on changes in mRNA expression of selected toll-like receptors (TLR2, TLR4, TLR7), stress cytokine prolactin (PRL), and pro- and anti-inflammatory cytokines (TNF-α, IL-6, IL-12, IL-10) in PBMs.

Material and Methods. The study involved 20 CD patients diagnosed according to the European Society for Pediatric Gastroenterology, Hepatology and Nutrition criteria and Marsh criteria: 10 recently-diagnosed cases (rCD) and 10 on a GFD for a minimum of one year. The control group comprised 10 age- and sex-matched healthy volunteers. PBMs from peripheral blood specimens were separated using immunomagnetic CD14+ beads. Total RNA was isolated using a standard commercial kit. Cytokine and TLR mRNA levels were quantified by relative qPCR with *PGK1* as a reference gene.

Results. Significantly higher expression of TLR4 and TLR7 mRNA was observed in PBMs from rCD patients compared to the healthy controls (1.63 times higher; $p < 0.05$). TLR7 mRNA levels in rCDs were also significantly elevated in comparison to the CD-GFD patients (2.11 times higher; $p < 0.01$). TNF-α mRNA expression tended to be higher in both groups of patients; by contrast, in IL-6 mRNA, a trend to a fourfold decrease was detected in PBMs from the CD-GFD subjects. IL-10, IL-12 and PRL levels did not differ among the groups.

Conclusions. The data suggest that the inflammatory process in rCD intestinal mucosa and submucosa reflecting enterocyte damage can be detected in PBMs in peripheral blood. Further, the cytokine and TLR expression profile in PBMs alters after one year of GFD treatment (**Adv Clin Exp Med 2016, 25, 5, 887–893**).

Key words: celiac disease, monocytes, cytokines, prolactin, innate immunity.

Celiac disease (CD) is defined as the loss of oral tolerance to gluten in genetically predisposed individuals; it is an organ-specific autoimmune disease with a prevalence of about 1% in Europe [1]. Clinical manifestation of the gluten-induced inflammatory response in celiac mucosa is highly variable and can occur both in childhood and in adulthood. The only possible treatment of CD is a lifelong gluten-free diet (GFD).

Imbalance in the innate immune mechanisms is known to contribute to the pathogenesis of CD.

* This study was funded by the Grant Agency of Charles University in Prague (grant 316211).

Gluten sensitivity

Gluten sensitivity as a neurological illness

M Hadjivassiliou, R A Grünewald, G A B Davies-Jones

From gut to brain

It has taken nearly 2000 years to appreciate that a common dietary protein introduced to the human diet relatively late in evolutionary terms (some 10 000 years ago), can produce human disease not only of the gut but also the skin and the nervous system. The protean neurological manifestations of gluten sensitivity can occur without gut involvement and neurologists must

this disease was the gut. The first report of neurological manifestations associated with CD was by Carnegie Brown in 1908.[3] In his book entitled *Sprue and its treatment* he mentioned two of his patients who developed "peripheral neuritis". Elders reported the association between "sprue" and ataxia in 1925.[4] The validity of these and other such reports before 1960 remains doubtful given that

may not be the sole protagonist in this disease.

THE NEUROLOGY OF COELIAC DISEASE

In 1966 Cooke published a landmark paper on 16 patients with neurological disorders associated with adult CD.[8] This was the first systematic review of the subject after the introduction of diagnostic criteria for CD. Ten of these patients had a severe progressive neuropathy. All patients had gait ataxia and some had limb ataxia. Neuropathological data from postmortem examinations showed extensive perivascular inflammatory changes affecting both the central and peripheral nervous systems. A striking feature was the loss of Purkinje cells with atrophy and gliosis of the cerebellum. All 16 patients had evidence of severe malabsorption as evidenced by anaemia and vitamin deficiencies as well as profound weight loss.

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 percentage of those patients with elevated antibodies to gluten is 57%.

This extract is from the book on chronic diseases by Aretaeus the Cappadocian, one of the most distinguished ancient Greek doctors of the first century AD. This chapter, entitled "on the coeliac diathesis", was the first description of coeliac disease (from the greek word κοιλιακη meaning abdominal). Aretaeus' books were first published in Latin in 1500 and the new Latin word coeliac was used to translate κοιλιακη. Coeliac disease (CD) remained obscure until 1887 when Samuel Gee gave a lecture entitled *On the coeliac affection*[2] at the Hospital for Sick Children, Great Ormond Street, London. In it he acknowledged Areteaus' contribution and went on to give an accurate description of CD based on his own clinical observations.

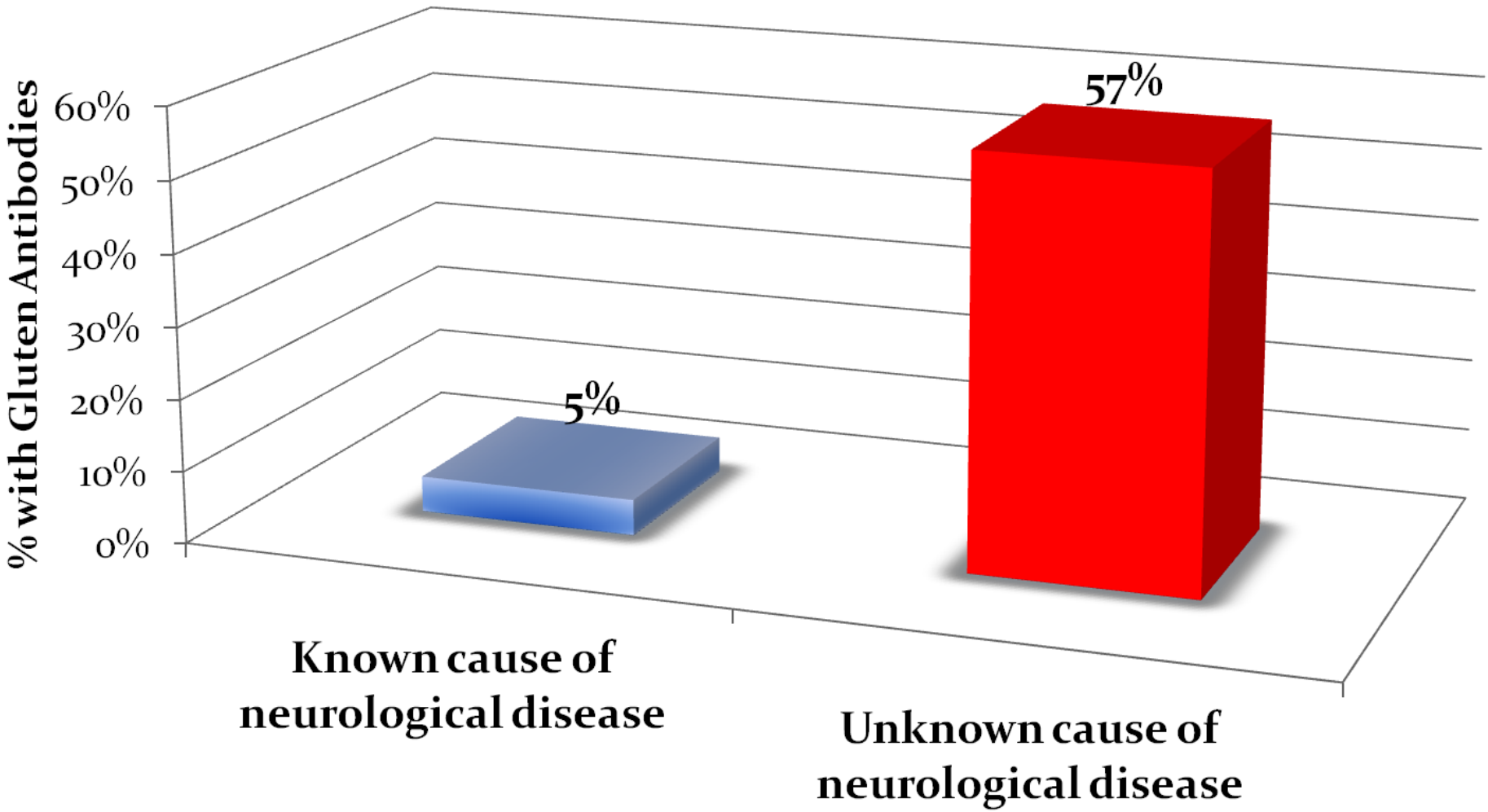
With clinical manifestations primarily confined to the gastrointestinal tract or attributable to malabsorption, it was logical to assume that the target organ and hence the key to the pathogenesis of

been the lack of satisfactory demonstration of antibodies to the protein concerned". He went on to demonstrate the presence of circulating antibodies against gliadin (antigliadin antibodies), the protein responsible for CD. This provided further evidence that CD was immunologically mediated and that the immune response is not confined to the mucosa of the small bowel. Antigliadin antibodies became a useful screening tool for the diagnosis of CD.

In 1966, Marks *et al* demonstrated an enteropathy in nine of 12 patients with dermatitis herpetiformis,[7] an itchy vesicular skin rash mainly occurring over the extensor aspect of the elbows and knees. The enteropathy had a striking similarity to that seen in CD. It was later shown that the enteropathy and the skin rash were gluten dependent but skin involvement could occur even without histological evidence of gut involvement. This was the first evidence that the gut

Peripheral neuropathy	29
Myopathy	13
Ataxia with myoclonus	9
Myelopathy	4
Dementia (usually with additional features)	6

A review of all such reports (with biopsy proved CD) from 1964 to date shows that ataxia and peripheral neuropathy are the commonest neurological manifestations seen in patients with established CD (table 1). Less common manifestations include inflammatory myopathies[10] and myoclonic ataxia.[11] Isolated dementia is uncommon and most cases tend to have additional neurological features (for example, ataxia or neuropathy). Patients with epilepsy associated with occipital calcifications on CT and CD have been described,[12] mainly in Italy. Most present with epilepsy in



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37

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BRAIN-REACTIVE ANTIBODIES IN TRAUMATIC BRAIN INJURY

*Aristo Vojdani**
Immunosciences Lab., Inc., Los Angeles, CA USA

ABSTRACT

It is estimated that the human brain contains more than ten billion capillaries, which translates into one vessel for each neuron. The total length of the capillaries in the human brain is about 400 miles.

Keywords: Autoimmune, traumatic brain injury, autoantigens, S100 B antibodies

INTRODUCTION

Autoimmune diseases affect about 7% of the world's population. In these disorders, pathogenic T_H1 cells, autoreactive T_H17 cells, antibodies and associated molecules attack antigens of various tissues, including brain tissue. Brain-reactive antibodies are detected in about 3% of the general population but do not contribute to brain pathology unless they cross the blood-brain barrier (BBB) [1].

The BBB is composed of highly specialized brain endothelial cells which are fully differentiated to the neurovascular system. It is estimated that the human brain contains more than ten billion capillaries, which translates into one vessel for each neuron. The total length of the capillaries in the human brain is about 400 miles. In conjunction with microglia, astrocytic foot processes and pericytes, the BBB separates the neurons from various components of the circulating blood [2]. The endothelial tight junctions, together with astrocytic foot processes, prevent the passage of all soluble

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

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

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

brain study was performed before and after a gluten free diet.

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

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

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

INTRODUCTION

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

Migraine is the most frequent subtype of primary headache, affecting about 15–18% of women and 6% of men in

neuropathy and cerebellar ataxia (5). Moreover, two recent reports have suggested a possible causative association between CD and migraine (6, 7).

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

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

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Triggers and Mediators of Systemic Inflammation

- **If You Trust For Now That the Studies Quoted Here are Accurate Representatives of Basic Physiology, Which Patients With Systemic Inflammation Would you Not Test for a Loss of Tolerance to Wheat/Gluten?**

Case Study #1
A 44 yr. old male with *'assumed'* rapidly progessing ALS

www.nature.com/clinicalpractice/neuro

A case of celiac disease mimicking amyotrophic lateral sclerosis

Martin R Turner, Gurjit Chohan, Gerardine Quaghebeur, Richard CD Greenhall, Marios Hadjivassiliou and Kevin Talbot*

SUMMARY

Background A 44-year-old male presented to a general neurology clinic with a 6-month history of progressive right-sided spastic hemiparesis without sensory symptoms or signs. The thigh muscle in the affected leg showed signs of wasting. The patient had a remote family history of celiac disease.

Investigations Neurological examination, neurophysiological studies, brain MRI scan, routine blood tests, duodenal biopsy, cerebrospinal fluid analysis including polymerase chain reaction test for JC virus DNA, serological testing for HIV and for the presence of serum antibodies to endomysium, gliadin and tissue transglutaminase.

Vanderbilt Continuing Medical Education online
This article offers the opportunity to earn one Category 1 credit toward the AMA Physician's Recognition Award.

THE CASE

A 44-year-old male was referred for a specialist neurological opinion with a 6-month history of progressive right leg weakness, and wasting and intermittent painful spasms of his right quadriceps. In the preceding month the patient had also noticed progressive weakness of his right arm

A 44-year-old male was referred for a neurological opinion with a 6-month history of progressive right leg weakness, wasting and intermittent painful spasms of his right quadriceps.

(Medical Research Council Grade 4–/5 in hip flexion, 4+/5 in hip extension, 4/5 in knee flexion and 4–/5 in ankle dorsiflexion) associated with mild wasting of the right quadriceps. The patient had generalized bilateral hyperreflexia, sustained right ankle clonus and a right extensor plantar response. Results of cranial nerve, cerebellar and sensory examinations were normal.

T_2 and fluid-attenuated inversion recovery brain MRI sequences revealed a region of hyperintensity along the course of the left corticospinal tract, arising from the subcortical white matter of the precentral gyrus and following the posterior limb of the internal capsule into the brainstem (Figure 1A). Gadolinium-enhanced MRI did not reveal any contrast enhancement. Repeat neuroimaging 2 months later revealed more-extensive changes in the same pattern, with additional involvement of the opposite (right) subcortical region of the precentral gyrus (Figure 1B).

Electromyography (EMG) of the masseter, biceps, first dorsal interosseous extensor digitorum

MR Turner is a Specialist Registrar in the Department of Neurology and G Quaghebeur is a Consultant Neuroradiologist in the Department of Neuroradiology at John Radcliffe Hospital, Oxford, UK. G Chohan is a Research Registrar at the National CJD Surveillance Unit, Edinburgh, UK. RCD Greenhall is a retired Consultant Neurologist formerly of the Radcliffe Infirmary, Oxford, UK. M Hadjivassiliou is a Consultant Neurologist at the Royal Hallamshire Hospital, Sheffield, UK. K Talbot is a Senior Clinical Lecturer and Consultant Neurologist in the Department of Clinical Neurology at Oxford University, Oxford, UK.

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In the preceding month the patient had also noticed progressive weakness of his right arm and difficulty when writing. He had no sensory symptoms. The patient's only past medical history of note was migraine with aura.

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The patient's initial presentation:

- ✓ **progressive motor syndrome with absence of sensory signs**
- ✓ **clinical evidence of upper and lower motor neuron degeneration**
- ✓ **electromyographic evidence of widespread acute denervation**
- ✓ **hyperintensity in the corticospinal tracts on MRI.**
- **A dx of Amyotrophic Lateral Sclerosis (ALS).**

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(Figure 1A). Gadolinium-enhanced MRI did not reveal any contrast enhancement. Repeat neuroimaging 2 months later revealed more-extensive changes in the same pattern, with additional involvement of the opposite (right) subcortical region of the precentral gyrus (Figure 1B).

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His family hx revealed that a maternal aunt had Celiac Disease, a sister had Crohn's disease, and his maternal grandmother had MS.

(Medical Research Council Grade 4–/5 in hip flexion, 4+/5 in hip extension, 4/5 in knee flexion and 4–/5 in ankle dorsiflexion) associated with mild wasting of the right quadriceps. The patient had generalized bilateral hyperreflexia, sustained right ankle clonus and a right extensor plantar response. Results of cranial nerve, cerebellar and sensory examinations were normal.

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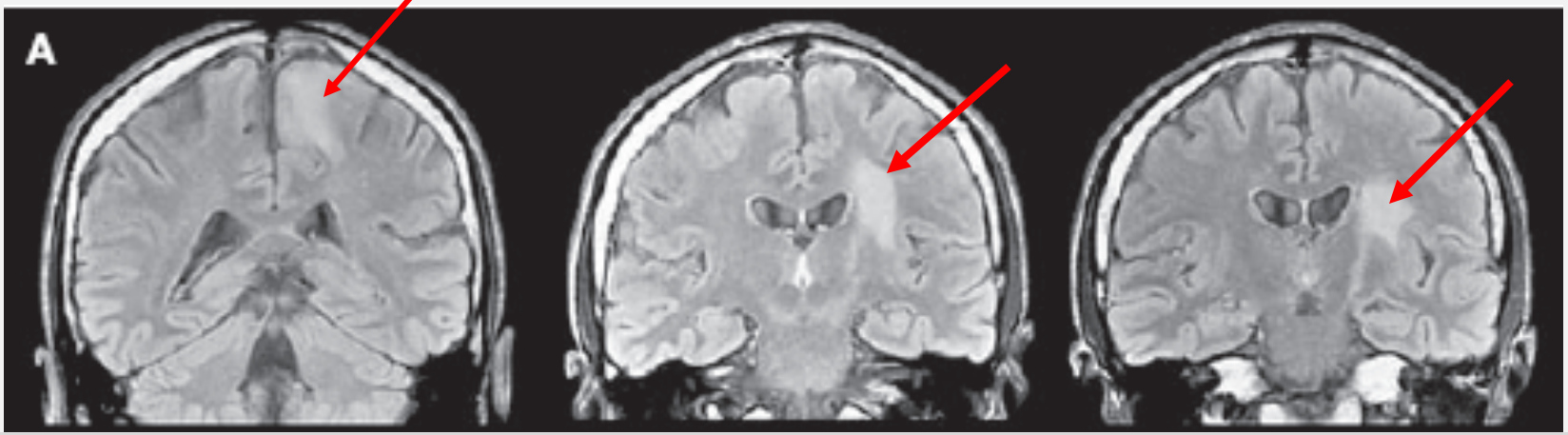

A is initial presentation, B is 2 months later

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A case of celiac disease mimicking amyotrophic lateral sclerosis

Martin R Turner, Gurjit Chohan, Gerardine Quaghebeur, Richard CD Greenhall, Marios Hadjivassiliou and Kevin Talbot*

SUMMARY

Background A 44-year-old male presented to a general neurology clinic with a 6-month history of progressive right-sided spastic hemiparesis without sensory symptoms or signs. The thigh muscle in the affected leg showed signs of wasting. The patient had a remote family history of celiac disease.

Investigations Neurological examination, neurophysiological studies, brain MRI scan, routine blood tests, duodenal biopsy, cerebrospinal fluid analysis including polymerase chain reaction test for JC virus DNA, serological testing for HIV and for the presence of serum antibodies to endo

Diag amy

Man

KEY celia

CM

Routine blood tests revealed:
- **a mild microcytic anemia**
- **↓ levels of serum iron**
- **↓ serum ferritin**
- **↓ serum folate**

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Nat Clin Pract Neurol., Oct 2007 vol.3, no.10

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Blood tests revealed:

- **elevated antiendomysial antibody**
- **duodenal biopsy demonstrated villous atrophy, crypt hyperplasia and increased intraepithelial lymphocytes (Marsh 3A), consistent with gluten-sensitive enteropathy (Celiac Disease)**

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The patient was started on a GFD approximately 7 months after the onset of his initial neurological symptoms. No drugs, including riluzole or other agents with neuroprotective potential were given.

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flexion, 4+/5 in hip extension, 4/5 in knee flexion and 4–/5 in ankle dorsiflexion) associated with mild wasting of the right quadriceps. The patient had generalized bilateral hyperreflexia, sustained right ankle clonus and a right extensor plantar response. Results of cranial nerve, cerebellar and sensory examinations were normal.

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9 months after initiation of treatment, the patient's right arm function had returned to normal.

Examination revealed right-sided spastic hemiparesis with a pyramidal pattern of leg weakness (Medical Research Council Grade 4–/5 in hip flexion, 4+/5 in hip extension, 4/5 in knee flexion and 4–/5 in ankle dorsiflexion) associated with mild wasting of the right quadriceps. The patient had generalized bilateral hyperreflexia, sustained right ankle clonus and a right extensor plantar response. Results of cranial nerve, cerebellar and sensory examinations were normal.

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Improvement in the patient's right leg function was noted, wasting was still present and there was some residual spasticity. He was now able to walk unaided, however, and his handwriting and ability to fasten buttons had returned to normal.

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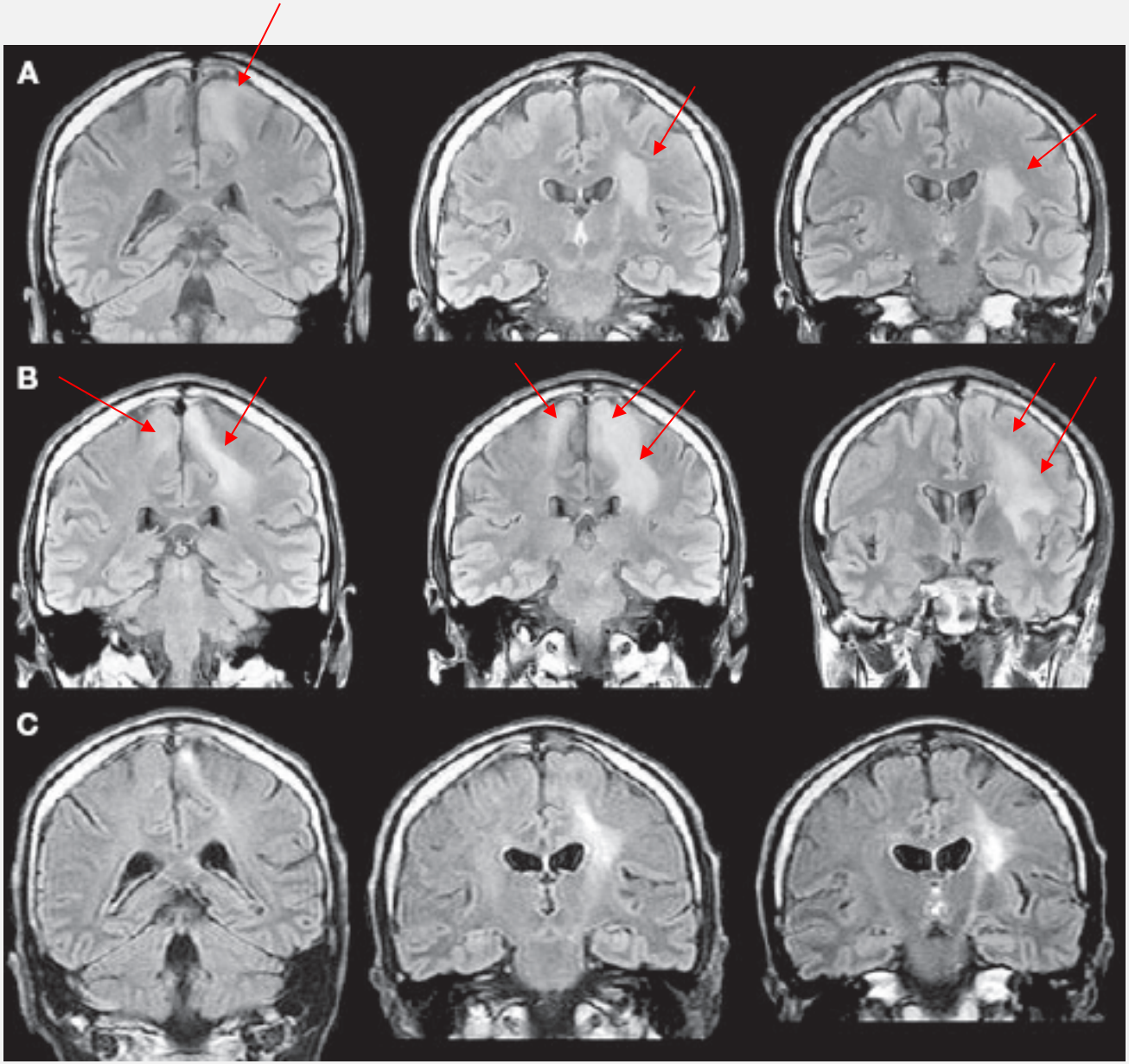
initial

2 months later

9 months after GFD



Nat Clin Pract Neurol., Oct 2007 vol.3, no 10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It is of critical clinical value to have valid tests identifying if the brain is suffering from chronic inflammatory conditions that eventually accumulates damage into become a disease.

Test, Don't Guess

Journal of Alzheimer's Disease 25 (2011) 605–622
DOI 10.3233/JAD-2011-110098
IOS Press

Brain-Reactive Autoantibodies Prevalent in Human Sera Increase Intraneuronal Amyloid-β_{1-42} Deposition

Robert G. Nagele[a,*], Peter M. Clifford[a], Gilbert Siu[a], Eli C. Levin[a], Nimish K. Acharya[a], Min Han[a], Mary C. Kosciuk[a], Venkat Venkataraman[b], Semah Zavareh[a], Shabnam Zarrabi[a], Kristin Kinsler[a], Nikhil G. Thaker[a], Eric P. Nagele[c], Jacqueline Dash[a], Hoau Y. Wang[d] and Andrew Levitas[e]
[a]*New Jersey Institute for Successful Aging, University of Medicine and Dentistry of New Jersey, Stratford, NJ, USA*

The identification of autoantibodies that play a role in the initiation phases of disease could be of possible therapeutic benefit. Not only could these autoantibodies be used to identify individuals at risk for developing AD prior to disease initiation, but they may also provide therapeutic targets.

related to their capacity to enhance intraneuronal $A\beta_{42}$ peptide accumulation and immunolabel neurons in AD brain sections. Replacement of human sera with antibodies targeting abundant neuronal surface proteins resulted in a comparable enhancement of $A\beta_{42}$ accumulation in mouse neurons. Overall, results suggest that brain-reactive autoantibodies are ubiquitous in the blood and that a defective BBB allows these antibodies to access the brain interstitium, bind to neuronal surfaces and enhance intraneuronal deposition of $A\beta_{42}$ in AD brains. Thus, in the context of BBB compromise, brain-reactive autoantibodies may be an important risk factor for the initiation and/or progression of AD as well as other neurodegenerative diseases.

Keywords: Alzheimer's disease, amyloid, autoantibodies, autoimmunity, blood brain barrier, neurodegenerative disease

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INTRODUCTION

Alzheimer's disease (AD) is a progressive and devastating neurodegenerative disorder of the elderly that is highlighted by a dramatic reduction of memory and

PLOS ONE

RESEARCH ARTICLE

Determination of B-Cell Epitopes in Patients with Celiac Disease: Peptide Microarrays

Rok Seon Choung[1], Eric V. Marietta[1], Carol T. Van Dyke[1], Tricia L. Brantner[1], John Rajasekaran[2], Pankaj J. Pasricha[3], Tianhao Wang[2], Kang Bei[2], Karthik Krishna[2], Hari K. Krishnamurthy[2], Melissa R. Snyder[4], Vasanth Jayaraman[2‡], Joseph A. Murray[1‡*]

1 Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, United States of America, 2 Vibrant Sciences LLC, San Carlos, CA, United States of America, 3 Center for Neurogastroenterology, Johns Hopkins University, Baltimore, MD, United States of America, 4 Division of Clinical Biochemistry and Immunology, Mayo Clinic, Rochester, MN, United States of America

‡ VJ and JAM are joint senior authors on this work.
* Murray.Joseph@mayo.edu

Abstract

We identified 2 distinct discontinuous gliadin sequence sets that, when combined, significantly improved the sensitivity (IgG, 97%; IgA, 99%) and specificity (IgG, 98%; IgA, 100%) (P < .001) for the diagnosis of CD.

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: JAM and RSC were supported by the Mayo Foundation. Vibrant Sciences LLC provided support in the form of salaries for authors JR, VJ, KB, TW, HKK and KK, but did not have any additional role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The specific roles of these authors are articulated in the 'author contributions' section.

Competing Interests: The authors have the following interests. John Rajasekaran, Vasanth

Results

Using a computational algorithm that considered disease specificity of peptide sequences, 2 distinct epitope sets were identified. Further, by combining the most discriminative 3-mer gliadin sequences with randomly interpolated3- or 6-mer peptide sequences, novel discontinuous epitopes were identified and further optimized to maximize disease discrimination. The final discontinuous epitope sets were tested in a confirmatory cohort of CD patients and controls, yielding 99% sensitivity and 100% specificity.

Conclusions

These novel sets of epitopes derived from gliadin have a high degree of accuracy in differentiating CD from controls, compared with standard serologic tests. The method of ultra-high-density peptide microarray described here would be broadly useful to develop high-fidelity diagnostic tests and explore pathogenesis.

PLOS ONE

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Abstract

The relative noninvasiveness, broad availability, and versatility of the high-throughput peptide microarrays make this technology well suited for incorporation into routine health care and also provide a promising new tool for biomarker discovery.

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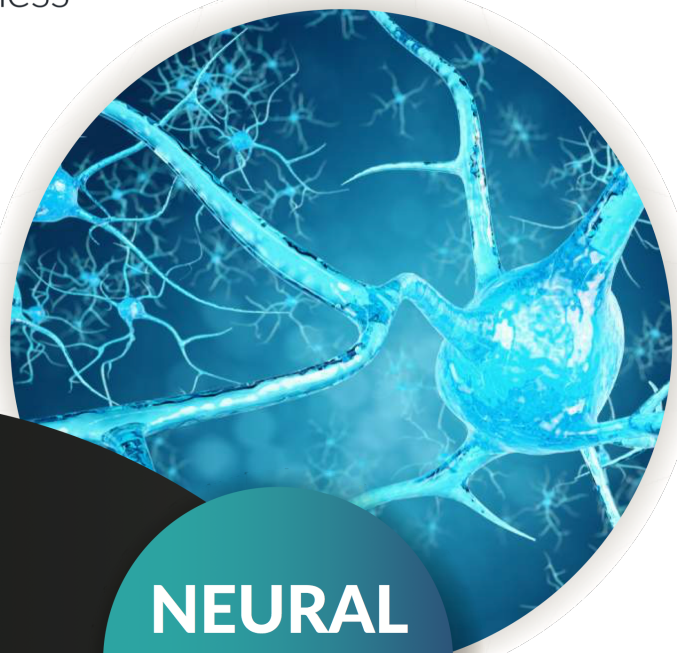

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- **Antibodies to systemic Brain autoimmunity**
- **Antibodies to bacteria in the Brain causing inflammation**
- **Antibodies to viruses in the Brain causing inflammation**
- **Antibodies creating demyelination**
- **Antibodies creating peripheral neuropathies**

Demyelination Antigens

Anti-Tubulin

Tubulin is a 55 kDa cytoplasm globular protein expressed in blood, nervous, secretory, reproductive, musculoskeletal and other internal cells. Anti-tubulin is associated with alcoholic liver disease, demyelinating disease, Grave's disease, Hashimoto's thyroiditis, infectious agent exposure PANDAS/ANDAS/OCD, rheumatoid arthritis, and recent onset type 1 diabetes.[2]

Anti-Myelin basic protein

Myelin basic protein (MBP) is a protein believed to be important in the process of myelination of nerves in the nervous system. Anti-Myelin basic protein is related to the risk for multiple sclerosis, autism, PANDAS/ANDAS/OCD, and systemic lupus erythematosus (SLE).[3]

Anti-Myelin oligodendrocyte glycoprotein

Myelin oligodendrocyte glycoprotein (MOG) is a glycoprotein associated with the myelination of nerves in the central nervous system (CNS). Antibodies against MOG are found in various demyelinating diseases, including multiple sclerosis, neuromyelitis optica spectrum disorders (NMOSD), idiopathic optic neuritis (ON), acute disseminated encephalomyelitis (ADEM), multiphasic disseminated encephalomyelitis (MDEM), Devic's disease, and tumefactive demyelinating disease.[4]

Anti-Myelin proteolipid protein

Myelin proteolipid protein (PLP) is the major membrane protein of CNS myelin and its expression is largely limited to oligodendrocytes.[5] Anti-PLP is a useful marker in patients with seronegative anti-myelin basic protein, the frequent marker in active multiple sclerosis and optic neuritis.[6-7]

Anti-Neurofascin

Neurofascin (NF), a cell adhesion molecule expressed in both the CNS and the peripheral nervous system (PNS), plays important roles in developing and maintaining neural structures. Anti-neurofascin autoantibodies are found mainly in combined central and peripheral demyelination (CCPD), a rare demyelinating condition affecting both CNS and peripheral nervous system (PNS) tissues[8], and also in chronic inflammatory demyelinating polyneuropathy (CIDP)[9] and axonal injury in patients with multiple sclerosis (MS).[10] Recognition of this antibody may be important in treatment management, becauseanti-neurofascin seropositive CCPD patients respond well to Intravenous Immunoglobulin or plasma exchange treatments.[11]

Anti-MAG

Myelin-associated glycoprotein (MAG) is a trans-membrane protein of both the CNS and peripheral nervous system (PNS) myelin, involved in the process of myelination. Anti-MAG peripheral neuropathy is a very rare disease caused by anti-MAG antibodies that destroy MAG protein leading to disruptions of normal myelin production and healthy peripheral nerve activity.[12]

Blood Brain Barrier Disruption

Anti-s100b

S100B is a calcium-binding protein produced mainly by astrocytes. This protein is localized in the cytoplasm and nucleus of a wide range of cells and involved in the regulation of several cellular processes such as cell cycle progression and differentiation. Studies have shown extravasated S100B may trigger a pathologic autoimmune reaction linking systemic and CNS immune responses.[13]

Anti-Glial fibrillary acidic protein

Glial fibrillary acidic protein (GFAP) is the major structural protein of the glial intermediate filament of astrocytes that forms part of the cytoskeleton of mature astrocytes and other glial cells, but is not found outside the CNS. Anti-GFAP is produced when the protein enters the bloodstream after a rupture of the blood brain barrier, thus serves as a blood based diagnostic marker of brain injury.[14]

LAST NAME	FIRST NAME	GENDER	DATE OF BIRTH	ACCESSION ID	DATE OF SERVICE
PETERSEN	KATELIN	FEMALE	1985-02-16	1909030006	09-23-2019

Anti-Microglia

Microglia are a type of macrophage located throughout the brain and spinal cord that act as the first and main form of active immune defense in the CNS. These markers indicate a destruction of the blood brain barrier and are found to play a role in tissue destruction of Alzheimer's disease.[14]

Anti-Glucose regulated protein 78

Glucose regulated protein 78 (GRP78) is a major endoplasmic reticulum (ER) chaperone protein critical for protein quality control of the ER, as well as controlling the activation of the ER-transmembrane signaling molecules. Studies show that antibodies targeting glucose-regulated protein 78 are able to activate brain microvascular endothelial cells and induce protein extravasation in cell lines and in mice with neuromyelitis optica. Thus, these findings suggest that glucose-regulated protein 78–targeted antibodies could instigate blood brain barrier breakdown and development of hallmark anti–aquaporin-4 autoantibody pathology. Therefore, the application of these antibodies may be useful to disrupt the blood brain barrier for transit of treatments for many CNS diseases.[15]

Optical and Autonomic Nervous System Disorders

Anti-Neuron specific enolase

Neuron specific enolase is a protein enzyme that is encoded by the ENO2 gene. It is found in mature neurons and cells of neuronal origin. Antibodies against neuron specific enolase are found in patients with optical neuropathies.

Anti-Aquaporin 4

Neuromyelitis optica is an inflammatory demyelinating disorder of the CNS. The discovery of circulating IgG antibodies against the astrocyte water channel protein aquaporin 4 (AQP4) and the evidence that AQP4-IgG is involved in the development of neuromyelitis optica revolutionized the understanding of the disease. Anti-aquaporin 4 antibodies have also been shown in patients with peripheral demyelination. In addition, human aquaporin 4 shows cross-reactivity with corn and soybean aquaporins,[17] hence, consider ordering Vibrant's Lectin Zoomer panel for a comprehensive assessment.

Anti-Recoverin

Anti-recoverin antibodies are one of the key components of antibody disorders of the CNS. They have also been shown to be associated with retinopathy, which is characterized by impaired vision and photosensitivity.

Anti-CV2

Anti-CV2 antibodies are a group of antibodies that react with a 66-kd brain protein belonging to the family of CRMP proteins. The manifestations associated with anti-CV2 antibodies include cerebellar degeneration, uveitis, and peripheral neuropathy, and mixed axonal and demyelinating peripheral neuropathy.[18]

Peripheral Neuropathy

Anti-GM1

Detection of ganglioside M1 (GM1) antibodies, usually of the IgM isotype, is associated with multi-focal motor neuropathy and lower motor neuropathy, characterized by muscle weakness and atrophy. Multi-focal motor neuropathy may occur with or without high serum titers of anti-GM1 antibodies. GM1 antibodies are detected in approximately 50 % of persons with multi-focal motor neuropathy.

Anti-GM2

GM2 ganglioside is a potential peripheral nerve antigen for neuropathy-associated autoantibodies. Anti-GM2 IgM antibodies have been reported in some patients with dysimmune neuropathy or lower motor neuron syndrome, in whom they were often associated with a concomitant reactivity with GM1.

Anti-Hu

The anti-Hu antibody is the most frequent manifestation of sensory neuropathy with frequent autonomic involvement. The clinical patterns of the neuropathies is in keeping with accordance with the cellular distribution of the HuD antigen.

Anti-Ri

Anti-Ri has been reported in serum and cerebrospinal fluid (CSF) of patients who present typically with a subacute neurological disorder involving the brainstem, cerebellum, and spinal cord. This antigen is also found in a rare disorder known as opsoclonus/myoclonus syndrome.[19]

Anti-Amphiphysin

Amphiphysin is a non-intrinsic membrane protein that is concentrated in nerve terminals. The serum of patients with stiff-person syndrome often contain antibodies to this protein. Stiff-person syndrome (SPS) is a neurological disorder characterized by progressive muscle stiffness (rigidity) and repeated episodes of painful muscle spasms.

Neuromuscular disorders

Anti-Acetylcholine receptors

Acetylcholine receptors are responsible for binding acetylcholine, a neurotransmitter for signal transduction in CNS. They are localized in neuromuscular junctions. Antibodies against acetylcholine receptor are found in myasthenia gravis disease, which destroys the receptor function, leading to a neuromuscular transmission defect, which then causes hypofunction, fatigue, and inflammation of skeletal muscles and produces serum antibodies against muscle antigens.[20]

Anti-Muscle specific kinase

Muscle-specific kinase (MuSK) is a single-pass transmembrane protein that has a critical role in signaling between motor neurons and skeletal muscle. Anti-MuSK is an important marker in patients without anti-acetylcholine receptor antibodies in myasthenia gravis disease.[21]

Anti-Voltage gated calcium channels

Voltage-gated calcium channels (VGCCs) are a group of voltage-gated ion channels found in the membrane of excitable cells such as muscle, glial cells, and neurons. They are key transducers of membrane potential changes into intracellular Ca2+ transients that initiate many physiological events. In neurons, voltage-gated Ca^{2+} channels initiate synaptic transmission. Anti-voltage-gated calcium channel autoantibodies are responsible for Lambert-Eaton myasthenic syndrome (LEMS), a rare autoimmune disorder of the neuromuscular junction.[22]

Anti-Voltage gated potassium channels

Voltage-gated potassium channels (Kv) play a vital role in a variety of cellular processes, including the functioning of excitable cells, regulation of apoptosis, cell growth and differentiation, the release of neurotransmitters and hormones, and maintenance of cardiac activity. They are found along the axon and at the synapse of the neurons, to propagate electrical signals. In neuromyotonia, the anti-voltage-gated potassium channel autoantibodies downregulate the potassium channels expressed on the peripheral nerve terminal leading to nerve hyperexcitability.[22]

Anti-Titin

Titin, also known as connectin, is a flexible filamentous protein, which is the largest protein known today. Titin is known to be important for myofibrillogenesis, sarcomere structure, and elasticity. Anti-titin antibodies are present in 70–90% of thymoma autoimmune myasthenia gravis (MG) patients, and in approximately 50% of late-onset acetylcholine-MG patients without thymoma. In general, anti-titin antibodies correlate with disease severity and may identify patients more likely to be refractory to therapy, including thymectomy.[23]

Brain Autoimmunity

Anti- Cerebellum

The cerebellum is a region of the brain that plays an important role in motor control. The cerebellum does not initiate movement, but contributes to coordination, precision, and accurate timing. It receives input from sensory systems of the spinal cord and from other parts of the brain and integrates these inputs to fine-tune motor activity. Cerebellar damage produces disorders in fine movement, equilibrium, posture, and motor learning. Anti-cerebellum antibodies implicates a possible damage to the cerebellum that could lead to ataxia.[24] In addition, these antibodies are associated with disorders like autism and may be useful as markers for specific behavioral characteristics of autism.[25]

Anti-Purkinje cell

Purkinje cells, or Purkinje neurons, are a class of GABAergic neurons located in the cerebellum. Purkinje cells are aligned like dominos stacked one in front of the other. Their large dendritic arbors form nearly two-dimensional layers through which parallel fibers from the deeper-layers pass.

Anti-Yo

Anti-Yo antibodies are found in the serum of patients with neurologic paraneoplastic syndromes and reported to have activity against Purkinje cells of the cerebellum. They are found in ataxic syndrome, which is the most common variant of paraneoplastic cerebellar degeneration (PCD).[26]

Anti-Amyloid beta (25-35)

Aβ is the cleavage product of the transmembrane amyloid-β precursor protein (APP). Major species of Aβ are Aβ40 and Aβ42, containing 40 and 42 amino acids, respectively. Although the pathogenesis of Alzheimer's disease (AD) is not fully understood, it is widely accepted that accumulation of Aβ in the brain, especially the more amyloidogenic Aβ42, due to overproduction (familial AD) or impaired clearance (sporadic AD) initiates the pathogenic cascade, ultimately leading to neurodegeneration and dementia. The levels of autoantibodies reacting with oligomers of a short but neurotoxic fragment of Aβ, Aβ (25-35), were significantly higher in AD patients than in the control group who had undetectable autoantibodies to the Aβ fragment.

Anti-Amyloid beta (1-42)

Beta-amyloid is a subunit of a larger protein called amyloid precursor protein (APP). APP extends from the inside of brain cells to the outside by passing through the fatty membrane around the cell. When APP is activated, it is cleaved to two different subunits, a chain containing 40 amino acids (the main form), and a chain containing 42 amino acids (amyloid beta 1–42). Amyloid-beta is one of the signature markers in Alzheimer's disease (AD). According to the "amyloid cascade hypothesis" that has been a cornerstone of the AD etiology for the last 20 years, the amyloid-beta deposition in the brain precipitates the formation of neurofibrillary tangles (NFTs).[27]

Anti-RAGE peptide

The receptor for advanced glycosylation end products (RAGE) has been identified as the major receptor at the blood brain barrier to mediate the flux of amyloid-β protein (Aβ) from the blood to the brain. The anti-RAGE antibodies were found in Alzheimer's disease patients. In addition, studies demonstrated that they were significantly higher in Alzheimer's disease patients with diabetes.[28]

Anti-Tau

Tau protein is found in the neurofibrillary tangles in brains of individuals who have Alzheimer's disease. Studies have shown that antibodies to the tau protein have been found in a number of AD patients when compared to healthy subjects. Other studies have also indicated that the levels of antibodies to tau are increased in patients with multiple sclerosis.

Anti-Glutamate

Glutamate is the major excitatory neurotransmitter of the CNS and it is crucially needed for numerous key neuronal functions. These autoimmune anti-glutamate antibodies can bind neurons in a few brain regions, activate glutamate receptors, decrease glutamate receptor expression, impair glutamate-induced signaling and function, activate blood brain barrier endothelial cells, kill neurons, damage the brain, and induce behavioral/psychiatric/cognitive abnormalities and ataxia. Most of these autoantibodies are found in epilepsy, encephalitis, cerebellar ataxia, systemic lupus erythematosus (SLE) and neuropsychiatric SLE, Sjogren's syndrome, schizophrenia, mania or stroke.[29]

Anti-Dopamine

Dopamine is a crucial neurotransmitter in the brain and dopaminergic dysfunction is thought to underlie common human diseases, such as Parkinson's disease, Tourette's syndrome, and schizophrenia. Anti-dopamine antibody positive patients with encephalitis were found to have movement disorders characterized by parkinsonism, dystonia, and Sydenham chorea.[30]

Anti-Hydroxytryptamine

Serotonin (5-hydroxytryptamine, 5-HT) is one of the most extensively studied neurotransmitters of the CNS. These autoantibodies are found mainly in autoimmune encephalitis.[31]

Anti-Alpha-synuclein

Alpha-synuclein is a presynaptic neuronal protein that is linked genetically and neuropathologically to Parkinson's disease. Anti-Alpha-synuclein autoantibodies are mainly elevated in Parkinson's disease and Alzheimer's disease.[32]

Anti-α1 and β2 adrenergic receptors

The adrenergic receptors (α1 and β2 adrenergic receptors) are a class of G protein-coupled receptors that are targets of many catecholamine neurotransmitters like norepinephrine (noradrenaline) and epinephrine (adrenaline). The anti-α1 and β2 adrenergic receptors were found mainly in patients with different dementia forms such as unclassified, Lewy body, vascular and Alzheimer's dementia.[33]

Anti-Endothelin A receptor

Endothelin peptides modulate the development of distinct neural cell types including Schwann cells, astrocytes, and neural crest cells as well as physiologic renal growth and development. The endothelin A receptor has a greater affinity for ET-1, one of the peptides of endothelin. The endothelin A receptor autoantibodies are found in vascular dementia.[34]

Brain Inflammation

Anti-NMDA receptor

N-methyl-D-aspartate (NMDA) is an amino acid derivative very similar to glutamate. Because glutamate is the excitatory neurotransmitter found in most synapses of the central nervous system, pharmacologists made this analogue called NMDA to activate a sub-type of glutamate receptors. Anti-NMDA receptor encephalitis, first identified in 2007, is an autoimmune disease that occurs when antibodies turn on the brain and cause it to swell.[35] Anti-NMDA receptor and anti-dsDNA, a major contributor in systemic lupus disease, share a common pentapeptide sequence, thus making them candidates for cross-reactivity.[36] Consider ordering Vibrant's Connective Tissue Disorder panel for the most comprehensive assessment.

Anti-AMPA receptor

AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) is a compound that is a specific agonist for the AMPA receptor, where it mimics the effects of the neurotransmitter glutamate. In some epilepsies, antibodies to AMPA receptors leads to neuron damage. The same is true for ischemia, where oxygen deprivation leads to excitotoxicity. Conversely, Alzheimer's disease is characterized by decreased AMPA activation and synapse loss.[37]

Anti-Dopamine receptor 1

Dopamine receptor 1 (DR1) expression in the central nervous system is highest in the dorsal striatum and ventral striatum. DR1 is the most abundant dopamine receptor in the central nervous system. It regulates neuronal growth and development, mediates some behavioral responses, and modulates dopamine receptor 2-mediated events. Antibodies associated with DR1 are mostly seen in brain inflammation and neuropsychiatric disorders.[38]

Anti-Dopamine receptor 2

Similar to dopamine receptor 1, dopamine receptor 2 (DR2) is highly expressed in basal ganglia, for example striatum, but also in the cortex, hippocampus, and substantia nigra. Modulation of DR2 expression in the basal ganglia has been associated with schizophrenia, depression, and movement disorders. Movement and psychiatric disorders associated with DR2 antibody are biologically plausible as DR2 is intimately linked to the control of movement and behavior.[30]

Anti-GABA receptors

Gamma-Amino Butyric acid (GABA) is an amino acid which acts as a neurotransmitter in the CNS. It inhibits nerve transmission in the brain, calming nervous activity. Temporal lobe epilepsy (TLE), Parkinson's disease (PD) and Huntington's disease (HD) are neurodegenerative disorders that involve disruptions in gamma-amino butyric acid (GABA) signaling.[39]

Anti-Dipeptidyl aminopeptidase-like protein 6

Dipeptidyl aminopeptidase-like protein 6 is a protein that in humans is encoded by the DPP6 gene. This gene encodes a single-pass type II membrane protein that is a member of the S9B family in clan SC of the serine proteases. Antibodies against dipeptidyl-peptidase-like protein-6 (DPPX), an auxiliary subunit of Kv4.2 potassium channels involved in signal transduction, were identified in 7 patients with encephalitis.[40]

Anti-Glycine receptor

Glycine accomplishes several functions as a transmitter in the CNS. As an inhibitory neurotransmitter, it participates in the processing of motor and sensory information that permits movement, vision, and audition. This action of glycine is mediated by the strychnine-sensitive glycine receptor, whose activation produces inhibitory post-synaptic potentials. Detection of glycine receptor antibodies may prove helpful in the diagnosis of patients with symptoms and signs that include ocular motor and other brainstem dysfunction, hyperekplexia, stiffness, rigidity, myoclonus and spasms, and their detection will support the use of immunotherapies that are likely to be clinically effective.[41]

Anti-Neurexin 3

Neurexin is a presynaptic protein that helps to connect neurons at the synapse. They are located mostly on the presynaptic membrane and contain a single transmembrane domain. Neurexin-3α autoantibodies associate with a severe but potentially treatable encephalitis in which the antibodies cause a decrease of neurexin-3α and alter synapse development.[42]

Anti-Contactin-associated protein-like 2 antibodies

CNTNAP2 (Contactin-associated protein-like 2) is a protein coding gene. This gene encodes a member of the neurexin family which functions in the vertebrate nervous system as cell adhesion molecules and receptors. Diseases associated with CNTNAP2 include Pitt-Hopkins-Like Syndrome 1 and Autism 15. Among its related pathways are neuroscience and cell adhesion molecules (CAMs).[43]

Anti-Leucine-rich glioma-inactivated protein (Anti-LGI1)

The leucine-rich glioma inactivated-1 gene is rearranged as a result of translocations in glioblastoma cell lines. The protein contains a hydrophobic segment representing a putative transmembrane domain with the amino terminus located outside the cell. It also contains leucine-rich repeats with conserved cysteine-rich flanking sequences. This gene is predominantly expressed in neural tissues and its expression is reduced in low grade brain tumors and significantly reduced or absent in malignant gliomas. LGI1 antibody–associated encephalitis has increasingly been recognized as a primary autoimmune disorder.[44]

Anti-Ma

Anti-Ma antibodies recognize Ma family proteins, which are exclusively found in neurons and testicular germ cells. Anti-Ma antibodies are found in patients with a wide range of neurological syndromes including limbic encephalitis (LE), diencephalic encephalitis (DE), or brainstem encephalitis (BE).[45]

Infections

Anti-HSV-1

Herpes simplex virus 1 (HSV-1) is a member of the herpesvirus family, Herpesviridae, that infect humans. HSV-1 (which produces most cold sores) is ubiquitous and contagious. As a neurotropic and neuroinvasive virus, HSV-1 persists in the body by becoming latent and hiding from the immune system in the cell bodies of neurons. HSV-1 has been reported to have a pathogenesis role in Herpes simplex encephalitis (HSE) and seropositivity to HSV-1 antibodies has been correlated with increased risk of Alzheimer's disease.[46]

Anti-HSV-2

Herpes simplex virus type 2 (HSV-2)-associated neurological disease may result from primary infection or reactivation of latent HSV-2. Herpes simplex encephalitis (HSE) is a disorder commonly associated with HSV-2. HSE due to HSV-2 may occur without meningitis features. Antibodies against HSV-2 have shown positive correlation in patients with symptoms of HSE.[47]

Anti-EBV

Central nervous system (CNS) complications of Epstein-Barr virus (EBV) infection occur in up to 18% of patients with infectious mononucleosis and include encephalitis, meningitis, and psychiatric abnormalities.[48] Antibodies against the EBV nuclear antigen complex (EBNAc) and EBNA-1 have been correlated with increased risk of multiple sclerosis (MS). The role of EBV in the pathogenesis of multiple sclerosis was attributed to molecular mimicry between EBV and central nervous system (CNS) antigen, myelin basic protein (MBP). [49]

Anti-CMV

Cytomegalovirus (CMV) infections have been reported frequently to be associated with Guillain–Barre syndrome (GBS). In GBS, anti-GM2 antibodies have been detected in 22-67% of CMV-infected patients. Studies showed that anti-ganglioside antibodies that can bind to peripheral nerves and interfere with neuromuscular transmission in CMV-infected GBS patients are induced by molecular mimicry between GM2 and antigens that are induced by a CMV infection.[50-51]

Anti-HHV-6

Human herpesvirus-6 (HHV-6) is frequently associated with neurologic diseases, including multiple sclerosis (MS), epilepsy, encephalitis, and febrile illness. This ubiquitous β-herpesvirus exists in two variants that share 95% sequence homology, HHV-6A and HHV-6B. The identical sequence homology was found between human herpesvirus-6 and myelin basic protein (MBP), one of the autoantigens implicated in MS pathology. High HHV-6 antibody titers were found in MS patients, implicating its role in MS.[52] Apart from MS, studies have shown increased HHV-6A in multiple brain regions in Alzheimer's disease (AD) patients implicating a potential neuropathological role in AD.[46, 53]

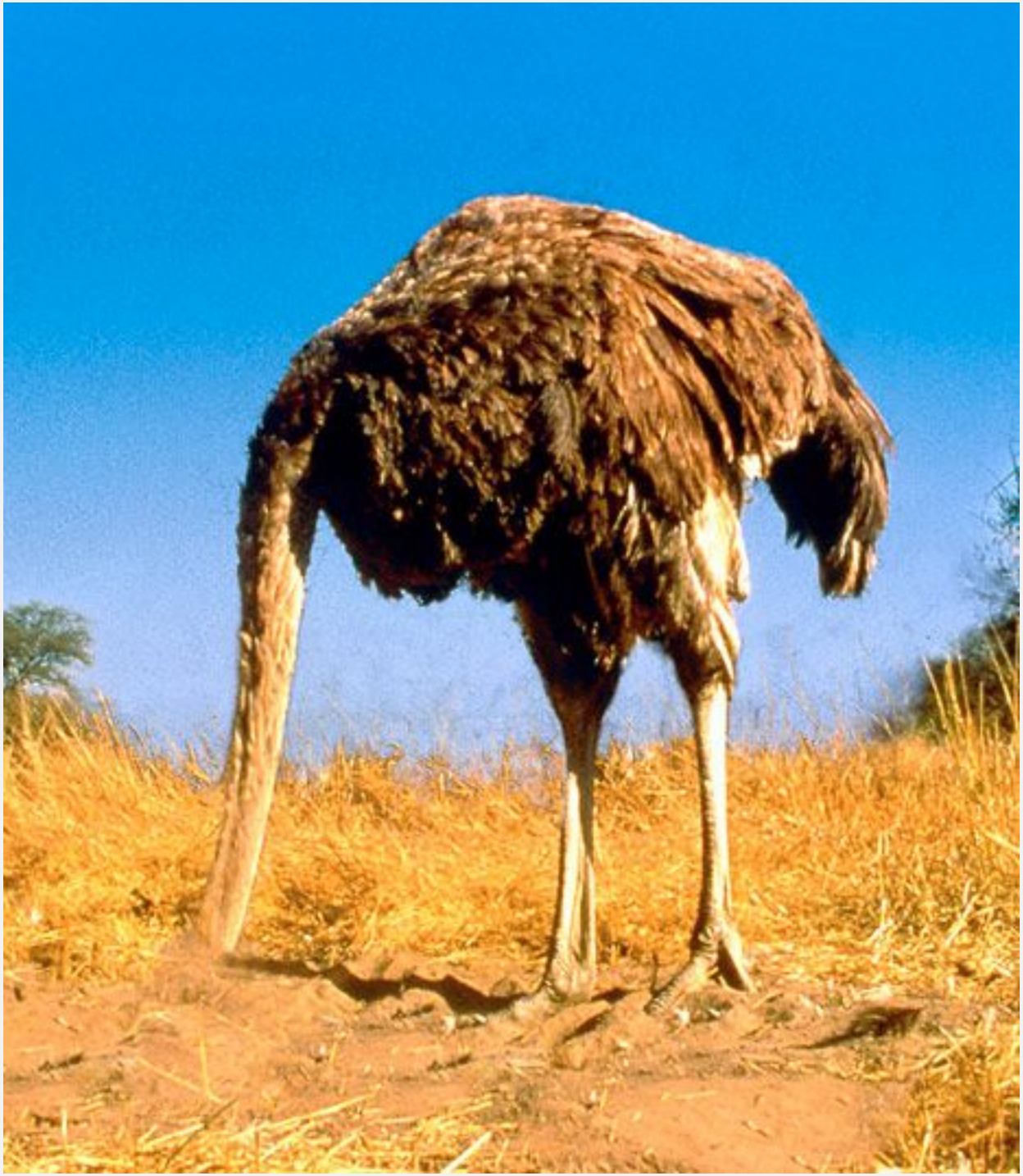
Anti-HHV-7

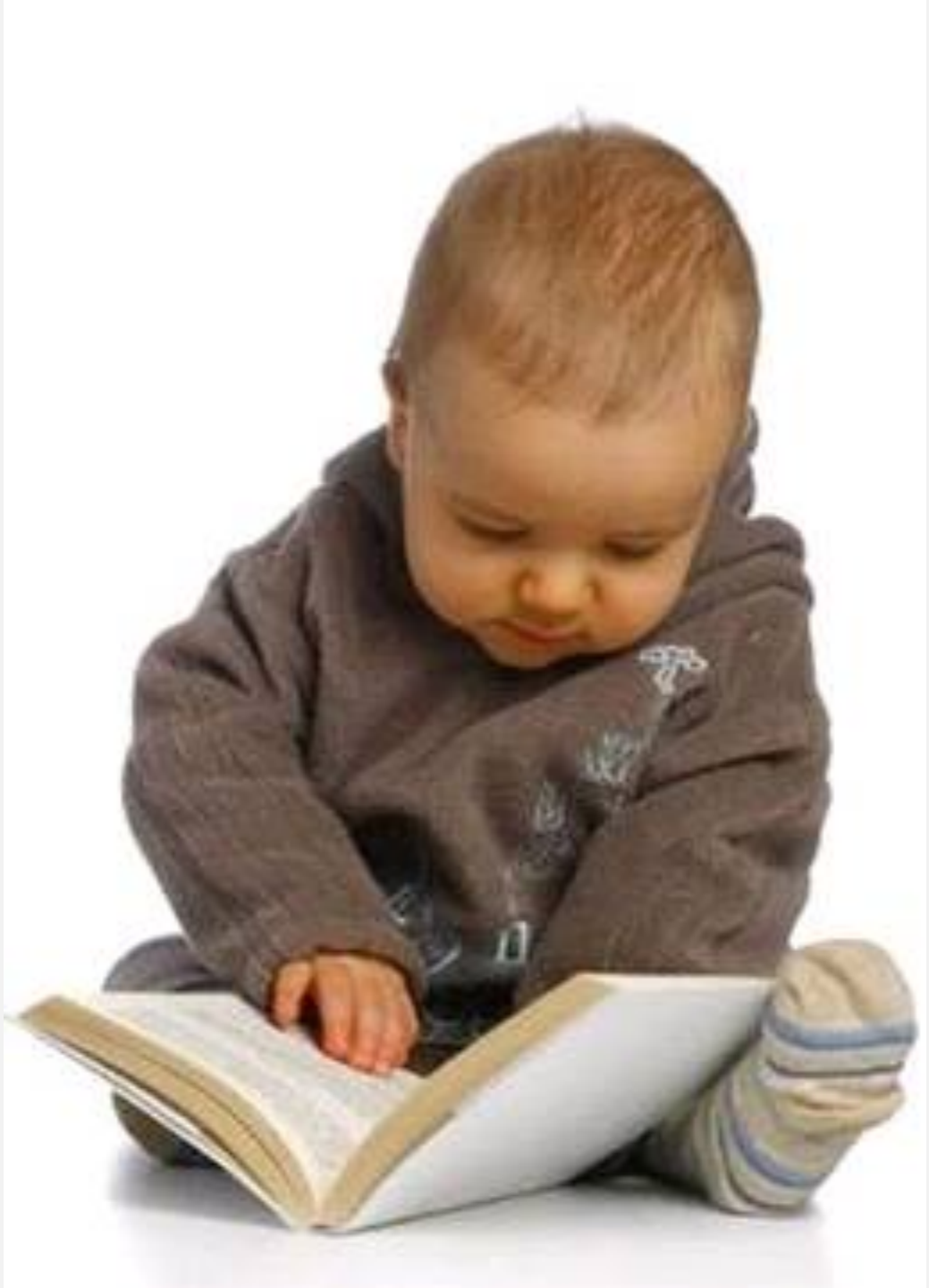
HHV-7 has been less frequently associated with CNS disease than HHV-6, but found to be associated with encephalitis, meningitis, and demyelinating conditions. Similar to HHV 6A, increased levels of HHV-7 were found in multiple brain regions in Alzheimer's disease (AD) patients. [46, 53]

Anti-Streptococcal A

Group A beta-haemolytic streptococcal (GABHS) tonsillitis, more frequently known as streptococcal pharyngitis, is highly prevalent in children, especially in those who are between the ages of 5 and 15 years. A subset of these children may develop PANDAS characterized by pediatric obsessive-compulsive disorder (OCD) and tic disorder, and Sydenham Chorea. Anti-streptococcal A antibodies are shown to cross react with different brain proteins that could lead to neuropsychiatric symptoms.[54]

How are we supposed to understand a test like this?





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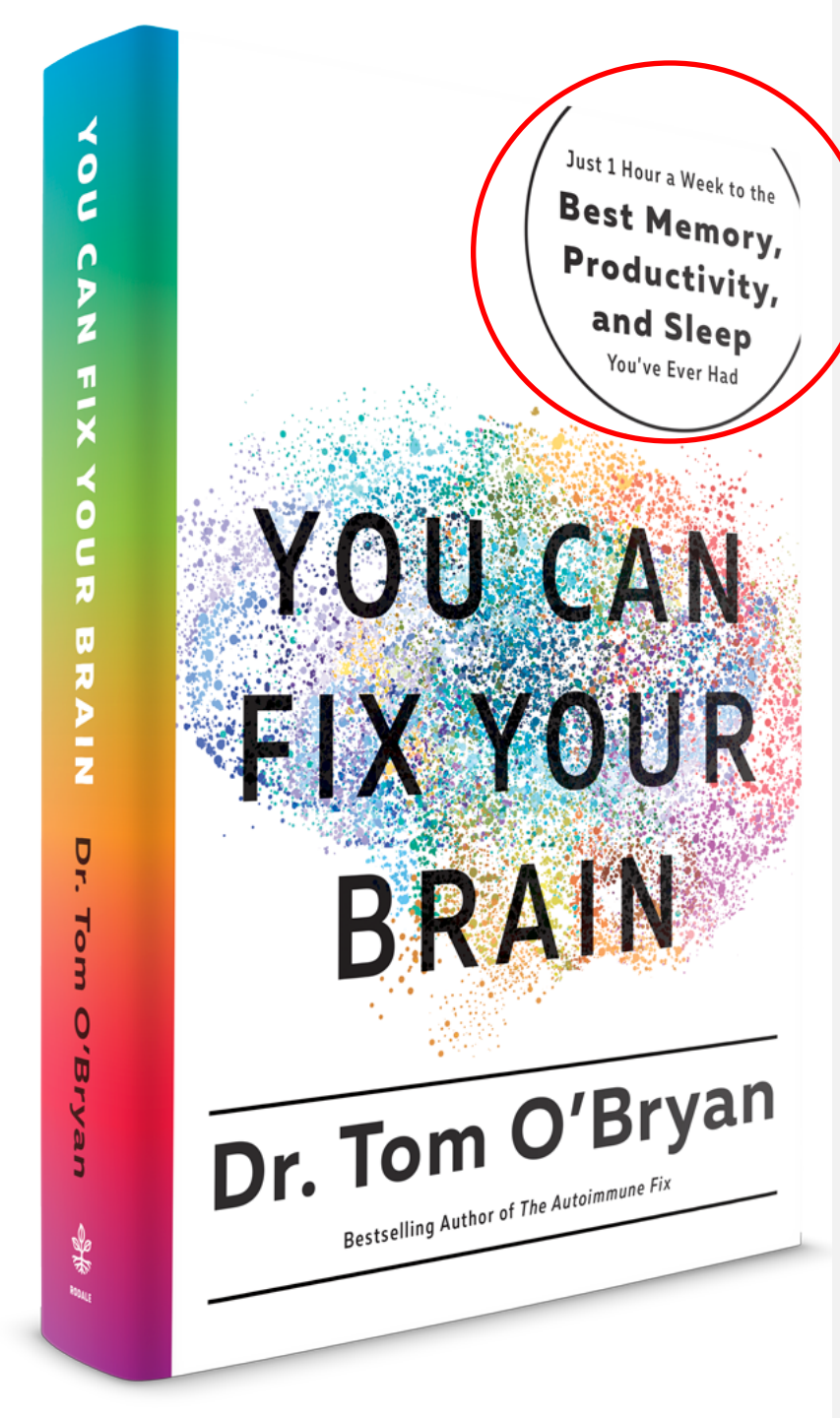

Positive		Moderate		Negative			
(IgG + IgA)	IgM	(IgG + IgA)	IgM				
Peripheral Neuropathy Anti-GM1 **Brain Autoimmunity** Anti-Purkinje cell		**Blood Brain Barrier Disruption** Anti-s100b **Optical and Autonomic nervous system disorder** Anti-Aquaporin4 **Brain Autoimmunity** Anti-RAGE peptide **Infection** Anti-HHV 6 Anti-Streptococcal A		**Demyelination Antigens**			
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				Anti-Neurofascin	Anti-MAG		
				Blood Brain Barrier Disruption			
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				Optical and Autonomic nervous system disorder			
				Anti-Neuron specific enolase	Anti-Recoverin	Anti-CV2	
				Peripheral Neuropathy			
				Anti-GM2	Anti-Hu	Anti-Ri	Anti-Amphiphysin
				Neuromuscular disorders			
				Anti-Acetylcholine receptors Anti-Titin	Anti-Muscle specific kinase	Anti-Voltage gated calcium channels	Anti-Voltage gated potassium channels
				Brain Autoimmunity			
				Anti-Cerebellum	Anti-Yo	Anti-Amyloid beta (25-35)	Anti-Amyloid beta (1-42)
				Anti-Tau	Anti-Glutamate	Anti-Dopamine	Anti-Hydroxytryptamine
				Anti-Alpha-synuclein	Anti-α1 and β2 adrenergic receptors	Anti-Endothelin A receptor	
				Brain Inflammation			
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				Anti-GABA receptors	Anti-Dipeptidyl aminopeptidase like protein 6	Anti-Glycine receptor	Anti-Neurexin 3
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				Infection			
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Ganglioside reactive antibodies in the neuropathy associated with celiac disease

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the most common neurological symptom in CD is peripheral neuropathies

22% of CD patients manifest symptoms of peripheral neuropathies

In this study, every one (100%) of these peripheral neuropathy CD patients had elevated anti-ganglioside antibodies

DQ8 molecules that are implicated in the presentation of gliadin to sensitized T cells infiltrating the lamina propria (Howell et al., 1986; Sollid et al., 1989).

Celiac disease is associated with several autoimmune phenomena, including autoantibodies to tissue transglutaminase (tTG) (Dieterich et al., 1998), and increased incidence of type I diabetes, Sjögren syndrome, and autoimmune thyroid disease (Ventura et al., 1999; Kumar et al., 2001; Larizza et al., 2001). The mechanism of autoimmunity is unclear, but in the case of tTG, the antibodies are thought to be induced by gliadin–tTG complexes, with activation of tTG-specific B

Chapman et al., 1978; Collin et al., 1991). These were assumed to be due to malabsorption, although nutritional deficiencies were rarely demonstrated, and no improvement of the neurological diseases was observed following vitamin therapy (Muller et al., 1996). Overall, very little research has been done into the mechanisms of the neurological complications of celiac disease.

As celiac disease is known to be linked to autoimmunity, we tested the patients for the presence of anti-ganglioside antibodies, which are associated with autoimmune neuropathies (O'Leary and Willison, 2000; Press et al., 2001). Sera were screened using a newly developed ganglioside agglutination immunoassay that detects antibodies to brain ganglio-

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BMC Gastroenterology

REVIEW Open Access

An updated overview of spectrum of gluten-related disorders: clinical and diagnostic aspects

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Abstract

There is a cross-reactivity between antigenic epitopes located at the level of Purkinje cells and gluten-related antibodies. In susceptible individuals, anti-gliadin antibodies may have a clinically significant direct or indirect neurotoxic effect

are considered to be allergic and non-autoimmune-allergic diseases [1–3].

GRDs are estimated to have a global prevalence of approximately 5% [4]. Until two decades ago, CD and other GRDs were considered to be almost exclusively found in European populations. Advances in the

tions and since then symptoms in keeping with GRDs were reported [6–9]. Much later the mechanization of agriculture and most recently, the industrial use of pesticides, nitrogen-based fertilizers, and genetic modification have led to the production of a vast amount of wheat, including new types of wheat with high gluten content. These gluten-rich wheats are used in the global food industry. These rapid changes in the amount and type of wheat being consumed may be responsible for the global increase in the prevalence of GRDs [5, 10]. In a short period of time, in evolutionary timescales, wheat has

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Original Article

S100B and S100B autoantibody as biomarkers for early detection of brain metastases in lung cancer

Humberto Choi[1], Vikram Puvenna[2], Chanda Brennan[2], Shamseldeen Mahmoud[3], Xiao-Feng Wang[4], Michael Phillips[3], Damir Janigro[2], Peter Mazzone[1]

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: H Choi, XF Wang, D Janigro, P Mazzone; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: S100B is an astrocytic protein that enters the blood stream when there is disruption of the blood-brain barrier (BBB). Over time, antibodies against S100B develop in the sera of patients who experience persistent or repeated BBB disruptions. We explored the use of serum S100B protein and S100B autoantibodies for the detection of brain metastasis in patients with lung cancer.

improving to 62.5% when combined with autoantibodies.

Conclusions: Serum S100B and S100B autoantibody levels may help to identify which lung cancer patients have brain metastases.

Keywords: Biomarker; brain metastasis; lung cancer; S100B; small vessel disease (SVD)

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S100B is an astrocytic protein that enters the blood stream when there is disruption of the blood-brain barrier (BBB)

Introduction

The identification of brain metastases has important implications for treatment and prognosis. A total of 10–15% of patients with lung cancer have brain metastases at diagnosis. The brain is a frequent site for progression of lung cancer because the blood-brain barrier (BBB) shelters the central nervous system (CNS) from systemic treatment (1). Guidelines suggest obtaining brain imaging at presentation in asymptomatic lung cancer patients with advanced stage non-small cell lung cancer, all patients with small cell carcinoma, and anyone with symptoms that could be related to the presence of brain metastases (2,3). On the other side, brain imaging is not routinely performed in longitudinal follow-up (4,5). The appropriate selection of patients at high risk of having brain metastasis could reduce the amount of unnecessary brain imaging, decrease costs and improve patient care. An accurate, inexpensive

Original Article

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autoantibody threshold of <2.00 absorbance units was used in conjunction with S100B, the sensitivity remained at 89%, and the specificity increased to 58%. The overall accuracy was 51% with S100B alone, improving to 62.5% when combined with autoantibodies.

Conclusions: Serum S100B and S100B autoantibody levels may help to identify which lung cancer patients have brain metastases.

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Positive		Moderate		Negative			
(IgG + IgA)	IgM	(IgG + IgA)	IgM				
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				Anti-Tubulin	Anti-Myelin basic protein	Anti-Myelin oligodendrocyte glycoprotein	Anti-Myelin proteolipid protein
				Anti-Neurofascin	Anti-MAG		
				Blood Brain Barrier Disruption			
				Anti-Glial fibrillary acidic protein	Anti-Microglia	Anti-Glucose regulated protein 78	
				Optical and Autonomic nervous system disorder			
				Anti-Neuron specific enolase	Anti-Recoverin	Anti-CV2	
				Peripheral Neuropathy			
				Anti-GM2	Anti-Hu	Anti-Ri	Anti-Amphiphysin
				Neuromuscular disorders			
				Anti-Acetylcholine receptors Anti-Titin	Anti-Muscle specific kinase	Anti-Voltage gated calcium channels	Anti-Voltage gated potassium channels
				Brain Autoimmunity			
				Anti-Cerebellum	Anti-Yo	Anti-Amyloid beta (25-35)	Anti-Amyloid beta (1-42)
				Anti-Tau	Anti-Glutamate	Anti-Dopamine	Anti-Hydroxytryptamine
				Anti-Alpha-synuclein	Anti-α1 and β2 adrenergic receptors	Anti-Endothelin A receptor	
				Brain Inflammation			
				Anti-NMDA receptor	Anti-AMPA receptor	Anti-Dopamine receptor 1	Anti-Dopamine receptor 2
				Anti-GABA receptors	Anti-Dipeptidyl aminopeptidase like protein 6	Anti-Glycine receptor	Anti-Neurexin 3
				Anti-Contactin-Associated Protein-like 2 Antibodies	Anti-Leucine-rich glioma-inactivated protein 1 (Anti-LGI1)	Anti-Ma	
				Infection			
				Anti-HSV1 Anti-HHV 7	Anti-HSV2	Anti-EBV	Anti-CMV

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Research Article

Detection of Antibodies against Human and Plant Aquaporins in Patients with Multiple Sclerosis

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A significant percentage of RRMS patients showed elevation not only in antibodies against human AQP4 and the aquaporins of soy, corn, tomato, and spinach, but also against MBP, MOG, and S100B.

neuroimmune disorders.

1. Introduction

Multiple sclerosis (MS) is characterized by the demyelination of a nerve's protective myelin sheaths in the brain and spinal cord, which occurs due to inflammation and attack by the body's own immune system [1, 2]. This myelin damage disrupts the communication between the brain and the rest of the body. Symptoms may include fatigue, vertigo, cognitive impairment, focal cortical deficits, unilateral painful loss of vision, postural and action tremor, dysarthria, limb incoordination and gait ataxia, diplopia, oscillopsia, pseudobulbar palsy, and bladder dysfunction. In 1996, the United States National Multiple Sclerosis Society described 4 clinical courses of the disease [3]. In 2013, this set of courses was reviewed by an international panel [4], resulting in the recognition of 4 main phenotypes of MS. The first type, relapsing-remitting multiple sclerosis (RRMS), affects around 90% of people who have MS. The defining elements of RRMS are episodes of acute worsening of neurologic function followed by a variable degree of recovery, with a stable course between attacks [3]. The remaining 10% have one of these three progressive forms: secondary progressive (SPMS), primary progressive (PPMS), and progressive relapsing (PRMS).

Aquaporin 4 (AQP4) is a class of water channels found in many cells of the body including the stomach, brain, lung, and skeletal muscle [5]. AQP4 is the predominant water channel in the central nervous system and is expressed in ependymocytes, endothelial cells, and astrocyte foot processes at the blood-brain barriers (BBB), but not in neurons [6, 7]. In the brain, AQP4 is believed to have a role in maintaining homeostasis and water exchange, electrical activity, and modulation of neuronal transmission and excitability [8, 9].

Neuromyelitis optica (NMO), or Devic's disease, is a severe inflammatory demyelinating disorder that affects the white and gray matter in the brain and is classically restricted to the optic nerves and spinal cord [10–12]. Studies have

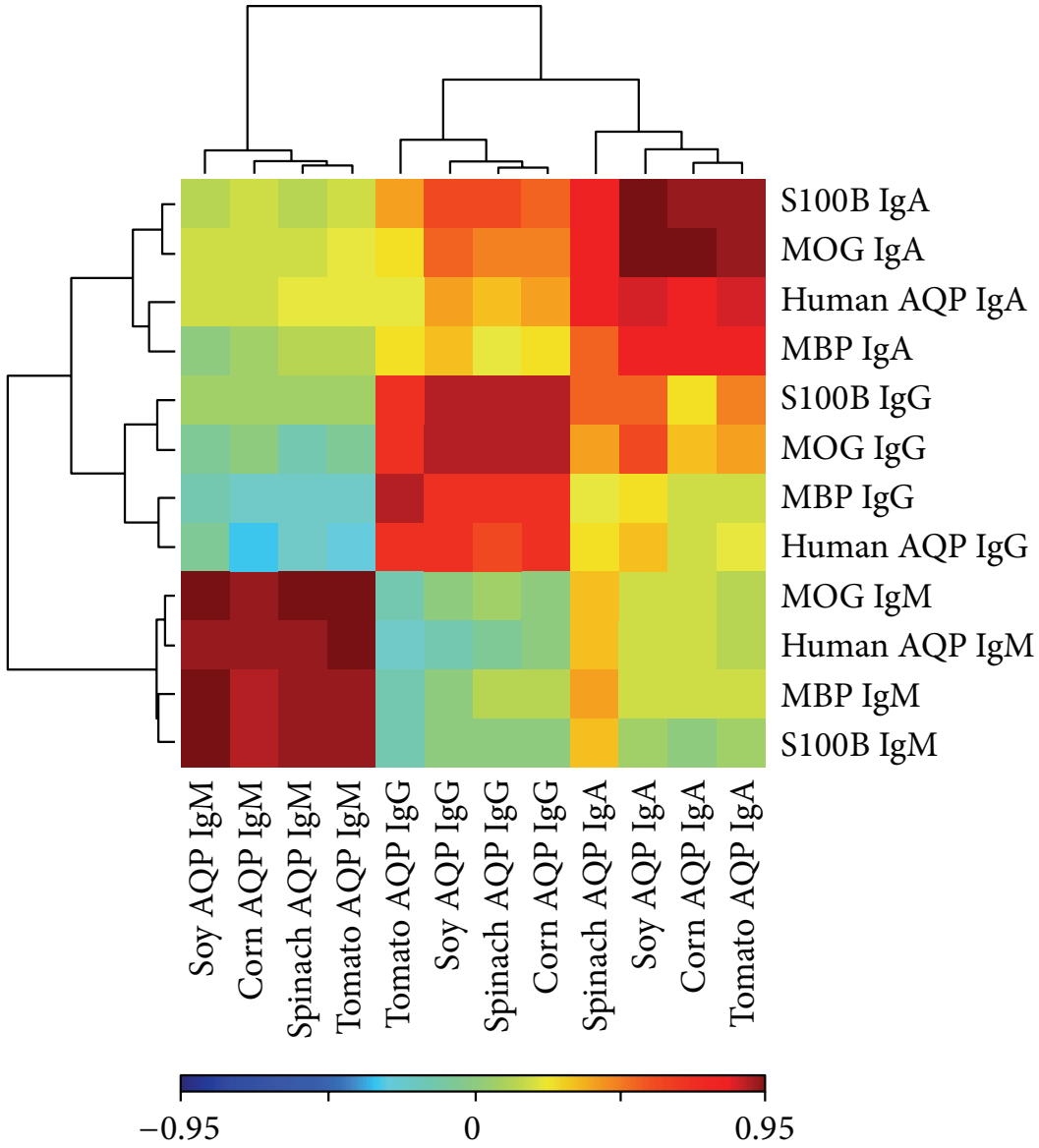

FIGURE 4: IgA, IgM, and IgG isotypes are clustered together with high correlations among the aquaporin peptides and brain proteins in each isotype.

Positive		Moderate		Negative			
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Review

Dietary advanced glycation endproducts (AGEs) and their health effects – PRO

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Thermal processing of food results in the formation of various novel compounds, among others advanced glycation endproducts (AGEs). AGEs result from nonenzymatic glycation reactions between reducing sugars and free amino groups of proteins, peptides, or amino acids. Due to their potential noxious effects, alimentary AGEs are also called glycotoxins. This review provides a summary of the available evidence on the health effects of exaggerated intake of thermally treated food. Data from experimental studies in rodents and from clinical studies in healthy volunteers and in patients suffering from selected diseases in which AGEs are of pathogenetic importance (diabetes

Thermal processing of food (cooking) leads to the formation of various novel compounds. Among these, advanced glycation end products (AGEs) are well-known compounds hypothesized to cause harmful health effects.

Thermal processing of food leads to the formation of various novel compounds. Among these, heterocyclic amines, acrylamide, and advanced glycation endproducts (AGEs) are well-known compounds hypothesized to cause harmful health effects. Recently, it has been demonstrated, that AGEs are at least partially absorbed into circulation [1]. Several lines of evidence favor the concept that exaggerated intake of thermally processed food might induce pathogenic pathways, or aggravate a pre-existing pathology, *in vivo*. In this paper, data from experimental and clinical studies sup-

thermally modified diets are reviewed.

2 Effects of exaggerated intake of thermally processed food in health

Observed deleterious effects of high-AGE diets on health in healthy animals or human studies are summarized in Table 1.

2.1 Animal studies

Two studies are reviewed. In the first one, male Wistar rats were pair-fed during 6 wk with AGEs-poor (content: 50% w/w commercial rat food Altromin, 25% w/w wheat starch, 23% w/w casein, 2% w/w cellulose) or AGEs rich diet (BC, wheat starch replaced by bread crusts [2, 3]. Average daily intake of AGE-N^{ε}-carboxymethyllysine (CML) in BC diet was about 11 mg/kg body weight/day, while in the AGEs-poor diet, CML contents were below the LOD (analyzed by GS-MS method) [4]. Consumption of BC diet resulted in increase of plasma levels of CML (by 32.9%), carboxyethyllysine (CEL, by 24.5%) (GS-MS method, both) and

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Abbreviations: AGEs, advanced glycation endproducts; **BC,** bread crusts; **CML,** N^{ε}**-carboxymethyllysine; CRI,** chronic renal insufficiency; **HA,** high-AGE; **HF,** high fat; **MG,** methylglyoxal; **NOD,** non-obese diabetic; **TGF-β_1,** transforming growth factor β_1; **VCAM-1,** vascular cell adhesion molecule-1


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Dietary Advanced Glycation End Products and Their Role in Health and Disease[1,2]

Jaime Uribarri,[3]* María Dolores del Castillo,[4] María Pía de la Maza,[5] Rosana Filip,[6] Alejandro Gugliucci,[7] Claudia Luevano-Contreras,[8] Maciste H Macías-Cervantes,[8] Deborah H Markowicz Bastos,[9] Alejandra Medrano,[10] Teresita Menini,[7] Manuel Portero-Otin,[11] Armando Rojas,[12] Geni Rodrigues Sampaio,[9] Kazimierz Wrobel,[13] Katarzyna Wrobel,[13] and Ma Eugenia Garay-Sevilla[8]

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Foods rich in both protein and fat, mostly of animal origin, and cooked at high and dry heat, such as in broiling, grilling, frying, and roasting, tend to be the richest dietary sources of AGEs

current methodologic problems with measurement of AGEs in different samples. The subject under discussion is complex and extensive and cannot be completely covered in a short review. Therefore, some areas of interest have been left out because of space. However, we hope this review illustrates currently known facts about dietary AGEs as well as pointing out areas that require further research. *Adv Nutr* 2015;6:461–73.

Keywords: nutrition, oxidative stress, inflammation, insulin resistance, RAGE, nutraceutical

Introduction

In October 2014 a meeting on the potential role of dietary advanced glycation end products (AGEs)[14] took place in Guanajuato, Mexico. Increasingly, it has become evident that food-derived AGEs make a substantial contribution to the systemic burden of AGEs and therefore predispose individuals to oxidative stress (OS) and inflammation, which play a major role in the causation of chronic diseases. A group of international experts in different areas of AGE research from the United States, Spain, Mexico, Brazil, Argentina, and Chile presented their work and discussed extensively what is currently known and what areas of research need to be emphasized to increase our understanding of the role of dietary AGEs in health and disease. Herein, we present a summary of the main presentations and discussions that took place during this 3 d symposium. This review is divided into the following 4 sections: *1*) general background on AGEs; *2*) molecular pharmacology of AGEs, in which we discuss how AGEs cause pathologic effects in the body, with particular attention to the receptor for advanced glycation end products

[1] The authors reported no funding received for this study.

[2] Author disclosures: J Uribarri, MD del Castillo, MP de la Maza, R Filip, A Gugliucci, C Luevano-Contreras, MH Macías-Cervantes, DH Markowicz Bantos, A Medrano, T Menini, M Portero-Otin, A Rojas, GR Sampaio, Kaz Wrobel, Kat Wrobel, and ME Garay-Sevilla, no conflicts of interest.

[14] Abbreviations used: ACE, angiotensin-converting enzyme; AGE, advanced glycation end product; AQC, 6-aminoquinonyl-*N*-hydroxysuccinimidyl-carbamate; CKD, chronic kidney disease; esRAGE, endogenous secretory RAGE; OPA, ortho-phthalaldehyde; OS, oxidative stress; RAGE, receptor for advanced glycation end products; sRAGE, soluble receptor for advanced glycation end products.

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CME Review Article

Advanced Glycation End-Products and Their Receptor-Mediated Roles: Inflammation and Oxidative Stress

Parisa Younessi[1,2], Ali Yoonessi[3,4]

Abstract

Glycation is a protein modification, which results in a change in a protein structure. Glycation is believed to be the etiology of various age-related diseases such as diabetes mellitus and Alzheimer's disease (AD). Activation of microglia and resident macrophages in the brain by glycated proteins with subsequent oxidative stress and cytokine release may be an important factor in the progression of AD. It is also suggested that interaction between an advanced glycation end product (AGE) and its re-

It is known that the blood brain barrier (BBB) is important for Aβ brain balance, and that BBB regulates the transport of Aβ through two receptors: the low density lipoprotein receptor related protein1 (LRP1) and RAGE.

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neous products, mostly fluorescent with nitrogen- and oxygen-containing heterocyclic compounds, called advanced glycation end products (AGEs) are formed. The formation of AEGs is irreversible, and causes a resistant protein deposition to protease.[4,5] The Maillard reaction was first described by L.C. Maillard a chemist, who reported the formation of brown products upon heating a solution of amino acid (AA) and sugar.[6] Schematic representation of the Maillard reaction (A) and structures of AGEs (B, C and D),[7] are shown in figure 1.

Pathological Consequences of AGEs

In vivo Glycation modifies the structural properties of proteins such as albumin and haemoglobin leading to inflammation and oxidative stress. The pathological role of AGEs in diseases such as diabetes mellitus (DM) is not fully understood. In addition to change of the protein structure, the receptor mediated mechanism of AGEs is of special interest.[8]

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The RAGE protein mediates the influx of amyloid protein from plasma to the brain, whereas, LRP protein mediates the efflux of amyloid protein through the BBB

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Generally, efflux which is mediated by LRP1 is greater than influx by RAGE. In AD, changes in RAGE expression create an imbalance between the rates of influx and efflux of Aβ peptide through the BBB.

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Review Article

A Review of the Science of Colorful, Plant-Based Food and Practical Strategies for "Eating the Rainbow"

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Over the past decades, thousands of published studies have amassed supporting recommendations to consume fruits and vegetables for physiological and psychological health.

throughout the lifespan. Other adjunctive strategies to heighten awareness of fruits and vegetables are discussed.

1. Introduction

While there continues to be debate about the inclusion of meat, dairy, grains, and legumes in a healthy diet, there would seem to be little disagreement in the scientific community that eating fruits and vegetables is beneficial for one's health. Eating plant-based foods is part of many diverse dietary patterns, including the well-studied Mediterranean diet [1], vegan and vegetarian approaches, the hunter-gatherer (Paleolithic) diet [2], and even the less well-studied, ketogenic diet [3]. The quantity and quality of in vitro, animal, and clinical data over several decades suggest that intake of fruits and vegetables is associated with reducing chronic disease risk, such as cardiovascular disease, diabetes, cataracts, cancer, dementia, obesity, and others [4–7].

The search strategy for this review article was to start with a scientific literature review of the health benefits of fruits and vegetables, along with the predominant issues surrounding deficiencies in intake. Secondly, the goal was to organize the findings into a categorical system for ease of understanding and application.

1.1. Phytonutrient Gap. Despite the widely known health benefits of consuming fruits and vegetables, low intakes are historically consistent, with recent data from the 2015 Behavioral Risk Factor Surveillance System indicating that most adults (particularly men, young adults, and those living in poverty) consume insufficient amounts [8]. Only nine percent and twelve percent of American adults met the recommendations for vegetables and fruits, respectively [8]. Moreover, a report [9] based on food consumption data from the National Health and Nutrition Examination Survey (NHANES) conducted in 2003-2004 and 2005-2006 found that eight out of ten Americans fall short in every color of phytonutrients (referred to as a "phytonutrient gap"), especially in the color category of purple/blue foods (88% of people neglected to meet their daily serving).

Table 3: Select foods, their (phyto)nutrient profile, and health benefits.

Color	Food	Some food formats researched	Basic (phyto)nutrient profile	Researched health benefits
Red	Tomatoes	Juice, powder, raw, sauce (prepared with and without oil)	Carotenoids (e.g., lycopene), flavonoids, vitamin C	(i) Reduction in inflammatory markers (ii) Reduction in postprandial inflammation (iii) Improvement in lipid markers
Red	Strawberries	Freeze-dried as beverage	Polyphenols (flavonoids, phenolic acids, tannins), vitamin C	(i) Reduction in postprandial inflammation (ii) Reduction in pain due to osteoarthritis
Red	Beets	Cooked, raw juice	Betalains	(i) Reduction in inflammatory markers
Orange	Wild yam	Cooked	Phytoestrogens	(i) Increase in estrogen and estrogen metabolites (ii) Phytoestrogenic activity
Orange	Carrots	Not specified	Alpha- and beta-carotene	(i) Decrease in rate of breast and prostate cancer (ii) Phytoestrogenic activity (iii) Association with estrogen metabolism
Orange	Orange fruits	Not specified	Bioflavonoids, beta-carotene, beta-cryptoxanthin	(i) Delay in ovarian senescence (ii) Lower risk for endometriosis
Yellow	Ginger	Standardized extract	Gingerols, shogaols	(i) Decrease in nausea (ii) Increase in gastric emptying
Yellow	Citrus (lemons)	Juice, raw	Hesperidin, nobiletin, rutin, vitamin C	(i) Protective against gastric ulcer (ii) Antidiabetic (iii) Reduction in glycemic impact
Yellow	Pineapple	Juice	Bromelain, serotonin	(i) Enzymatic activity
Yellow	Bananas	Raw	Prebiotic fiber, serotonin	(i) Increase in bifidobacteria (ii) Reduction in bloating
Green	Leafy greens	Raw, spinach	Chlorophyll, folate, nitrates, phylloquinone	(i) Reduction in blood pressure (ii) Increase in nitric oxide (iii) Increase in blood flow
Green	Cruciferous vegetables	Not specified	Glucosinolates, isothiocyanates, sulforaphane	(i) Antioxidant action (ii) Reduction in platelet aggregation (iii) Reduction in thrombus formation
Blue-purple	Concord grape juice	Juice	Phenolic acids, stilbenes, anthocyanins, proanthocyanins	(i) Improvement in spatial memory and performance (ii) Improvement in reaction time on attention (iii) Increase in calm ratings
Blue-purple	Blueberries	Beverage, freeze-dried, raw	Flavonoids, procyanidins (monomeric and oligomeric form), flavonols (i.e., kaempferol, quercetin, myricetin), phenolic acids (mainly hydroxycinnamic acids), derivatives of stilbenes	(i) Improvement in measures of cognition (ii) Benefit to mood (iii) Improvement in neuroplasticity

This table provides a summary of certain foods and accompanying animal and/or clinical research studies as discussed in this review article. Details on the studies can be found in the respective color section in the text.

IFM Phytonutrient Spectrum

ORANGE

Foods
- Acorn squash
- Apricots
- Bell pepper
- Butternut squash
- Cantaloupe
- Carrots
- Dried fruit (apricot, mango, papaya)
- Grapefruit
- Mango
- Nectarine
- Orange
- Papaya
- Sweet potato
- Turmeric root
- Winter squash

Benefits
- Anti-cancer
- Anti-bacterial
- Immune health
- Cell protection
- Reduced mortality
- Reproductive health
- Skin health
- Source of vitamin A

YELLOW

Foods
- Bell peppers
- Corn
- Corn-on-the-cob
- Greens
- Kale
- Popcorn
- Spinach
- Succotash
- Squash (yellow)

Benefits
- Anti-cancer
- Anti-inflammatory
- Cell protection
- Cognition
- Eye health
- Heart health
- Skin health
- Vascular health

GREEN

Foods
- Artichoke
- Asparagus
- Avocado
- Bamboo sprouts
- Bean sprouts
- Bell Peppers
- Bok choy
- Broccoli
- Brussels sprouts
- Cabbage
- Celery
- Chard/Swiss chard
- Cucumbers
- Green beans
- Green peas
- Green tea
- Greens (beet, collard, dandelion, kale, mustard, turnip)
- Lettuce
- Okra
- Olives
- Rosemary
- Spinach
- Soy (edamame, beans, tempeh, tofu, tofu burger, miso, natto, soy cheese, soy milk, soy yogurt)
- Snow peas
- Watercress

Benefits
- Anti-cancer
- Anti-inflammatory
- Brain health
- Cell protection
- Skin health
- Hormone balance
- Heart health
- Liver health

RED

Foods
- Adzuki beans
- Apples
- Applesauce
- Bell Peppers (red)
- Cranberries
- Cherries
- Kidney beans
- Plums (red)
- Pomegranate
- Radishes
- Raspberries
- Red grapefruit
- Red grapes
- Shrimp
- Strawberries
- Sweet red peppers
- Rooibos tea
- Tomato

Benefits
- Anti-cancer
- Anti-inflammatory
- Cell protection
- DNA health
- Immune health
- Prostate health
- Vascular health

WHITE / TAN

Foods
- Bean dips
- Cauliflower
- Cinnamon
- Clove
- Dark chocolate
- Flaxseed meal
- Garlic
- Ginger
- Hummus
- Legumes
- Nuts
- Onions
- Refried beans, low-fat
- Sesame seeds
- Shallots
- Soy (edamame, beans, tempeh, tofu, tofu burger, miso, natto, soy cheese, soy milk, soy yogurt)
- Tahini
- Whole flaxseeds
- Whole grains (quinoa, brown rice, wheat, spelt)

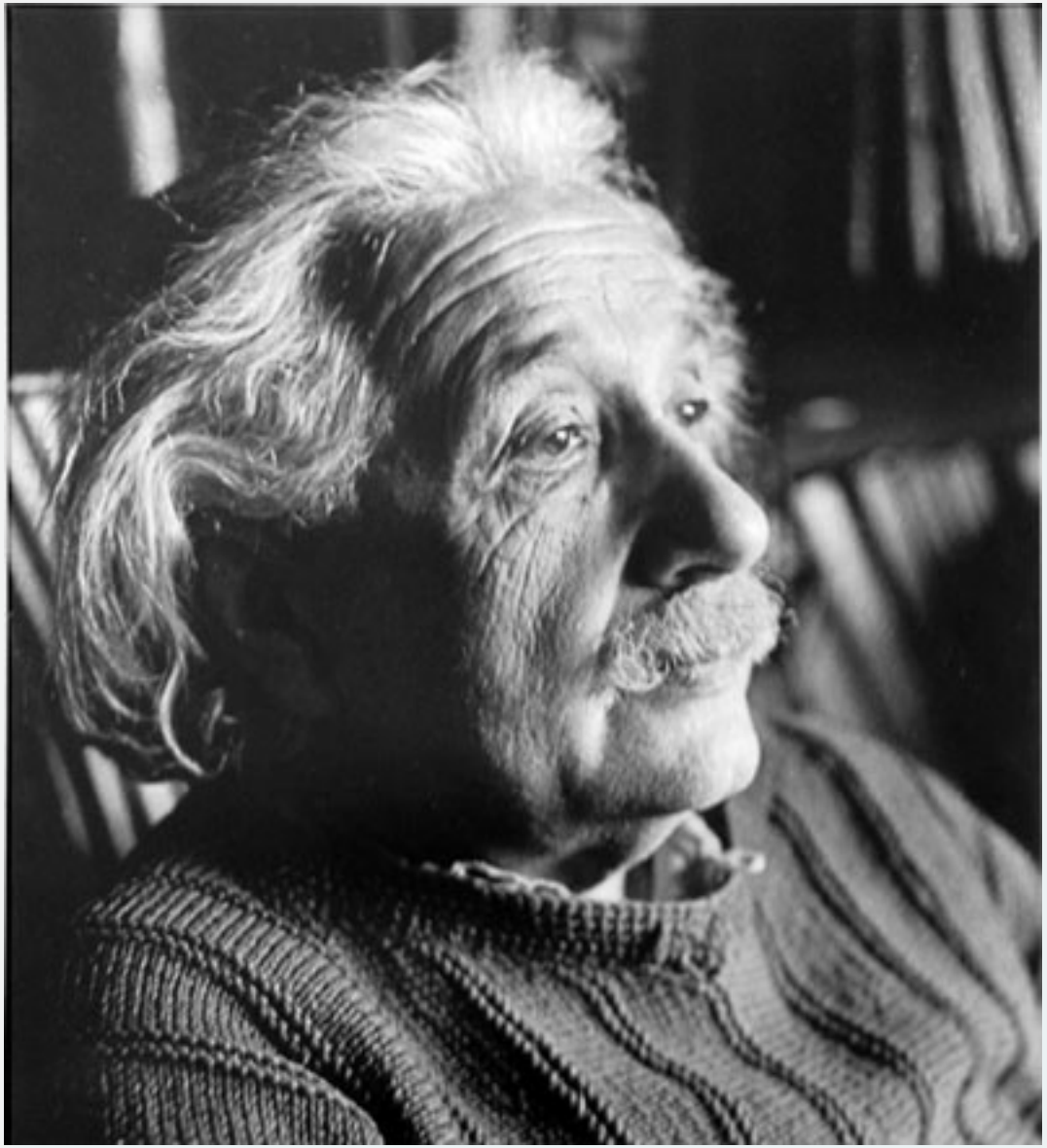
Benefits
- Anti-cancer
- Anti-microbial
- Cell protection
- Gastrointestinal health
- Heart health
- Hormone balance
- Liver health

BLUE / PURPLE

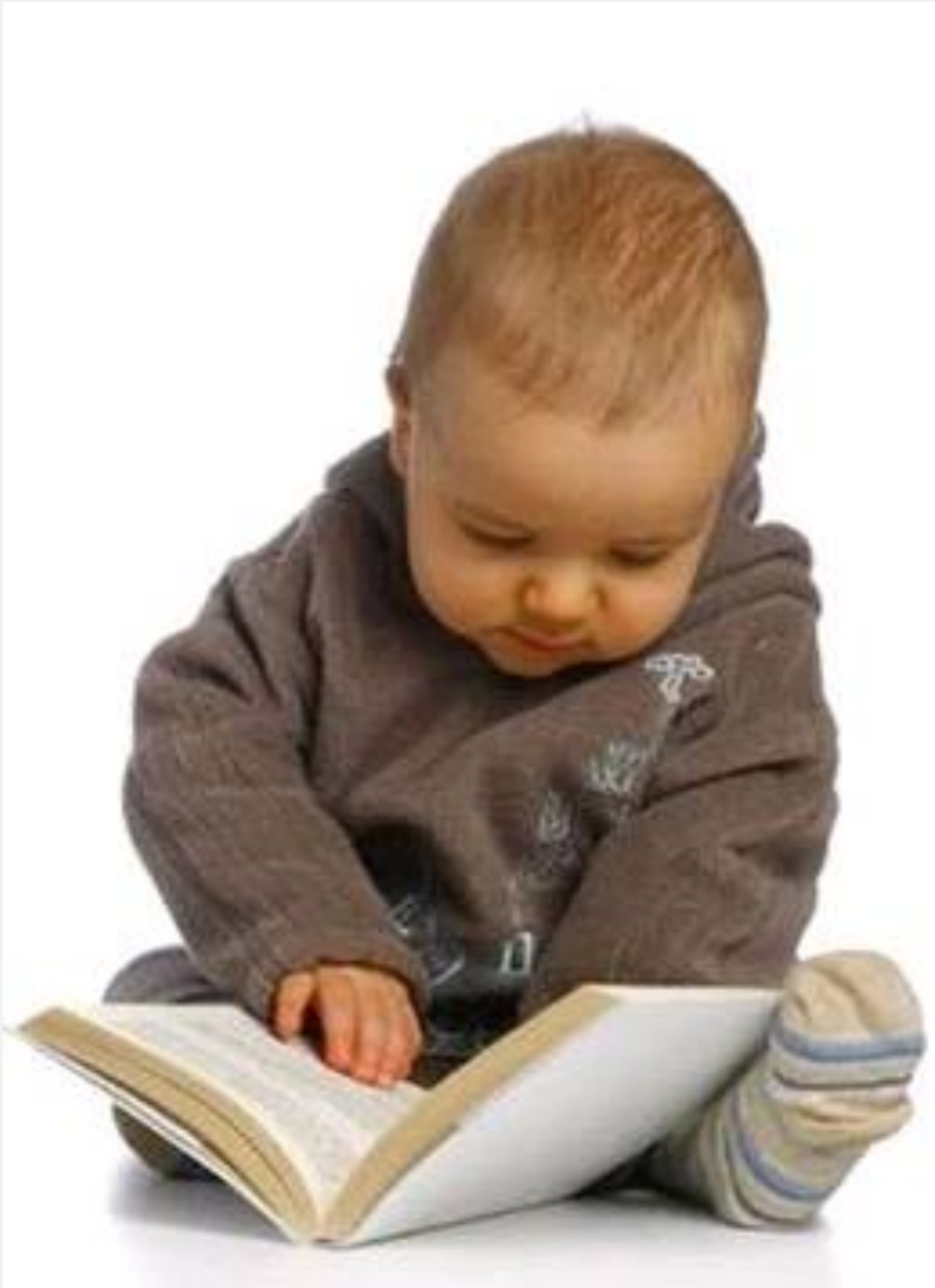
Foods
- Berries, (blue or black)
- Cabbage (purple)
- Carrots (purple)
- Cauliflower (purple)
- Dates
- Eggplant
- Figs
- Grapes (purple)
- Kale (purple)
- Olives (purple)
- Plums (purple)
- Potatoes (purple)
- Prunes
- Raisins
- Rice, (black or purple)

Benefits
- Anti-cancer
- Anti-inflammatory
- Cell protection
- Cognitive health
- Heart health

Positive		Moderate		Negative			
(IgG + IgA)	IgM	(IgG + IgA)	IgM				
Peripheral Neuropathy Anti-GM1 **Brain Autoimmunity** Anti-Purkinje cell		**Blood Brain Barrier Disruption** Anti-s100b **Optical and Autonomic nervous system disorder** Anti-Aquaporin4 **Brain Autoimmunity** Anti-RAGE peptide **Infection** Anti-HHV 6 Anti-Streptococcal A		**Demyelination Antigens**			
				Anti-Tubulin	Anti-Myelin basic protein	Anti-Myelin oligodendrocyte glycoprotein	Anti-Myelin proteolipid protein
				Anti-Neurofascin	Anti-MAG		
				Blood Brain Barrier Disruption			
				Anti-Glial fibrillary acidic protein	Anti-Microglia	Anti-Glucose regulated protein 78	
				Optical and Autonomic nervous system disorder			
				Anti-Neuron specific enolase	Anti-Recoverin	Anti-CV2	
				Peripheral Neuropathy			
				Anti-GM2	Anti-Hu	Anti-Ri	Anti-Amphiphysin
				Neuromuscular disorders			
				Anti-Acetylcholine receptors Anti-Titin	Anti-Muscle specific kinase	Anti-Voltage gated calcium channels	Anti-Voltage gated potassium channels
				Brain Autoimmunity			
				Anti-Cerebellum	Anti-Yo	Anti-Amyloid beta (25-35)	Anti-Amyloid beta (1-42)
				Anti-Tau	Anti-Glutamate	Anti-Dopamine	Anti-Hydroxytryptamine
				Anti-Alpha-synuclein	Anti-α1 and β2 adrenergic receptors	Anti-Endothelin A receptor	
				Brain Inflammation			
				Anti-NMDA receptor	Anti-AMPA receptor	Anti-Dopamine receptor 1	Anti-Dopamine receptor 2
				Anti-GABA receptors	Anti-Dipeptidyl aminopeptidase like protein 6	Anti-Glycine receptor	Anti-Neurexin 3
				Anti-Contactin-Associated Protein-like 2 Antibodies	Anti-Leucine-rich glioma-inactivated protein 1 (Anti-LGI1)	Anti-Ma	
				Infection			
				Anti-HSV1 Anti-HHV 7	Anti-HSV2	Anti-EBV	Anti-CMV



Time For a Paradigm Shift



What is the CGP Program?

The most comprehensive practitioner education available for Non-Celiac Gluten Sensitivity (NCGS), Celiac Disease (CD) and their impact on the development of Autoimmune Disorders.

This course provides research based education, the facts about celiac and non-celiac gluten sensitivity and related autoimmune disorders.

Identify and assess overt signs, as well as hidden symptoms

Administer and understand proper testing

Provide protocols based on test results and your assessments

Educate your clients on the need for the care you can now provide them

What To Expect

100% Online Course

Video lectures and supplemental reading material

8 Modules, 8 Hours

90 Days to complete at your own pace

Quizzes and Final Exam

Once you pass, you have access to the exclusive member portal

And it doesn't end here …

Ongoing Support and Education

Lifetime access to Resource Center
Webinars with Dr. O'Bryan and Guests
Lab Test Interpretation webinars
Patient/Client Education Material
Certificate of Completion
Important Research and Studies

As a Certified Gluten Practitioner, You Will …

Be THE Gluten practitioner, for everyone who walks into your office.
Be the go-to practitioner on autoimmune conditions.
Increase patient retention, referrals, and compliance.

Testimonials Keep Coming!

“This has been a fantastic learning experience, and I believe a "missing link" in the functional medicine part of my practice. I have been particularly impressed with the research that supports everything taught, as well as the good, the bad and the ugly about both testing and treatment protocol expectations. I am eager to incorporate what I have learned in my personal life and in my practice.”
- Melvin Mashner

“Dr. O'Bryan offers invaluable information and copious data (which I love!) to support my work with clients. The course provided compelling evidence in favor of screening for gluten sensitivity, not just in clients presenting with digestive symptoms. What an AHA! The course information on non-digestive systemic effects was really illuminating! Thank you so much for this invaluable program. I am looking forward to continuing to grow as a member of the Certified Gluten Practitioner community.”
- Francine Bernitz

“Cutting-edge information, broad application to so many symptoms of dysfunction. Fundamental and foundational. Well-done. It shouldn’t be missed. It should be mandatory.”
- Dona J M.D.

The Brain is your
‘Yellow Canary in the Coal Mine’

Take Care of Yourself

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


“Thank You for Your Kind Attention”


Wishing you Sunrises of Beauty throughout your life