

neurological aspects of coeliac disease and gluten sensitivity

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gluten related disorders

a group of autoimmune diseases triggered by eating gluten:
coeliac disease, dermatitis herpetiformis,
gluten sensitivity-related neurological disorders

the term gluten sensitivity when used in the neurology cohort,
refers to patients (with and without enteropathy) who are
serologically positive for one or more of the gluten-related
antibodies and present or develop neurological dysfunction

the start of the journey...

Does cryptic gluten sensitivity play a part in neurological illness?

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

Summary

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

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

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

Lancet 1996; **347**: 369–71

gluten sensitivity is common in patients with unexplained neurological dysfunction

the frequency of antigliadin antibodies amongst patients with neurological dysfunction of unknown cause was 57% compared to 12% in blood donors

the frequency of coeliac disease within the same group was at least 16% vs 1% in healthy population

gluten sensitivity without coeliac disease

72% of the neurology patients with positive antigliadin antibodies did not have enteropathy

yet they improved on gluten free diet

thus introducing the concept of gluten related neurological dysfunction without enteropathy

diagnostic problems with serological screening

tissue transglutaminase (TGG) and endomysium (EMA) antibodies are specific to CD (these are most commonly available in immunology laboratories)

only 1/3 of patients with gluten related neurological dysfunction have CD so these antibodies alone will miss the majority of patients with potentially treatable neurological deficits

antigliadin antibodies (AGA) are sensitive to the whole spectrum of gluten sensitivity but are no longer readily available in immunology laboratories

the spectrum of neurological involvement

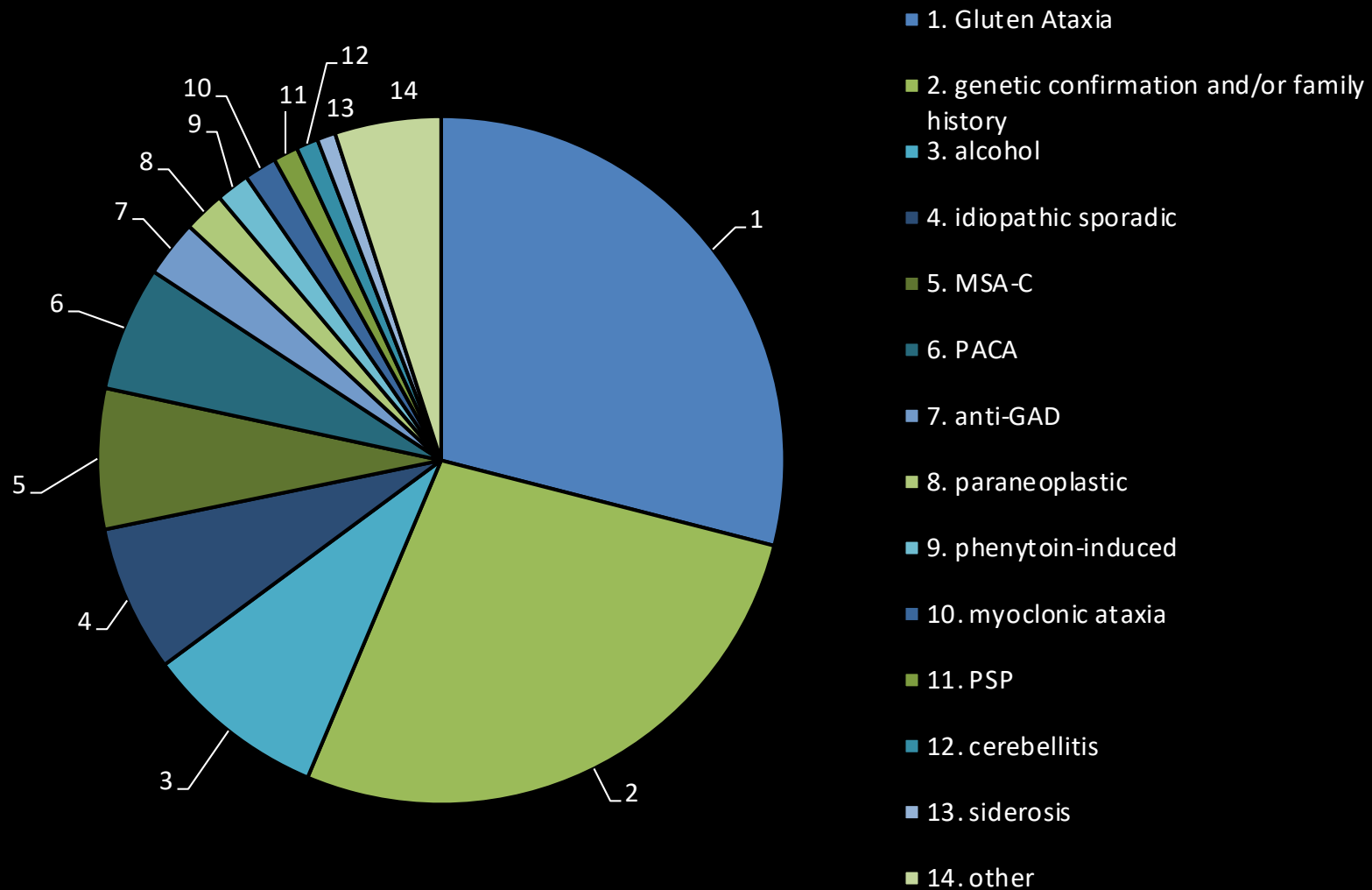
1831 patients seen in the Sheffield Gluten Sensitivity-Neurology Clinic, all positive for one or more gluten-sensitivity related antibodies (1994 – November 2023)

	no (of total)	enteropathy
ataxia	1202 (62%)	48%
peripheral neuropathy	462 (24%)	34%
encephalopathy	269 (14%)	70%

less common manifestations include: myoclonic ataxia (24), SPS (26), myopathy (26), myelopathy (19), neuromyotonia (8)

gluten ataxia

causes of ataxia in 3000 patients with progressive ataxia





the commonest pitfall in the diagnosis of gluten ataxia: incomplete serological testing

MR Studies of brain do reveal quite marked cerebellar atrophy although there is no abnormality on neurological examination other than for a moderately severe degree of mid-line ataxia.

Various investigations including genetic studies for the SCA mutations, anti-GAD antibodies, anti-tissue transglutaminase and various other blood tests have been normal or negative.

She does describe a recent increase in the upper limb sensory disturbance some of which does sound reminiscent of carpal tunnel syndrome and repeat Nerve Conduction Studies have been requested in relation to this although I am unclear as to direct relationship between this and the underlying aetiology of the ataxia.

I would be most grateful for your further definitive opinion.

lab results

Reasons for Request:
ataxia.

Sample II618419F (SERUM) Collected 15 Jul 2019 17:00 Received 15 Jul 2019 19:36

Imm Coeliac Screen

Endomysium Antibody:IgA

Negative

Negative IgA anti-endomysial antibodies make Coeliac Disease highly unlikely if individuals have been on a diet containing adequate gluten (e.g. 4 slices of bread daily) for 6 weeks prior to the test. If strong clinical suspicion of Coeliac Disease and in patients with IgA deficiency, suggest referral to gastroenterology for further assessment.

Imm Anti-Gliadin Abs

IgA-Gliadin Ab

*

128.0

U/mL

0.0 - 7

IgG Gliadin Ab

*

64.0

U/mL

0.0 - 7

IgA and IgG Gliadin Antibodies reference range (U/mL): 0 to 7.0
Negative; 7.1 to 10.0 = Equivocal; >10.0 Positive.

Imm IgA t-Transglutaminase Ab

IgA t-Transglutaminase Ab

1.7

U/mL

0.0 - 7.0

second commonest pitfall in patients with known CD who develop neurological dysfunction

I would be grateful if you could see Jonathan who has had coeliac disease since 1999. During this time he admits that the control of his disease has been quite poor although he is now back on track. His last tgg was 11.6 but the one before that was 103.

He presents with a range of neurological symptoms which I suspect maybe related to gluten ataxia. He experiences a general loss of balance with intermittent vertigo. He also had intermittent tingling in various areas. His main problem though is the vertigo and the balance issue. On examination there are no obvious neurological findings. He is a little unsteady but not obviously ataxic. I have arranged a series of bloods to rule out any other
looking cause and they all seem to be normal.

Sample II920713E (SERUM) Collected 26 Jun 2018 11:20 Received 26 Jun 2018 15:20

Imm Coeliac Screen

Endomysium Antibody:IgA

Negative

Negative IgA anti-endomysial antibodies make Coeliac Disease highly unlikely if individuals have been on a diet containing adequate gluten (e.g. 4 slices of bread daily) for 6 weeks prior to the test. If strong clinical suspicion of Coeliac Disease and in patients with IgA deficiency, suggest referral to gastroenterology for further assessment.

Imm Anti-Gliadin Abs

IgA-Gliadin Ab

*

8.6

U/mL

0 - 7

IgG Gliadin Ab

*

7.6

U/mL

0 - 7

IgA and IgG Gliadin Antibodies reference range (U/mL): 0 to 7.0
Negative; 7.1 to 10.0 = Equivocal; >10.0 Positive.

Imm IgA t-Transglutaminase Ab

IgA t-Transglutaminase Ab

1.4

U/mL

0 - 7.0



IgG Gliadin Ab - (across all investigations) [U/mL] ▼

Reference range: (0 - 7) Units: U/mL

Sample Collected Date	Sample ID	Value	Range
17 Dec 2021 12:50:00	II819994N	1.6	(0.0 - 7)
06 May 2021 12:45:00	II767908C	1.7	(0.0 - 7)
17 Sep 2020 14:45:00	II719167F	1.4	(0.0 - 7)
28 Jan 2020 13:00:00	II689410Z	2.1	(0.0 - 7)
16 Jul 2019 13:10:00	II618844W	5.0	(0.0 - 7)
15 Jan 2019 12:30:00	II549760V	*7.7	(0 - 7)
26 Jun 2018 11:20:00	II920713E	*7.6	(0 - 7)

dietary treatment of gluten ataxia

improvement of the ataxia within a year of
strict gluten-free diet even in those
patients without enteropathy (NCGS)
based on 43 patients

(Hadjivassiliou et al J Neurol Neurosurg
Psychiatry 2003;74(9):1221-1224)

the importance of early diagnosis
and treatment

22565
M 43Y
16:11
08-JAN-1998
IMAGE 82
STUDY 4

H

MAGNETOM IMPACT
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+ : F A L

ti1m7 180
°R 2000

TR 2000.0
TE 90.0/1
TA 04:21
AC 1

SP 0.0
SL 5.0
FoV 250°250
196 °256o
Sag

W 1346
C 679

28466
M 44Y
09:41
20-MAY-1999
IMAGE 55
STUDY 3

HR

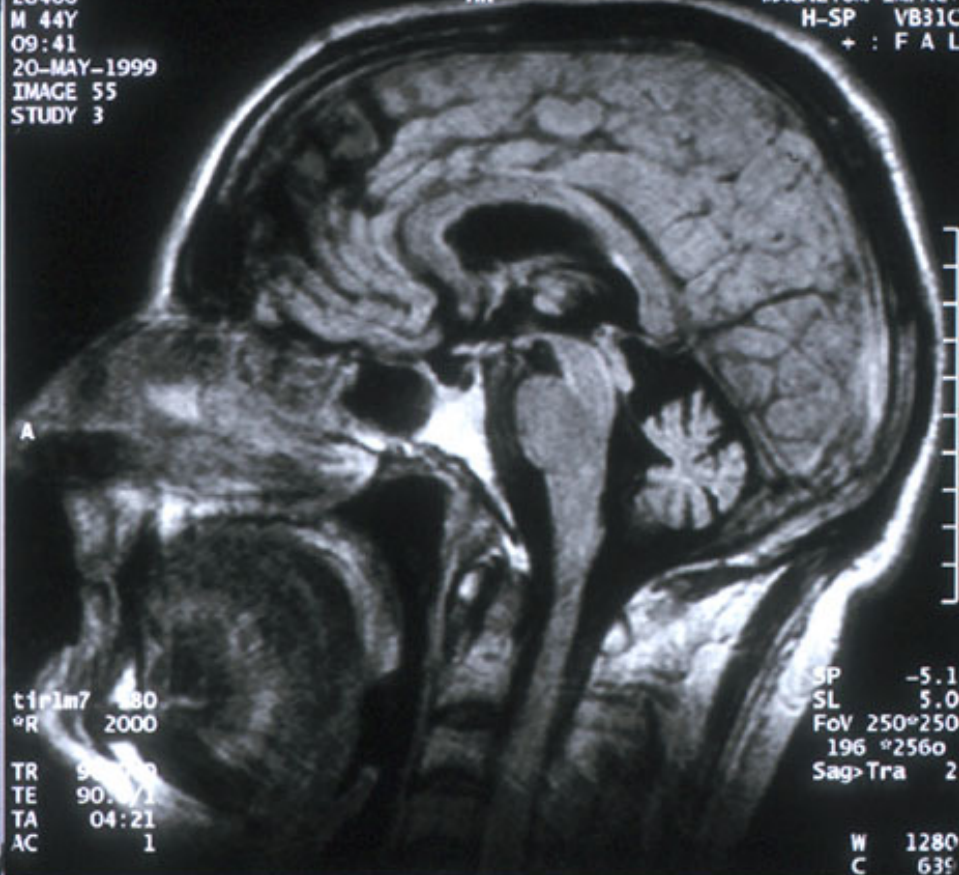
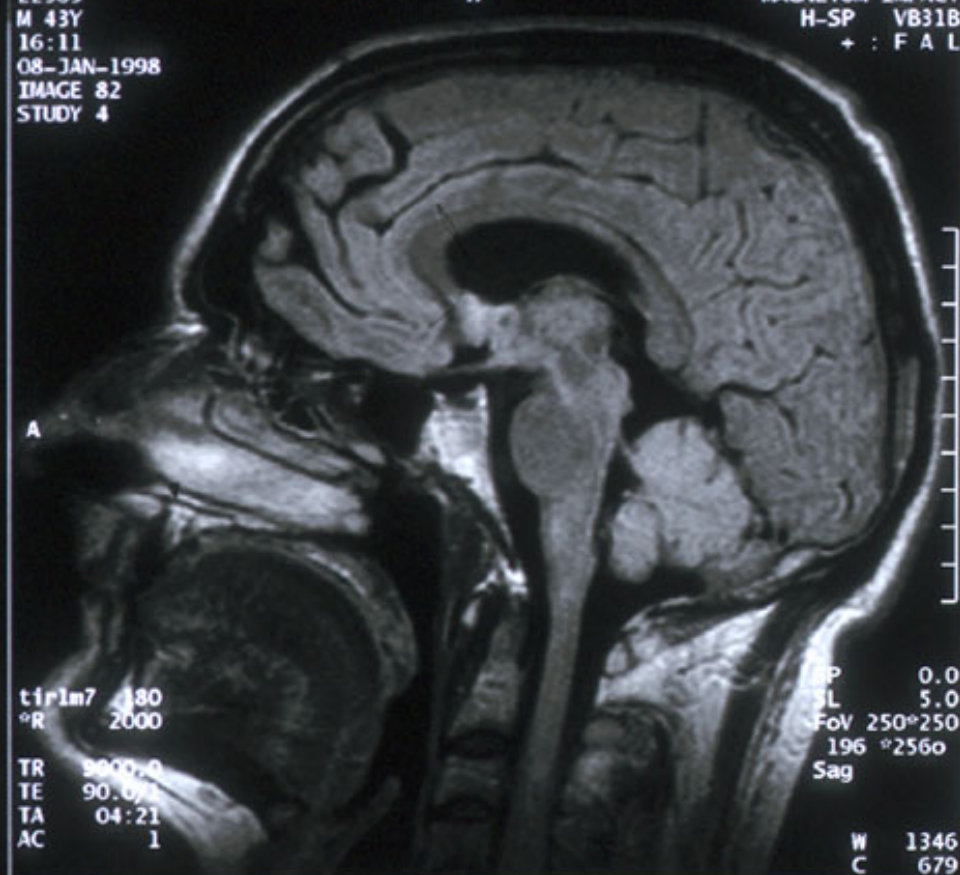
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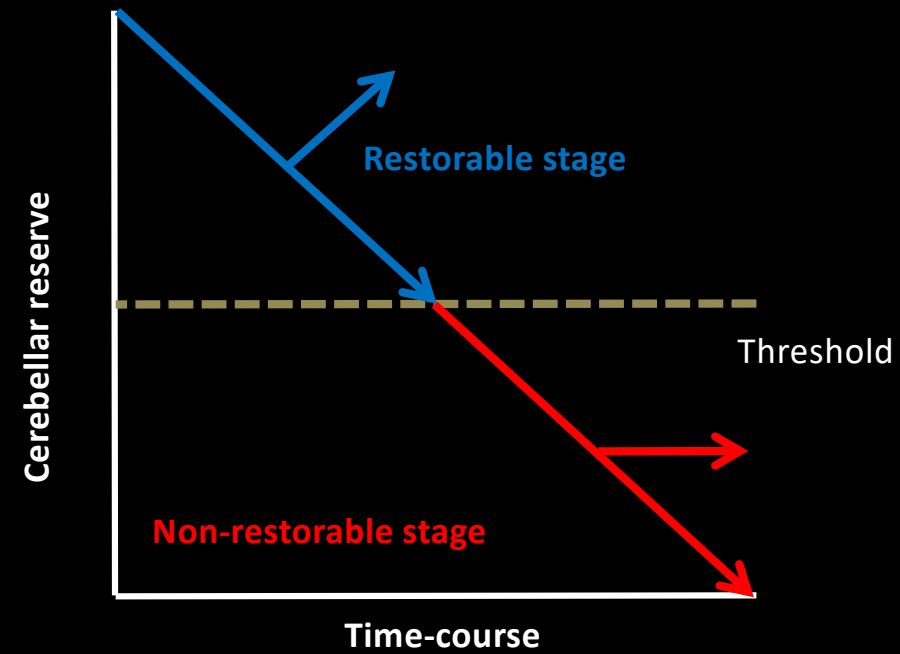
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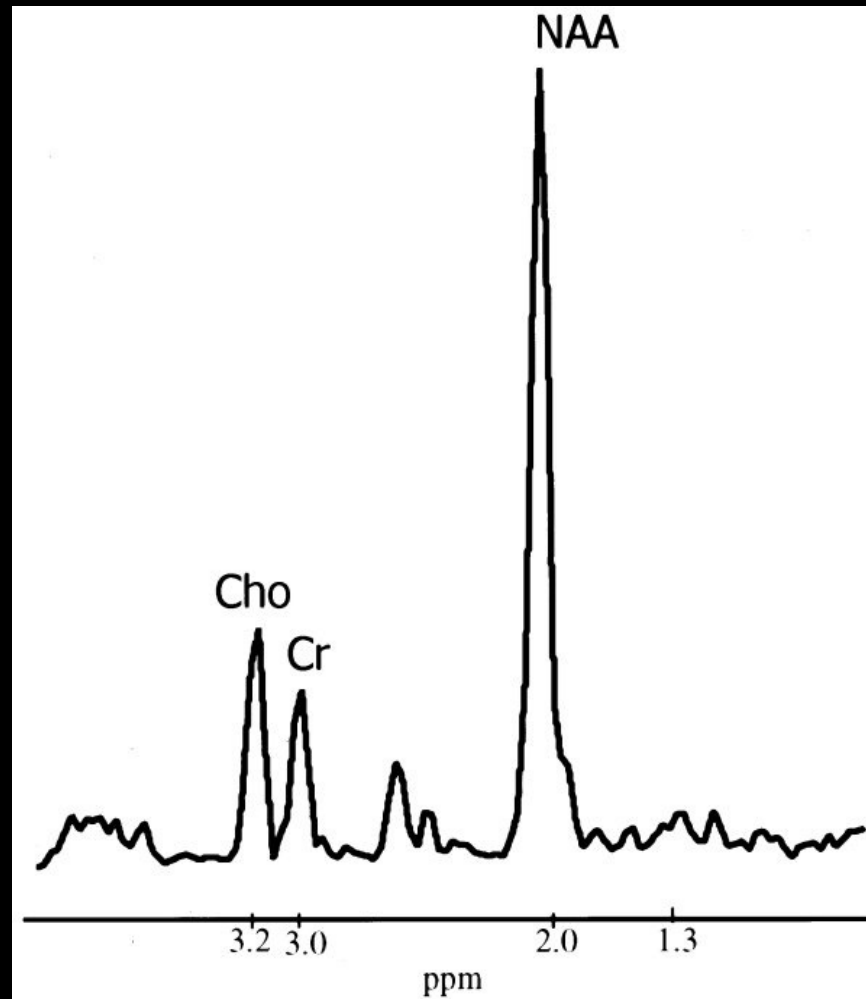
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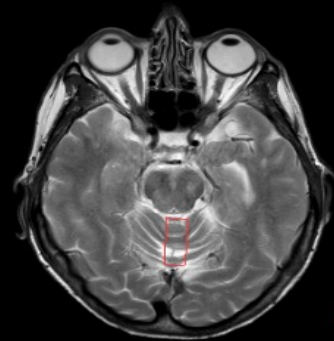


how do we monitor patients with
gluten ataxia

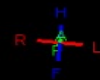
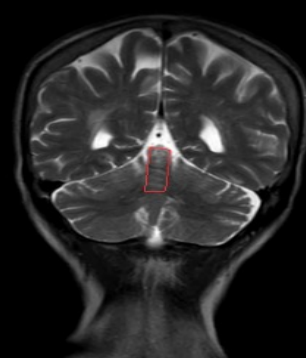
MR spectroscopy: a more dynamic assessment of cerebellar function



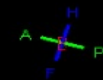
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TSE/M



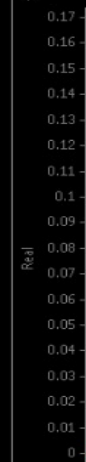
Sc 2, 1 / 9
TSE/M



Sc 4, 1 / 66
T1TSE/M

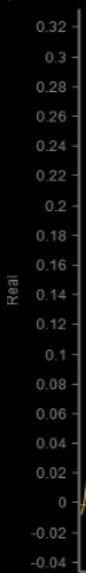


1,1



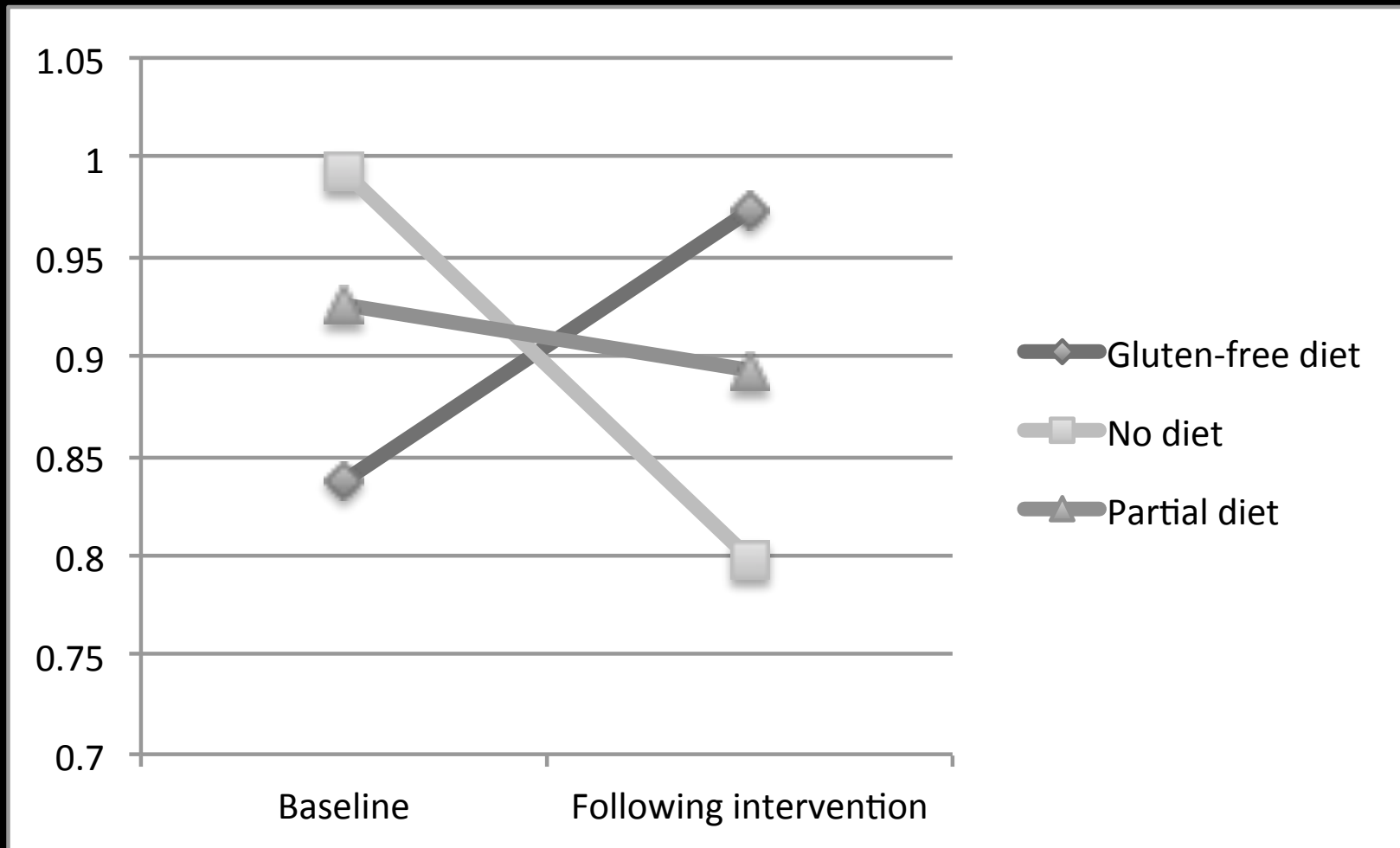
NAA/Cr 0.92
NAA/Cr(h) 0.84
Cho/Cr 0.76
Cho/Cr(h) 0.75
NAA/Cho 1.21
NAA/Cho(h) 1.12
Cho/NAA 0.83
Cho/NAA(h) 0.89

.1

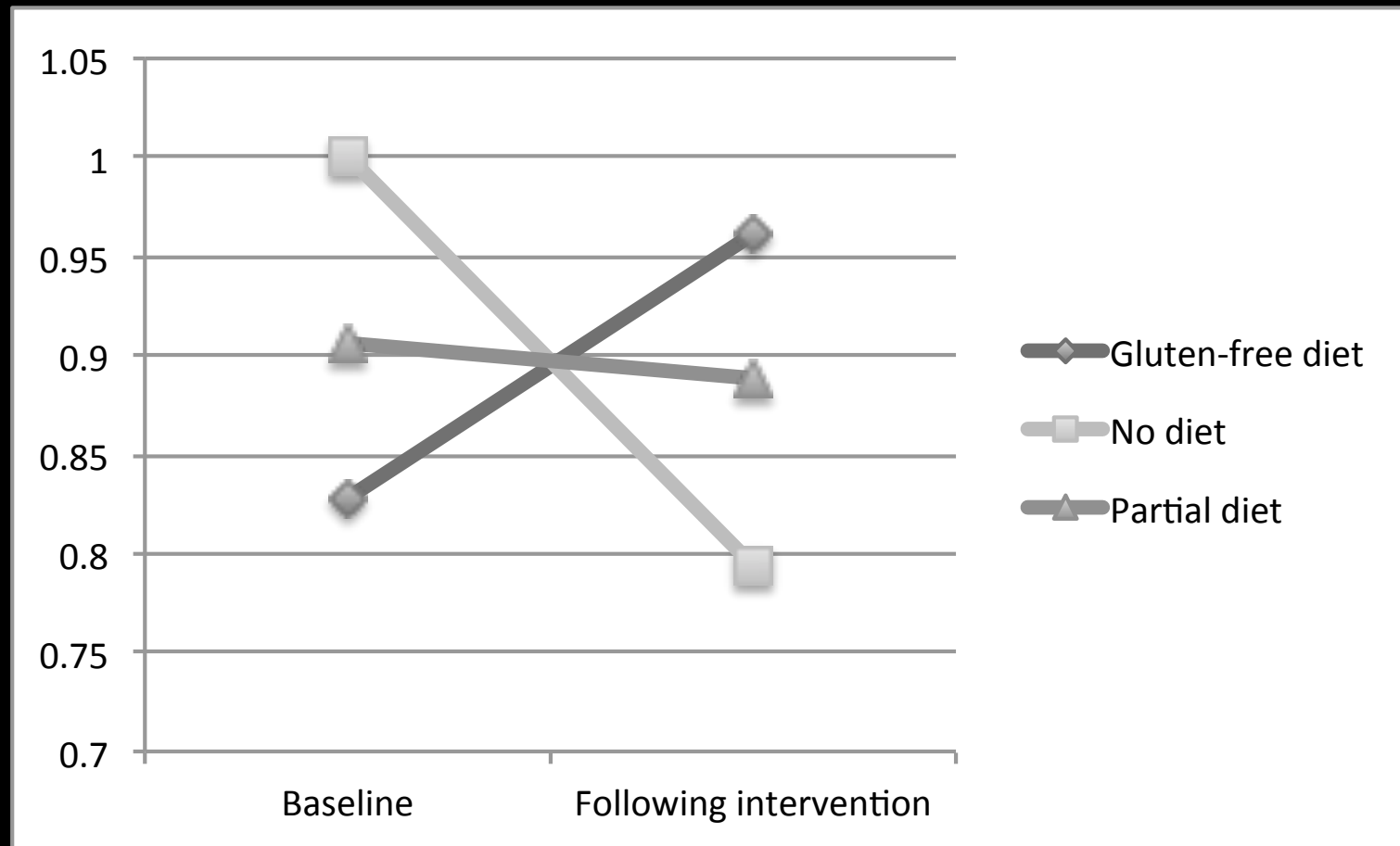


NAA/Cr 1.18
NAA/Cr(h) 1.13
Cho/Cr 0.69
Cho/Cr(h) 0.73
NAA/Cho 1.71
NAA/Cho(h) 1.55
Cho/NAA 0.58
Cho/NAA(h) 0.65

overall effect of GFD on MRS in patients with GA with enteropathy



overall effect of GFD on MRS in patients with GA without enteropathy



additional treatments

if despite a strict gluten free diet with elimination of antibodies there is evidence of progression, firstly review the diagnosis and if still GA consider immunosuppression (mycophenolate, rituximab)

others (Japan/Germany) have used IVIGs to good effect

rapidly progressive GA

Newrick et al. *Cerebellum & Ataxias* (2021) 8:16
<https://doi.org/10.1186/s40673-021-00139-z>

Cerebellum & Ataxias

CASE REPORT

Open Access

Recognition and management of rapid-onset gluten ataxias: case series



Laurence Newrick¹, Nigel Hoggard² and Marios Hadjivassiliou^{1*} 

Abstract

Background: Most immune-mediated cerebellar ataxias, including those associated with gluten sensitivity (Gluten Ataxia), tend to present subacutely and usually progress gradually. Acute presentations with rapid progression outside the context of paraneoplastic cerebellar degeneration require prompt diagnosis and early access to disease-modifying immunotherapy in order to avert severe and permanent neurological disability.

Case presentations: We describe three cases of rapid-onset Gluten Ataxia, an immune-mediated cerebellar ataxia due to gluten sensitivity. We detail their presentation, clinical and neuroimaging findings, and our treatment strategy with immunotherapy.

Conclusions: Our cases highlight the potential for immune-mediated cerebellar ataxias to present acutely, with rapid-onset symptoms and devastating neurological consequences. We caution against the diagnosis of 'post-infective cerebellitis' in adults, and advocate early consideration of an immune-mediated cerebellar ataxia and initiation of immunotherapy to prevent irreversible cerebellar damage.





myoclonic ataxia: the gluten
CNS hyperexcitability spectrum;
beware of refractory CD



gluten neuropathy

sensorimotor length dependent axonal (75%)

sensory ganglionopathy

small fibre neuropathy

clinical characteristics

mean age at symptom onset 56 years

mean age at diagnosis 60 years

78% could walk independently at last FU

gluten neuropathy: prevalence

accounts for 26% of all neuropathies

neuropathy was found in 21% of patients with coeliac disease on gluten-free diet

coeliac disease was associated with a 2.5-fold increased risk of neuropathy (Thawani et al, JAMA Neurol 2015)

effect of gluten-free diet

neurophysiological evidence of improvement of the neuropathy within a year of adherence to a strict gluten-free diet

irrespective of the presence of enteropathy

(Hadjivassiliou et al, Muscle and Nerve 2006;34:762-66)

gluten neuropathy and pain

pain is prevalent in gluten neuropathy (55%) and is associated with poorer mental health status

strict GFD with elimination of all antibodies was associated with significant reduction of the odds for neuropathic pain

(Zis et al, 2018 Journal of Neurology)

gluten encephalopathy

episodic often severe and intractable headaches

migraine like

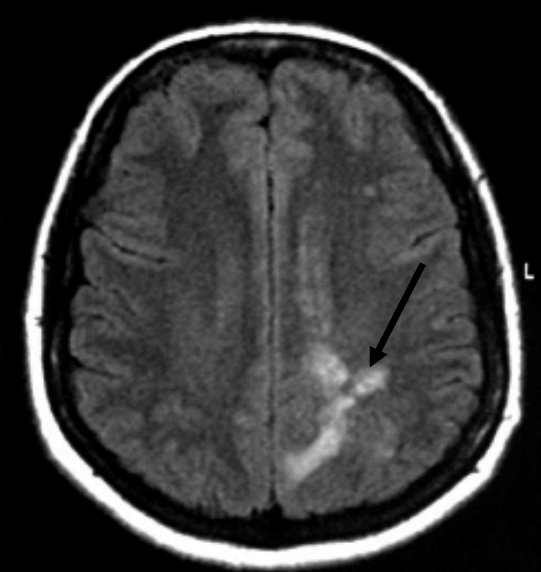
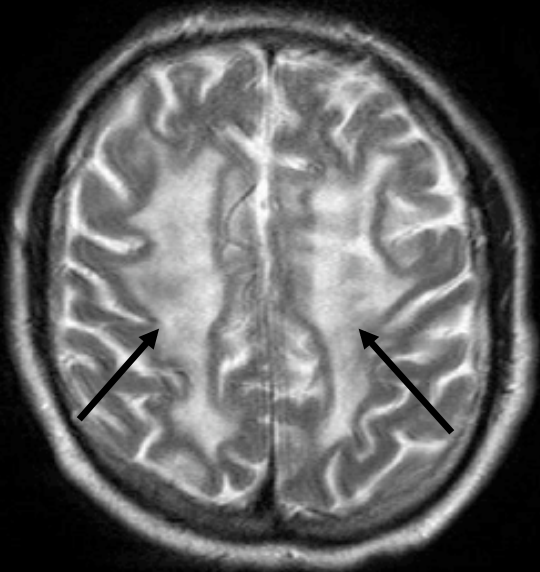
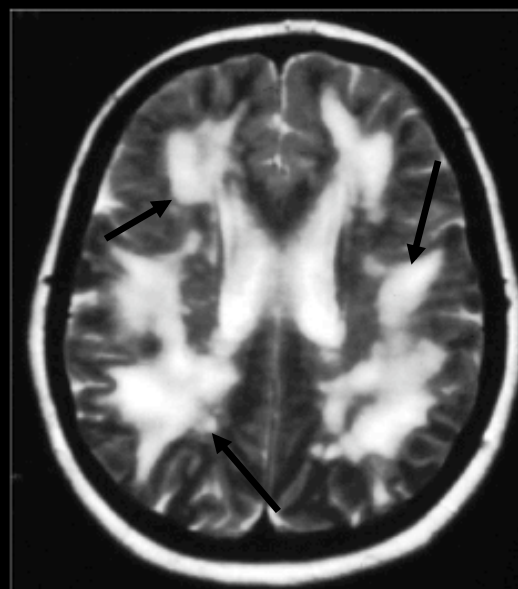
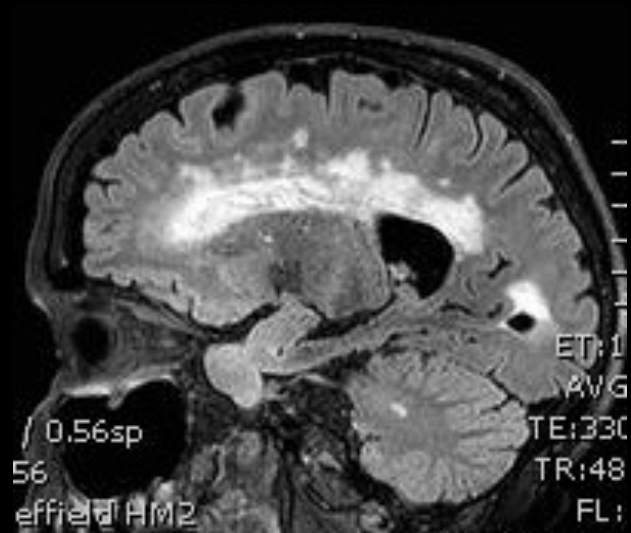
white matter abnormalities on MRI

headache improves on gluten-free diet

cognitive slowing (foggy brain)

slow speed of processing

can significantly interfere with work and everyday life



contribution to vascular dementia?

risk of dementia in patients with coeliac disease:
a population-based study

(Lebwohl et al. J Alzheimers DIS 2016;49:179-85)

“patients with CD are not at increased risk of dementia overall but subgroup analysis suggests that they may be at increased risk of vascular dementia”

cognition in CD

Gastroenterology 2020;158:2112–2122

Cognitive Deficit and White Matter Changes in Persons With Celiac Disease: A Population-Based Study



Iain D. Croall,^{1,4} David S. Sanders,² Marios Hadjivassiliou,³ and Nigel Hoggard^{1,4}

¹University of Sheffield, Academic Unit of Radiology, Royal Hallamshire Hospital, Sheffield, United Kingdom; ²Academic Unit of Gastroenterology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals National Health Service Foundation Trust, Sheffield, United Kingdom; ³Department of Neurology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals National Health Service Foundation Trust, Sheffield, United Kingdom; and ⁴University of Sheffield, Institute for in silico Medicine (INSIGNEO), Sheffield, United Kingdom

groups. **CONCLUSIONS:** In an analysis of data from the UK Biobank, we found participants with celiac disease to have cognitive deficit, indications of worsened mental health, and white matter changes, based on analyses of brain images. These findings support the concept that celiac disease is associated with neurologic and psychological features.

CD and headaches

risk of headache in patients with Celiac disease:
a population-based study

significant association between CD and
headache HR 1.66;95%CI 1.56-1.77;p<0.0001

also true for patients with normal mucosa but
positive serology

is neurological involvement in classic
CD presentation rare?

a 3 year prospective study

100 newly diagnosed CD patients
underwent neurological examination
followed by brain imaging

prospective CD study results

61% had neurological symptoms
(42% headache, 24% balance, 12% sensory)

on clinical examination

(29% had evidence of gait instability, 11% had
nystagmus and 5% sensory signs)

in total 67/100 patients had neurological
symptoms and/or signs

brain imaging in newly diagnosed patients with CD

46% had abnormal MR spectroscopy of the cerebellum

white matter lesions over and above what is expected for age was 19% (3% in healthy controls)

FU study 7 years later

prevalence of headaches dropped from 47% to 20%

patients with co-ordination problems at baseline reported improvement

some patients reported new onset of co-ordination difficulties, ALL of which had positive serology at FU

FU study imaging and the importance of monitoring

greater rate of cerebellar grey matter atrophy in the antibody positive vs antibody negative group
concluding that:

patients with classic CD who do not adhere to a strict GFD and are serological positive are at risk of developing ataxia

why such diverse manifestations?
pathophysiology

the transglutaminase story

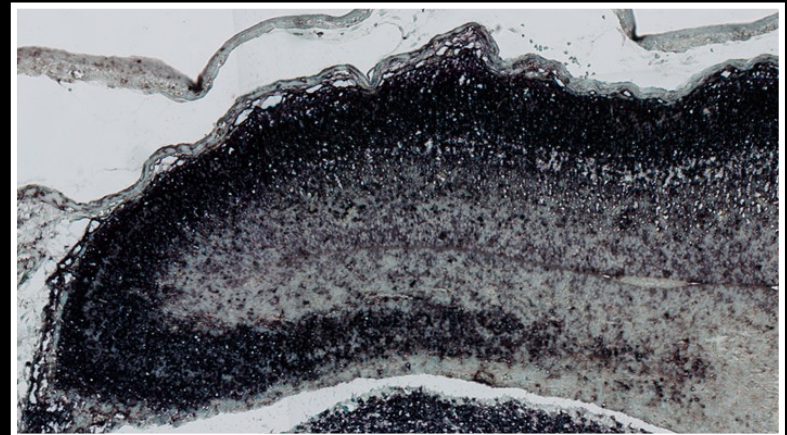
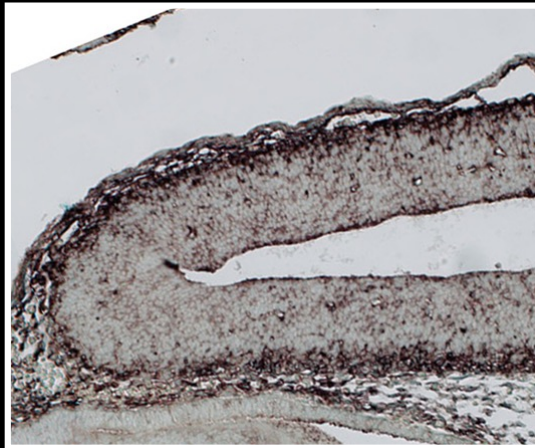
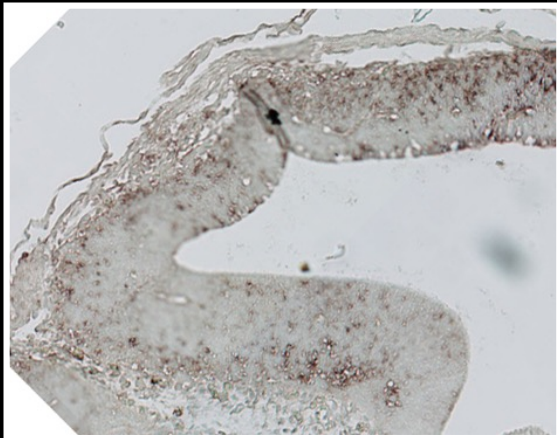
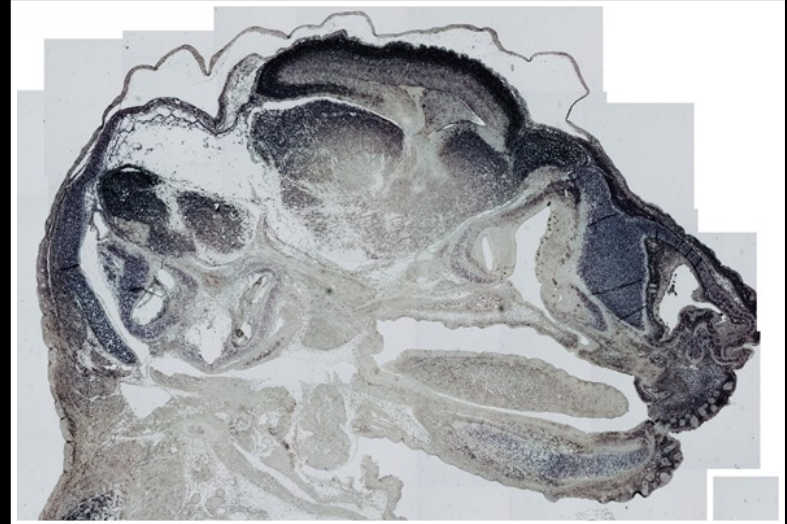
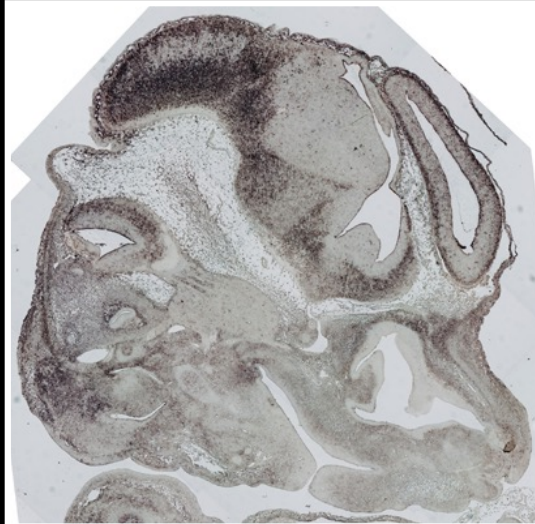
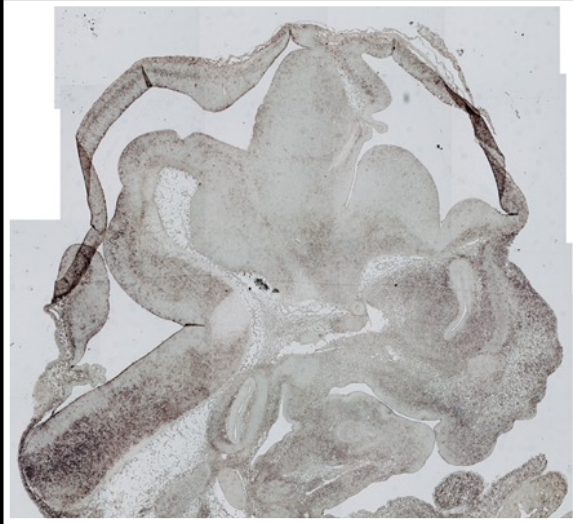
transglutaminases are enzymes found in humans and other species, involved in tissue repair
they break down gluten into immunogenic peptides
BUT

inadvertently initiate an immune response that causes self harm (autoimmunity) to those who are GS

TG2 (tissue transglutaminase) was found to be the autoantigen in CD (1997)

TG3 (epidermal transglutaminase) was found to be the autoantigen in dermatitis herpetiformis (2002)

**TG6, primarily expressed in brain
(presented at ICDS in Paris 2002 by Daniel Aeschlimann)**



Autoantibodies in Gluten Ataxia Recognize a Novel Neuronal Transglutaminase

Marios Hadjivassiliou, MD,¹ Pascale Aeschlimann, BSc,² Alexander Strigun, MSc,² David S. Sanders, MD,³
Nicola Woodroffe, PhD,⁴ and Daniel Aeschlimann, PhD²

Objective: Gluten sensitivity typically presents as celiac disease, a chronic, autoimmune-mediated, small-intestinal disorder. Neurological disorders occur with a frequency of up to 10% in these patients. However, neurological dysfunction can also be the sole presenting feature of gluten sensitivity. Development of autoimmunity directed toward different members of the transglutaminase gene family could offer an explanation for the diversity in manifestations of gluten sensitivity. We have identified a novel neuronal transglutaminase isozyme and investigated whether this enzyme is the target of the immune response in patients with neurological dysfunction.

Methods: Using recombinant human transglutaminases, we developed enzyme-linked immunosorbent assays and inhibition assays to analyze serum samples of patients with gluten-sensitive gastrointestinal and neurological disorders, and various control groups including unrelated inherited or immune conditions for the presence and specificity of autoantibodies.

Results: Whereas the development of anti-transglutaminase 2 IgA is linked with gastrointestinal disease, an anti-transglutaminase 6 IgG and IgA response is prevalent in gluten ataxia, independent of intestinal involvement. Such antibodies are absent in ataxia of defined genetic origin or in healthy individuals. Inhibition studies showed that in those patients with ataxia and enteropathy, separate antibody populations react with the two different transglutaminase isozymes. Furthermore, postmortem analysis of brain tissue showed cerebellar IgA deposits that contained transglutaminase 6.

Interpretation: Antibodies against transglutaminase 6 can serve as a marker in addition to human leukocyte antigen type and detection of anti-gliadin and anti-transglutaminase 2 antibodies to identify a subgroup of patients with gluten sensitivity who may be at risk for development of neurological disease.

the significance of TG6 antibodies

Clinical Gastroenterology and Hepatology 2019;17:2678–2686

Neurologic Deficits in Patients With Newly Diagnosed Celiac Disease Are Frequent and Linked With Autoimmunity to Transglutaminase 6



Marios Hadjivassiliou,^{*} Iain D. Croall,[§] Panagiotis Zis,^{*} Ptolemaios G. Sarrigiannis,^{*} David S. Sanders,[‡] Pascale Aeschlimann,^{||} Richard A. Grünewald,^{*} Paul A. Armitage,[§] Daniel Connolly,[§] Daniel Aeschlimann,^{||} and Nigel Hoggard[§]

^{*}Academic Department of Neurosciences, [‡]Department of Gastroenterology, [§]Department of Neuroradiology, Sheffield Teaching Hospitals National Health Service Trust, Sheffield, United Kingdom; ^{||}Matrix Biology and Tissue Repair Research Unit, College of Biomedical and Life Sciences, School of Dentistry, Cardiff University, Cardiff, United Kingdom

our experience with TG6 antibodies

CD (adult classical UK)	40%
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CD (adult classical Finland)	14%
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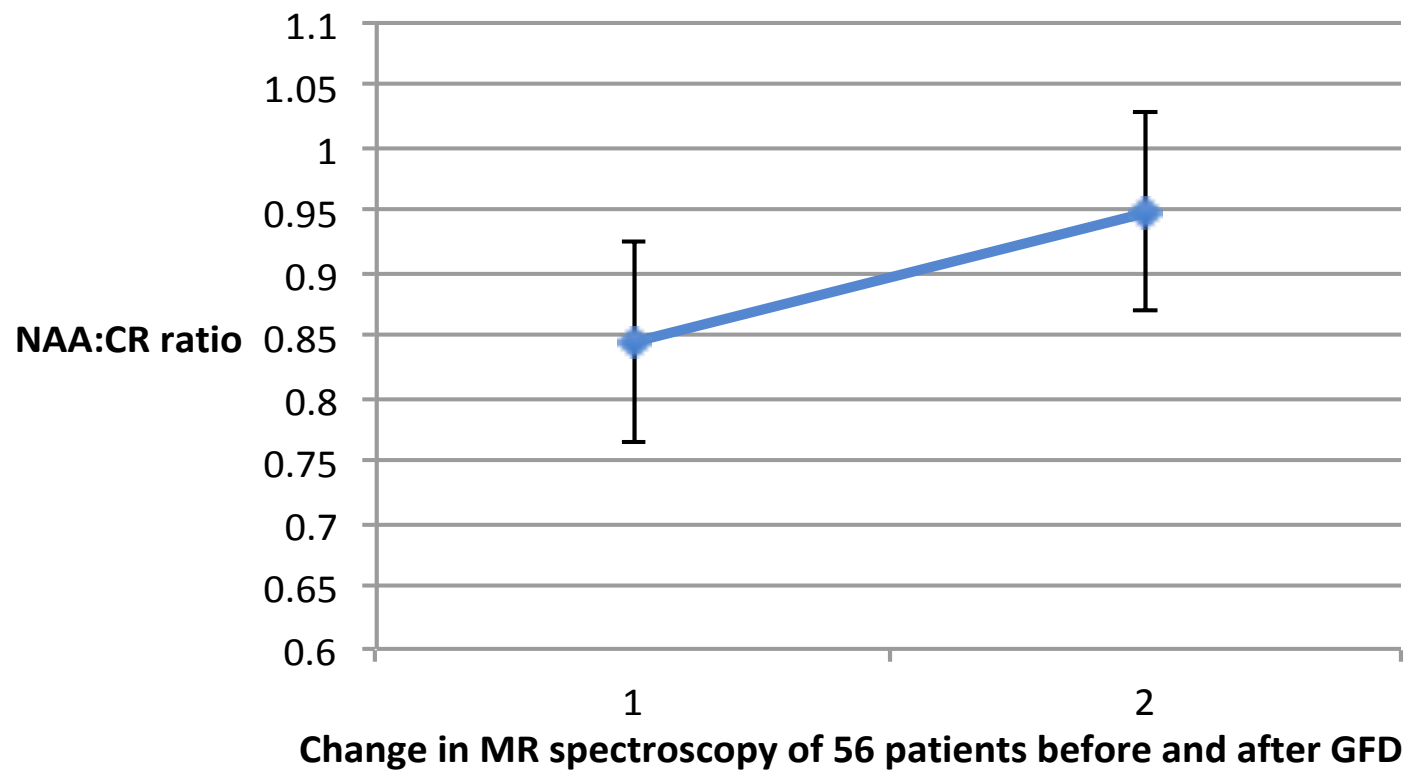
DH (Finland)	44%
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CD (paediatric classical, Italy)	25%
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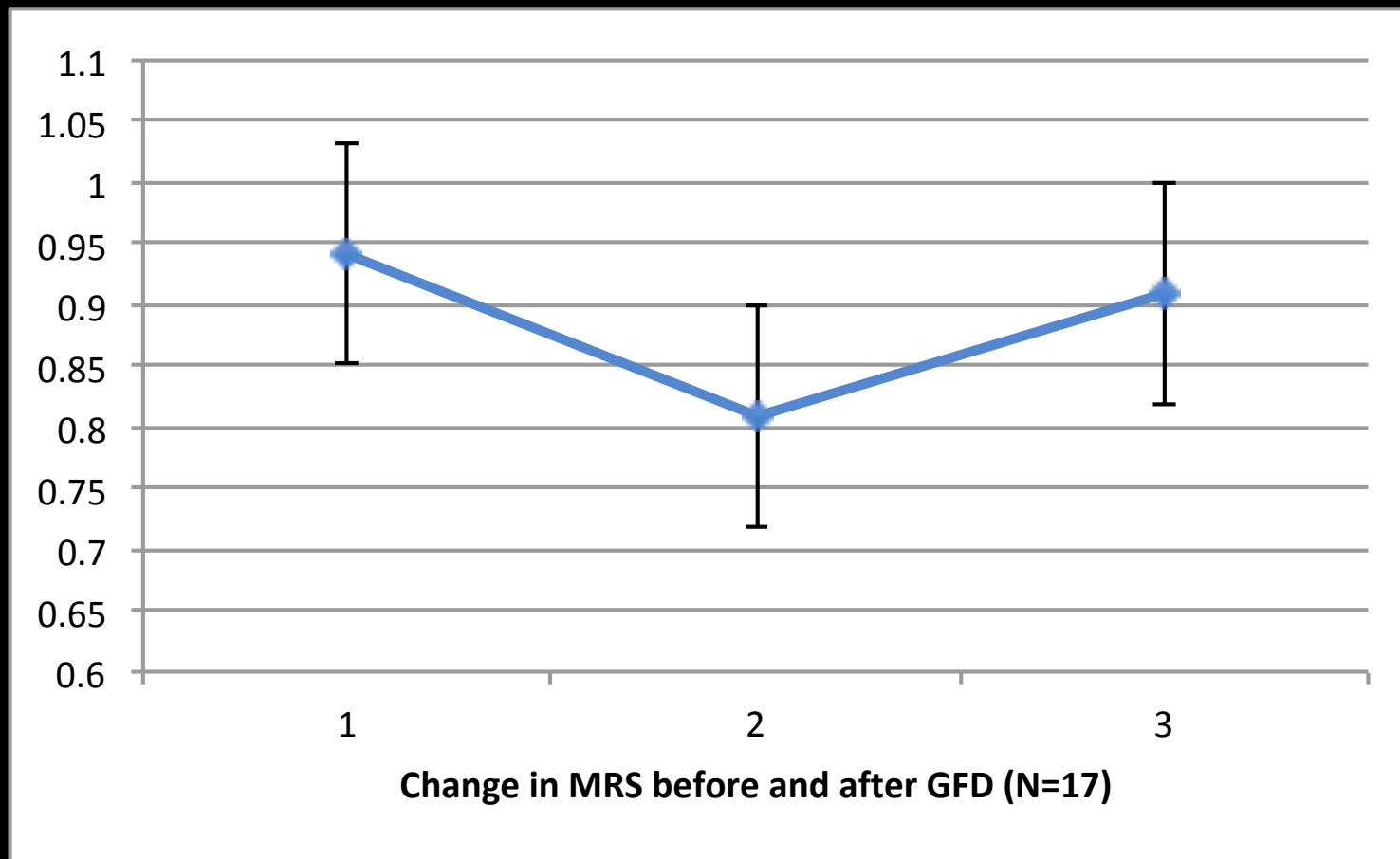
gluten ataxia (with/without CD)	96%
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many patients with idiopathic ataxia are only
positive for TG6

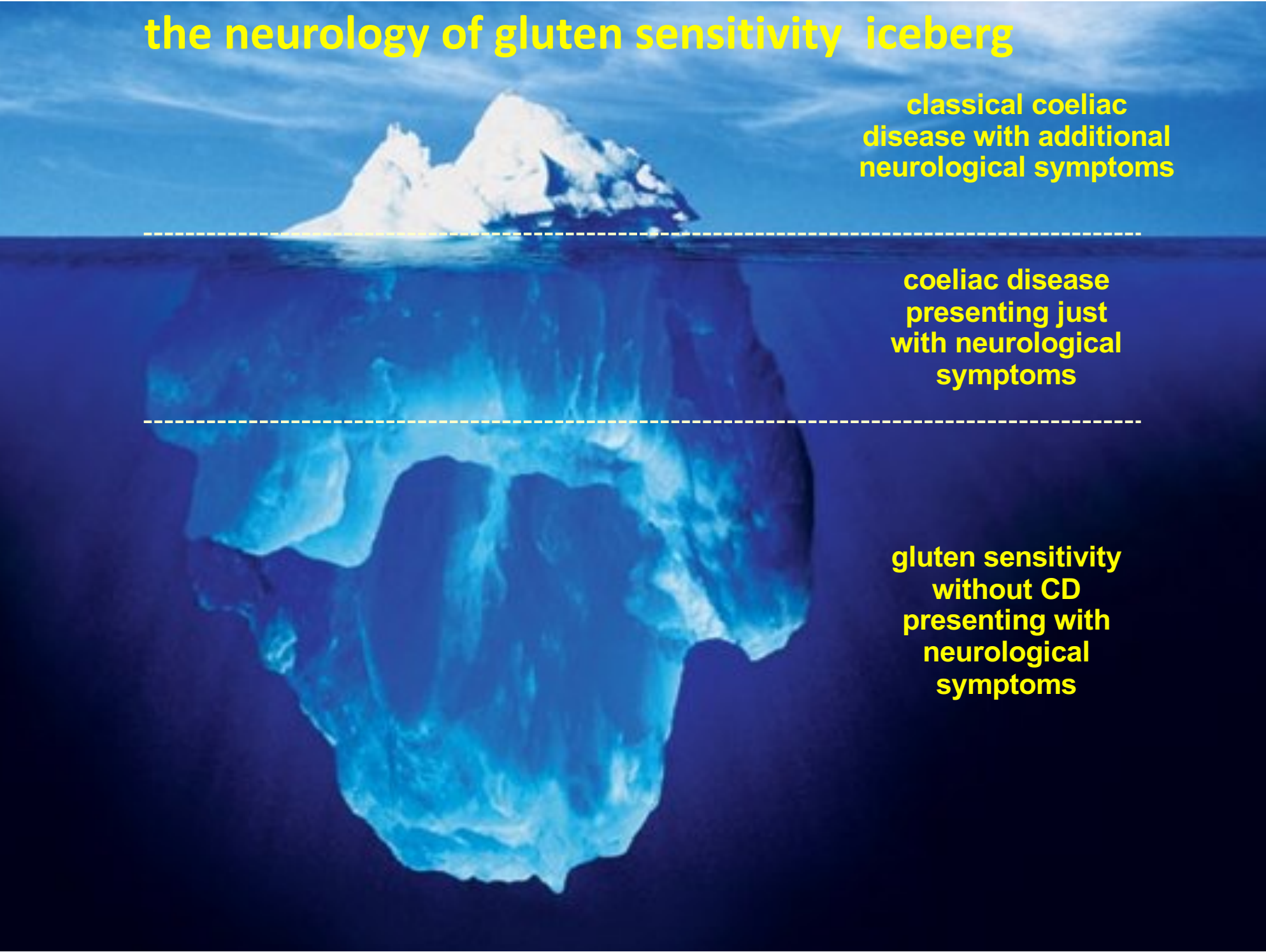
TG6 ataxia



TG6 ataxia



the neurology of gluten sensitivity iceberg

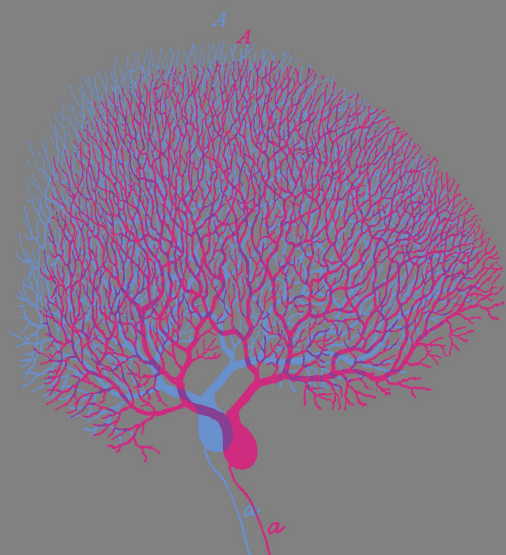


The image is a conceptual diagram using an iceberg to represent the prevalence of different gluten-related conditions. The iceberg is divided into three horizontal sections by two dashed white lines. The top section, which is the smallest and visible above the water, represents 'classical coeliac disease with additional neurological symptoms'. The middle section, submerged below the water, represents 'coeliac disease presenting just with neurological symptoms'. The bottom section, which is the largest and also submerged, represents 'gluten sensitivity without CD presenting with neurological symptoms'. The background of the entire image is a photograph of a blue sky and a dark blue ocean.

classical coeliac
disease with additional
neurological symptoms

coeliac disease
presenting just
with neurological
symptoms

gluten sensitivity
without CD
presenting with
neurological
symptoms



SHEFFIELD ATAXIA CENTRE



SHEFFIELD INSTITUTE
of GLUTEN RELATED DISORDERS