EMERGING ISSUES IN THE DIAGNOSIS OF COELIAC DISEASE IN PAEDIATRICS

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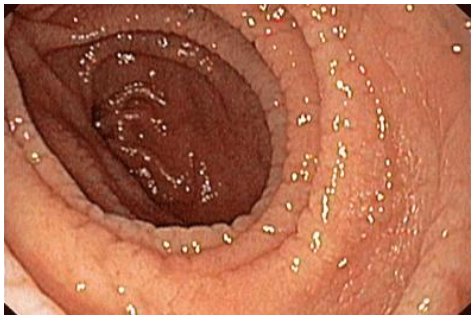
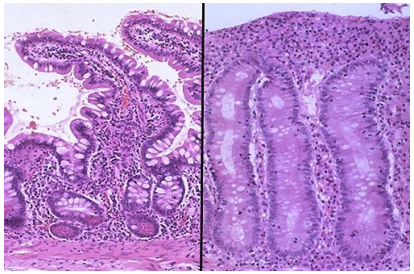
CUK Research Conference
March 2016

ESPGHAN pre-1990,1990 – 2012

- Three biopsy schedule…..
- Serology, biopsy and follow up
  - Anti-gliadin
  - Anti-EmA (1992, Chorzelski)
  - anti tTG (1997, Schuppan)
- Capsule succeeded by endoscopic biopsy
  - D2 and then D1 as standard in addition
- All was good with the world……





ESPGHAN / BSPGHAN 2012 - 13

Adult GI guidelines BSG Gut 2014

Gut Online First, published on June 10, 2014 as 10.1136/gutjnl-2013-306578

OPEN ACCESS

Diagnosis and management of adult coeliac disease: guidelines from the British Society of Gastroenterology

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ABSTRACT
A multidisciplinary panel of 18 physicians and 3 non-physicians from eight countries (Sweden, UK, Argentina, Australia, Italy, Finland, Norway and the USA) reviewed the literature on diagnosis and management of adult coeliac disease (CD). This paper presents the recommendations of the British Society of Gastroenterology. Areas of controversies were explored through phone meetings and web surveys. Nine working groups examined the following areas of CD diagnosis and management: classification of CD; genetics and immunology; diagnostics; serology and endoscopy; follow-up; gluten-free diet; refractory CD and malignancies; quality of life; novel treatments; patient support; and screening for CD.

Recommendations

- Diagnosis of CD requires duodenal biopsy when the patient is on a gluten-containing diet and for the vast majority of adult patients also positive serology. (Grade B)
- Biopsy remains essential for the diagnosis of adult CD and cannot be replaced by serology. Follow-up should aim at strict adherence to a gluten-free diet. (Grade B)

INTRODUCTION

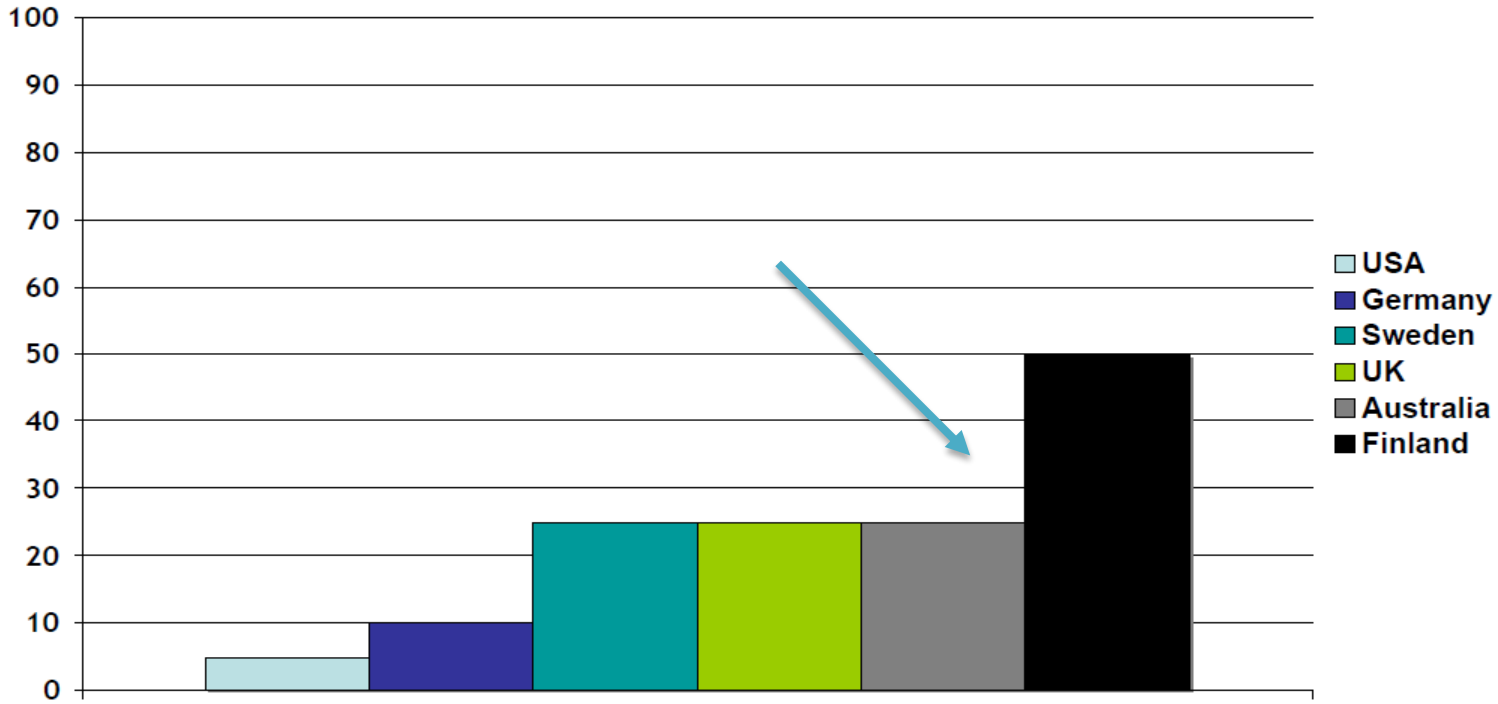
last 8 years). As a result, the Clinical Services and Standards Committee of the BSG commissioned these guidelines, subject to rigorous peer review and based on a comprehensive review of the recent literature, including data from any available randomised controlled trials, systematic reviews, meta-analyses, cohort studies, prospective and retrospective studies.

A multidisciplinary panel of 18 physicians from eight countries (Sweden, UK, Argentina, Australia, Italy, Finland, Norway and the USA), a dietitian and a representative and a patient advocate from Coeliac UK reviewed the literature on the management of CD. These individuals were involved in the original stakeholder meetings and with revision of the manuscript.

Intent and levels of evidence

All aspects of the contemporary diagnosis and management of patients with adult CD were considered. PubMed literature was searched from 1900 to 2012 to obtain evidence for these guidelines. Also there was input from all authors who have considerable expertise and experience in diagnosis and management of CD. The panel of international experts previously collaborated in the publication of definitions of CD[7] and were invited by the BSG through coauthor DSS. Our task force contained representatives from the clinical disciplines gastroenterology, paediatrics, histopathology, neurology,

Medical Awareness: % cases diagnosed



Alimentary Pharmacology & Therapeutics

Coeliac disease: a biopsy is not always necessary for diagnosis

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SUMMARY

Background
In view of the high diagnostic accuracy of immunoglobulin-A-tissue transglutaminase antibodies for detecting coeliac disease, we have explored whether a small bowel biopsy is always required to establish the diagnosis.

Aim
To define the transglutaminase antibody level giving a positive predictive value for coeliac disease of 100% and to subsequently assess the proportion of new diagnoses of coeliac disease having such a result.

Methods
The Celikey kit (Phadia GmbH, Frieburg, Germany) was used to measure transglutaminase antibody levels.

Results
All patients with transglutaminase antibody levels >30 U/mL, i.e. 10 × upper limit of normal in 2002/2003 had characteristic small bowel mucosal lesions. In a subsequent audit, 58% of 112 new diagnoses of coeliac disease in 2004/2005 had levels above this cut-off value.

Conclusions
We have shown that a transglutaminase antibody level can be defined which gives a positive predictive value of 100% for coeliac disease. From published data, these observations can be extended to most second-generation transglutaminase antibody kits. Our data provide further evidence that diagnostic guidelines could be modified so that small bowel biopsy is no longer regarded as mandatory in patients with such high transglutaminase antibody levels. This will avoid an invasive procedure and lead to a more rapid diagnosis and earlier treatment for over half of the new patients with coeliac disease.

ESPGHAN 2012

CLINICAL GUIDELINE

European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Guidelines for the Diagnosis of Coeliac Disease

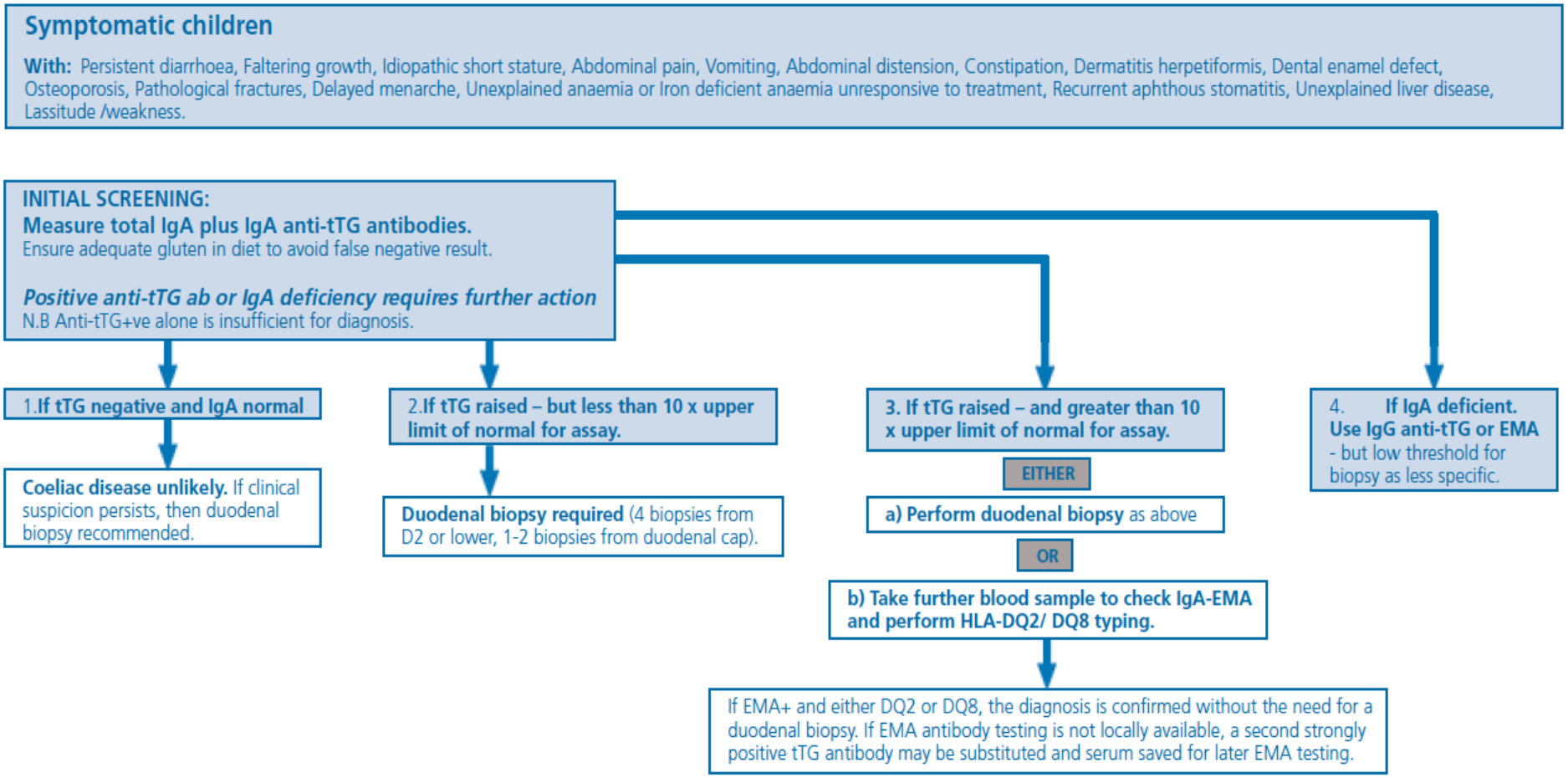
*S. Husby, †S. Koletzko, ‡I.R. Korponay-Szabó, §M.L. Mearin, ||A. Phillips, ¶R. Shamir, #R. Troncone, **K. Giersiepen, ††D. Branski, ‡‡C. Catassi, §§M. Lelgeman, ||||M. Mäki, ¶¶C. Ribes-Koninckx, ##A. Ventura, and ****K.P. Zimmer, for the ESPGHAN Working Group on Coeliac Disease Diagnosis, on behalf of the ESPGHAN Gastroenterology Committee

ABSTRACT

Objective: Diagnostic criteria for coeliac disease (CD) from the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) were published in 1990. Since then, the autoantigen in CD, tissue

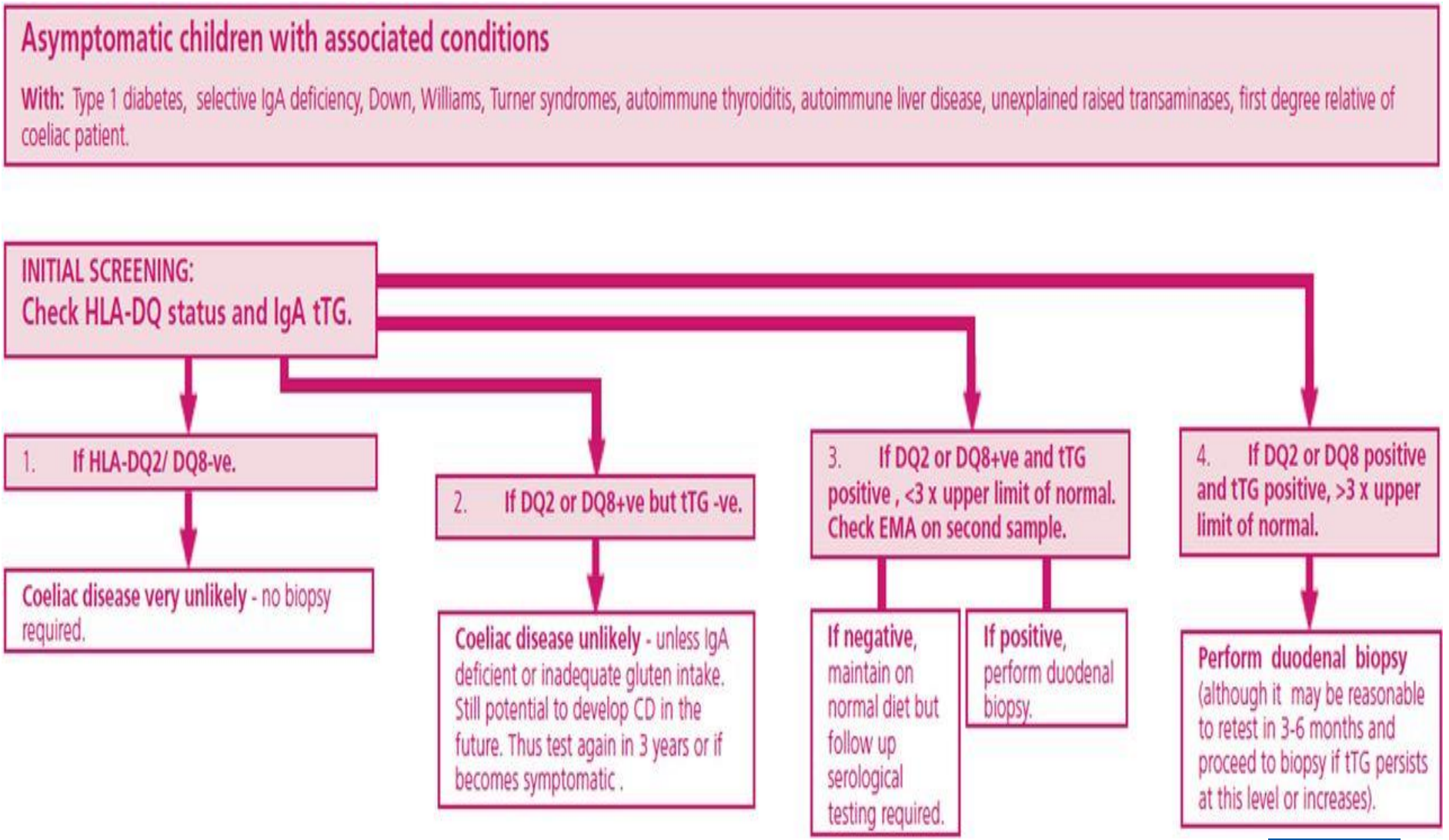
Results: In group 1, the diagnosis of CD is based on symptoms, positive serology, and histology that is consistent with CD. If immunoglobulin A anti-tissue transglutaminase type 2 antibody titers are high (>10 times the upper limit of normal), then the option is to diagnose CD without duodenal

BSPGHAN/Coeliac UK guidelines for the diagnosis and management of coeliac disease in children



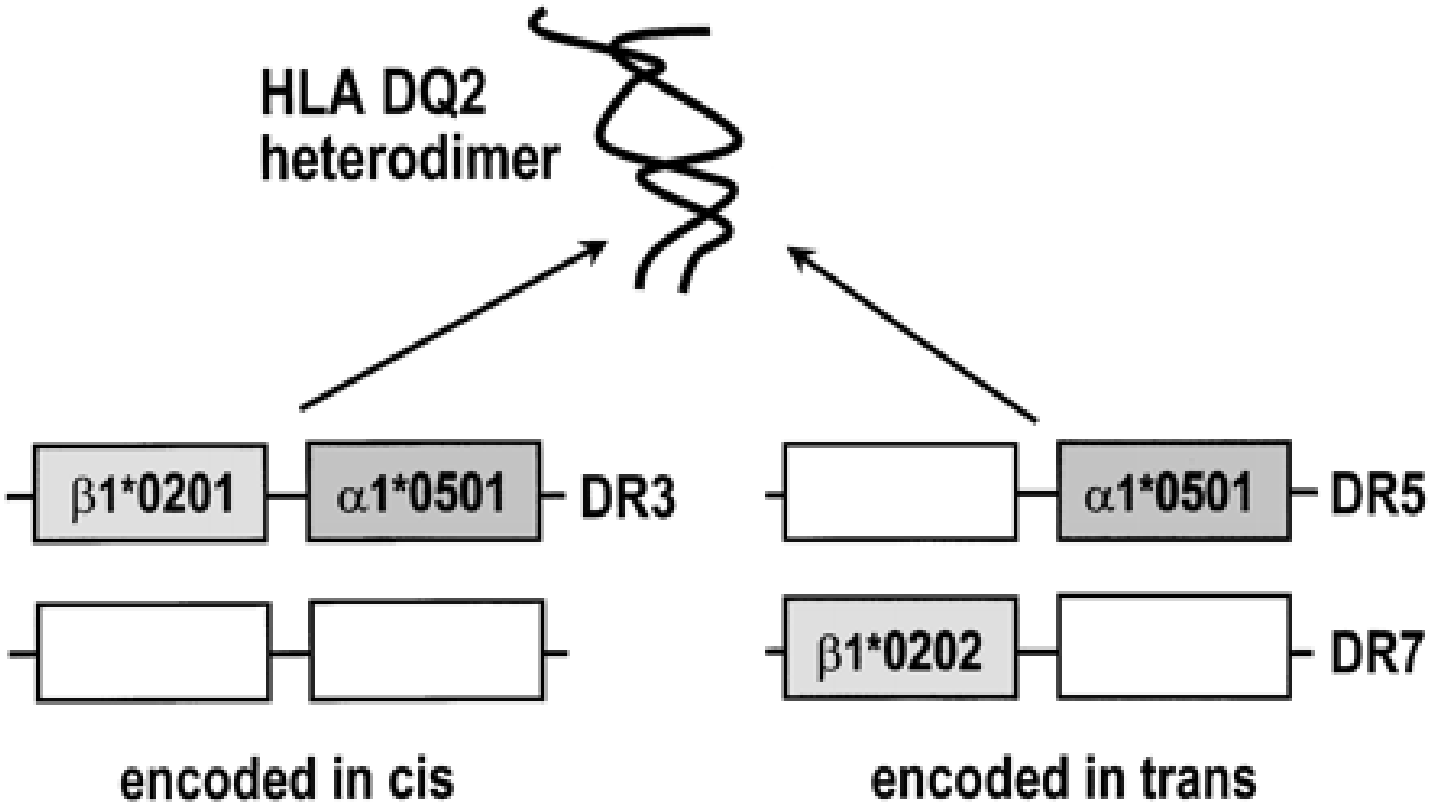
ADC

BSPGHAN/Coeliac UK guidelines for the diagnosis and management of coeliac disease in children



Murch S et al. Arch Dis Child 2013;98:806-811

ADC


HLA DQ2
heterodimer
β1*0201
α1*0501
DR3
α1*0501
DR5
β1*0202
DR7
encoded in cis
encoded in trans

DQ typing in practise

The HLA type of this patient is:

HLA-A*03, A*-; B*[illegible], B*14(65); DRB1*03(17), DRB1*07; DQB1*0201, DQB1*0202; DQA1*0201, DQA1*05.

ie. **POSITIVE** for DQ2 and **NEGATIVE** for DQ8.

05/06/10

Comments

Patient is Positive for DQB1*02:01/02 and/or DQB1*03:02 and DQA1*05:01/05. 90-95% of Coeliac Disease Patients are positive for DQB1*02:01 and DQA1*05:01 or DQB1*02:02 and DQA1*05:05. A Positive result must be used as part of the diagnosis of CD.

These alleles are present in approximately 20% of the healthy population therefore further risk factors for CD must be involved. A DQ2/DQ8 genotyping result has a low positive prediction value, but a very high negative prediction value for CD.

Signed: HFerguson

INTERNAL MEDICINE JOURNAL

Internal Medicine Journal **45** (2015)

POSITION PAPER

Appropriate clinical use of human leukocyte antigen typing for coeliac disease: an Australasian perspective

J. A. Tye-Din,[1,2,3,4] D. J. S. Cameron,[4,5,6] A. J. Daveson,[4,7] A. S. Day,[4,8] P. Dellsperger,[4,9] C. Hogan,[4,10] E. D. Newnham,[4,11,12] S. J. Shepherd,[4,13] R. H. Steele,[4,14] L. Wienholt[4,15] and M. D. Varney[16]

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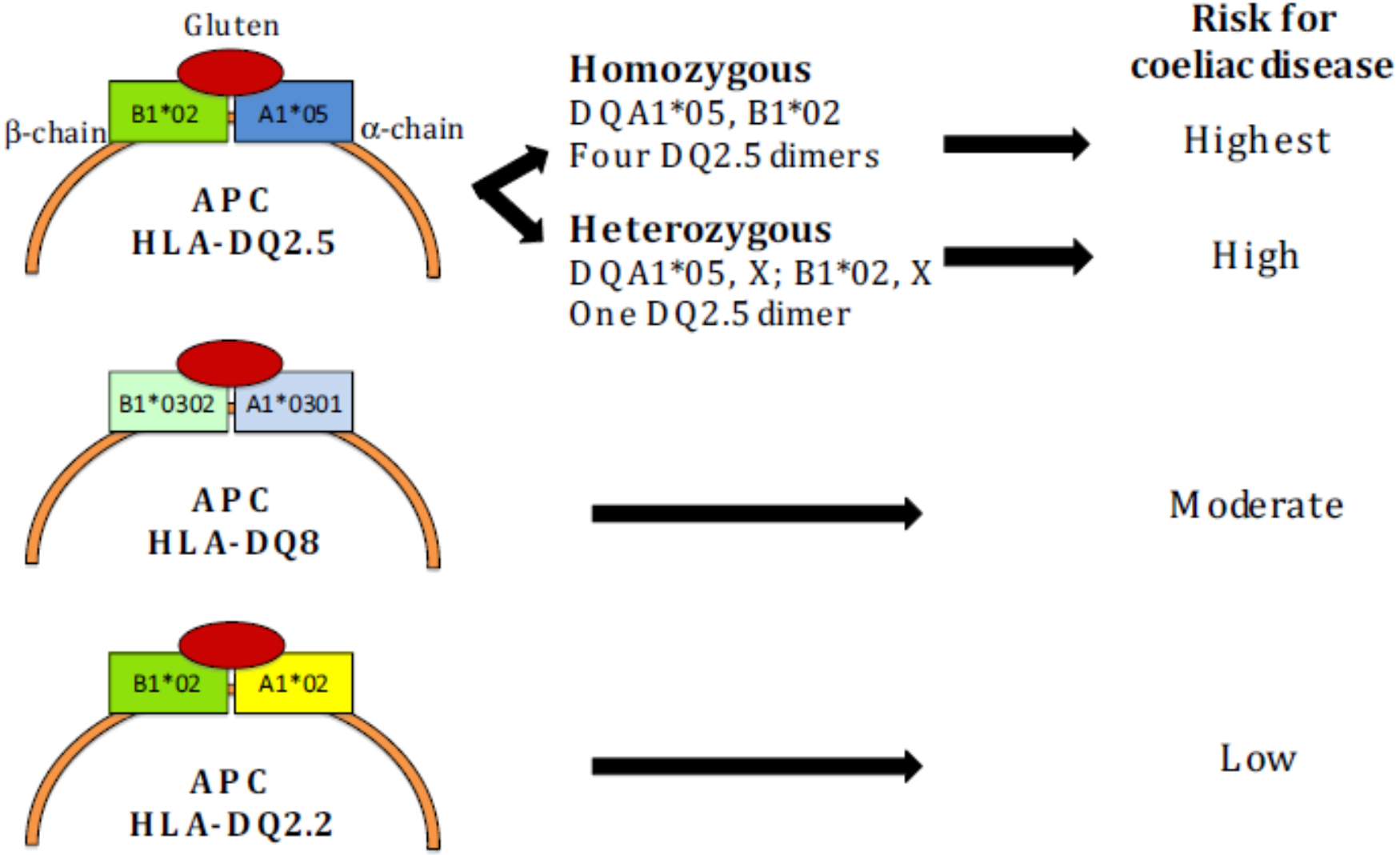
Gluten
β-chain
B1*02
A1*05
α-chain
APC
HLA-DQ2.5
Homozygous
DQA1*05, B1*02
Four DQ2.5 dimers
Heterozygous
DQA1*05, X; B1*02, X
One DQ2.5 dimer
Risk for coeliac disease
Highest
High
B1*0302
A1*0301
APC
HLA-DQ8
Moderate
B1*02
A1*02
APC
HLA-DQ2.2
Low

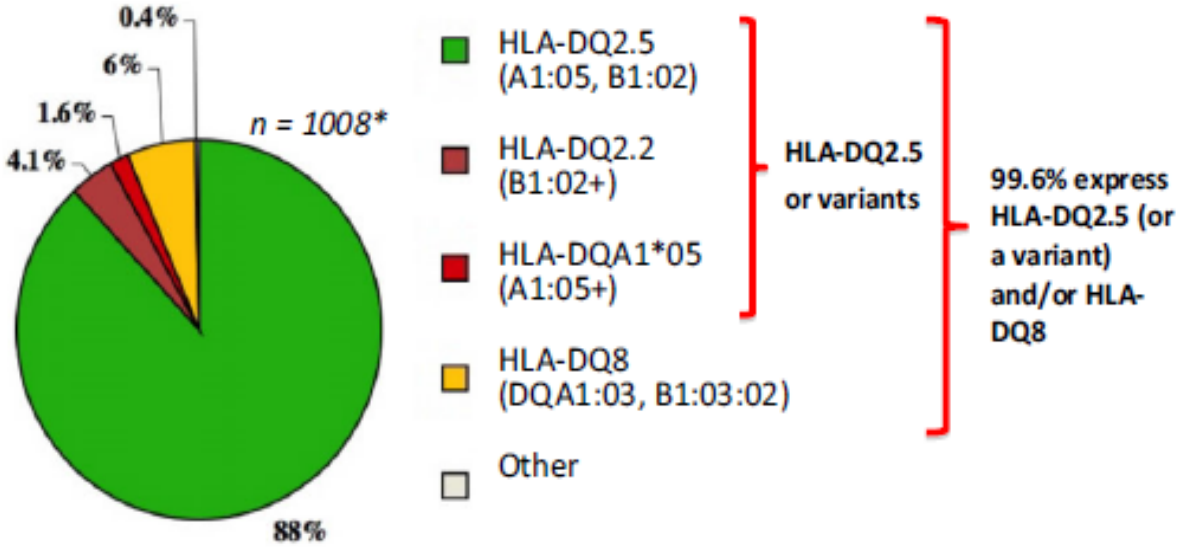

Figure 2 Human leukocyte antigen (HLA) genotypes associated with coeliac disease (CD). 99.6% of 1008 patients with coeliac disease from Finland, France, Italy, Norway, Sweden and the UK expressed HLA-DQ2.5, a variant of HLA-DQ2.5 and/or HLA-DQ8. Similar proportions have been confirmed in Australia.[11] This exceptionally strong HLA association imparts high negative predictive value for CD when these genotypes are absent. Notably, the high prevalence of these susceptibility genes in the general population (~30–50%) renders HLA typing unhelpful as a stand-alone diagnostic for CD due to poor positive predictive value for CD. Green: HLA-DQ2.5 (A1:05, B1:02); Brown: HLA-DQ2.2 (B1:02+); Red: HLA-DQA1*05 (A1:05+); Yellow: HLA-DQ8 (DQA1:03, B1:03:02). HLA-DQ2.5 and variants are represented by green, brown and red. *Karell *et al*.[22]

All on the rise !

Open

Incidence and Prevalence of Celiac Disease and Dermatitis Herpetiformis in the UK Over Two Decades: Population-Based Study

Joe West, PhD[1,2], Kate M. Fleming, PhD[1], Laila J. Tata, PhD[1], Timothy R. Card, PhD[1,2] and Colin J. Crooks, PhD[1]

OBJECTIVES: **Few studies have quantified the incidence and prevalence of celiac disease (CD) and dermatitis herpetiformis (DH) nationally and regionally by time and age groups. Understanding this epidemiology is crucial for hypothesizing about causes and quantifying the burden of disease.**

METHODS: **Patients with CD or DH were identified in the Clinical Practice Research Datalink between 1990 and 2011. Incidence rates and prevalence were calculated by age, sex, year, and region of residence. Incidence rate ratios (IRR) adjusted for age, sex, and region were calculated with Poisson regression.**

RESULTS: **A total of 9,089 incident cases of CD and 809 incident cases of DH were identified. Between 1990 and 2011, the incidence rate of CD increased from 5.2 per 100,000 (95% confidence interval (CI), 3.8–6.8) to 19.1 per 100,000 person-years (95% CI, 17.8–20.5; IRR, 3.6; 95% CI, 2.7–4.8). The incidence of DH decreased over the same time period from 1.8 per 100,000 to 0.8 per 100,000 person-years (average annual IRR, 0.96; 95% CI, 0.94–0.97). The absolute incidence of CD per 100,000 person-years ranged from 22.3 in Northern Ireland to 10 in London. There were large regional variations in prevalence for CD but not DH.**

CONCLUSIONS: **We found a fourfold increase in the incidence of CD in the United Kingdom over 22 years, with large regional variations in prevalence. This contrasted with a 4% annual decrease in the incidence of DH, with minimal regional variations in prevalence. These contrasts could reflect differences in diagnosis between CD (serological diagnosis and case finding) and DH (symptomatic presentation) or the possibility that diagnosing and treating CD prevents the development of DH.**

Incidence and presentation of reported coeliac disease in Cardiff and the Vale of Glamorgan: the next 10 years

Joanna J. Hurley[a], Bee Lee[b], Jeffrey K. Turner[b], Amanda Beale[c], Huw R. Jenkins[d] and Gillian L. Swift[b]

Original article

The epidemiology of coeliac disease in South Wales: a 28-year perspective

Lisa A Whyte, Huw R Jenkins

The Rising Incidence of Celiac Disease in Scotland

BSc,[a] Victoria M. Merrick, MBChB,
rman, RD, PhD,[a] Richard K. Russell,
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on, MBChB, MRPCH, PhD,[b] David C.
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Glasgow, United Kingdom; [d]Department of Paediatric Gastroenterology, Bristol Royal Children's Hospital, Bristol, United Kingdom; and [e]Department of Child Life and Health, University of Edinburgh, Edinburgh, United Kingdom

WHAT'S KNOWN ON THIS SUBJECT: The overall incidence of pediatric celiac disease (CD) is rising, as are other autoimmune conditions. Additionally, increasing numbers of children are older at the point of diagnosis and are diagnosed with CD through active screening.

WHAT THIS STUDY ADDS: Accounting for screened and nonclassic cases, there is an independent 2.5-fold rise in the incidence of classically presenting cases of pediatric CD (Oslo definitions). Thus, indicating a true rise in pediatric CD incidence in southeast Scotland in 20 years.

Original article

Childhood coeliac disease diagnoses in Scotland 2009–2010: the SPSU project

Lois E White,[1] Elaine Bannerman,[1] Paraic McGrogan,[2] Dagmar Kastner-Cole,[3] Elsie Carnegie,[4] Peter M Gillett[5]

THE RISING INCIDENCE OF CLASSICAL AND NON-CLASSICAL COELIAC DISEASE IN SOUTHEAST SCOTLAND

Lister MF [1], McKerrow L[2], Menzies E[2], Tybulewicz A[3], Rosie L [1], Gillett PM [1]

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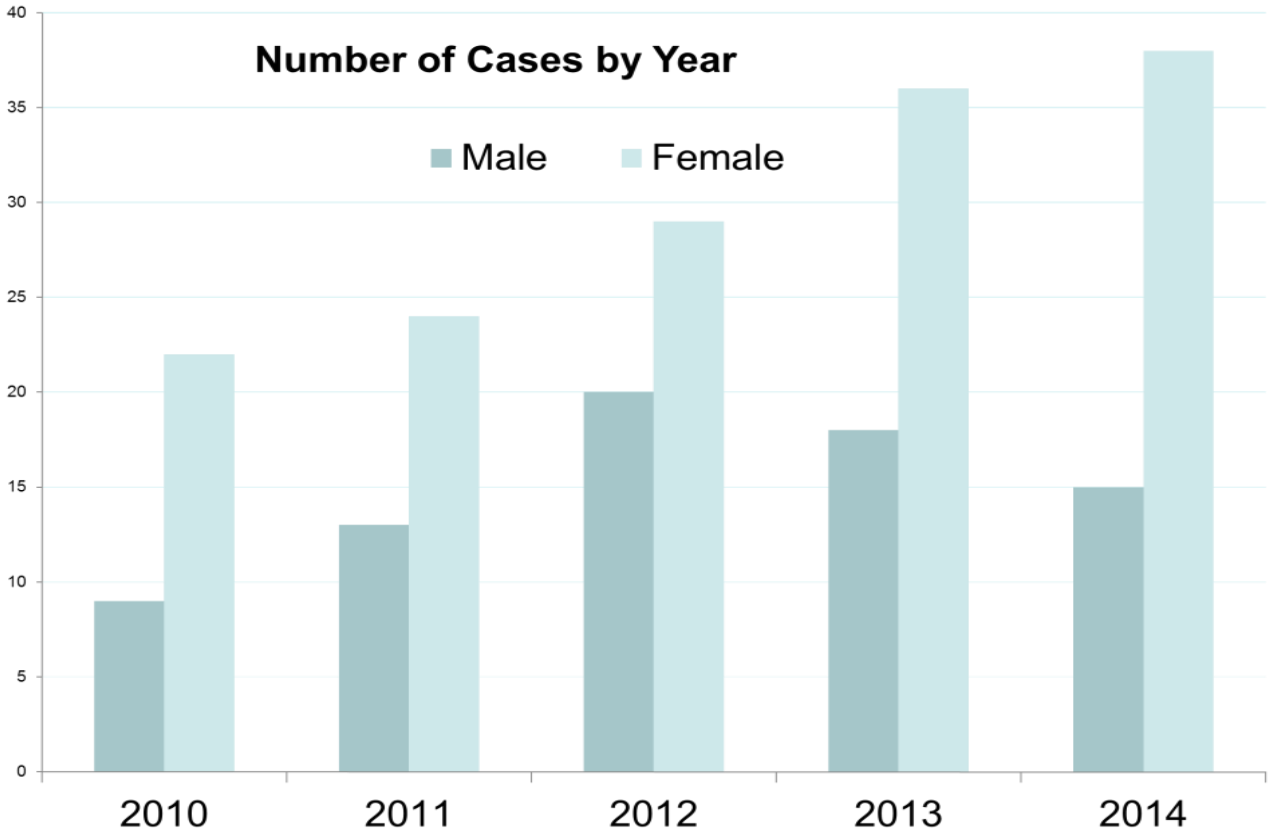

Results

224 patients (149 female, 75 male) were diagnosed with CD in Southeast Scotland over the study period. Median age at diagnosis was 7 years 6 months (range: 1 year 65 days to 16 years). In 2010 there were 31, 2011: 37, 2012: 49, 2013: 54 and in 2015: 53 patients identified.

Incidence increased from 2010 to 2014 (13.6 to 23.2/100 000). Classical cases[3] rose from 6.6/100 000 in 2010 to 14/100 000 in 2014. Non-classical cases showed a similar rise from 3.9 to 8.3/100 000 between 2010 and 2014.

In addition, 16 asymptomatic cases were identified by screening individuals with associated conditions, and in 6 cases the presentation was unknown.

Serology testing from Lothian and Fife is sent to a central laboratory (accounting for 72% of the region's population). There has been an increase in the number of anti-TTG requests from 2274 in 2010 to 3489 in 2014. The percentage of positive tests rose.

Conclusions

- Over a 5 year period, the incidence has nearly doubled to over 23 per 100 000 in Southeast Scotland.
- The incidence of both classical and non-classical presentations has risen.
- The proportion of positive results is increasing confirming a true rise in the incidence of CD.
- Better awareness and active case finding is clearly improving and one of the main reasons for the increase.
- Comparison again with other regions in Scotland (and UK-wide) would be vital information for clinicians and Coeliac UK to help target awareness campaigns and improve diagnosis.

Genetic testing for coeliac susceptibility genes in children with Type 1 Diabetes Mellitus

DQ TYPING IN 'AT RISK' GROUPS IN PRACTICE

DIABETICMedicine

DOI: 10.1111/dme.12658

Short Report: Genetics

Clinical relevance and cost-effectiveness of HLA genotyping in children with Type 1 diabetes mellitus in screening for coeliac disease in the Netherlands

J. Elias[1,2], J. J. G. Hoorweg-Nijman[1] and W. A. Balemans[1]

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Accepted 1 December 2014

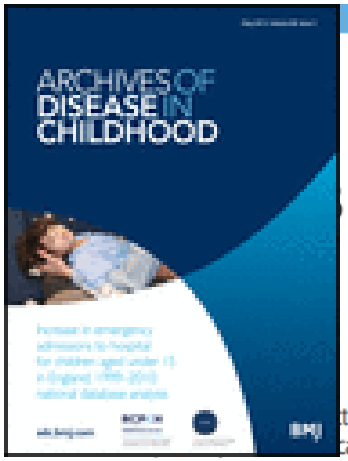
Abstract

Aims To investigate the clinical relevance and cost-effectiveness of human leukocyte antigen (HLA)-genotyping in the Netherlands as a screening tool for the development of coeliac disease in children with Type 1 diabetes mellitus.

Methods A retrospective analysis was performed in 110 children with Type 1 diabetes mellitus diagnosed between January 1996 and January 2013. All children were screened for coeliac disease using coeliac disease-specific antibodies and HLA genotyping was performed in all children.

Results One hundred and ten children were screened for coeliac disease, and coeliac disease could be confirmed in seven. Eighty-six per cent of the children with Type 1 diabetes mellitus had one of the variants of HLA–DQ2.5 and DQ8. HLA genotypes observed in children with Type 1 diabetes mellitus children and coeliac disease were heterozygote DQ2.5, homozygote DQ2.5 and heterozygote DQ2.5/DQ8. HLA genotyping in coeliac disease screening in children with Type 1 diabetes mellitus is more expensive than screening for coeliac disease with antibodies alone (€326 vs. €182 per child).

Conclusions The risk of coeliac disease development in children with Type 1 diabetes mellitus is increased when they are heterozygote DQ2.5/DQ8, homozygote or heterozygote DQ2.5. The implementation of HLA genotyping as a first-line screening tool has to be reconsidered because it is not distinctive or cost-effective.



Coeliac screening in a Scottish cohort of children with type 1 diabetes mellitus: is DQ typing the way forward?

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ABSTRACT

Background Children with type 1 diabetes mellitus (T1DM) are at increased risk of coeliac disease (CD). Recent guidelines indicate coeliac screening should include HLA typing for CD predisposing (DQ2/DQ8) alleles and those negative for these alleles require no further coeliac screening.

Methods Children (n=176) with T1DM attending clinics across two Scottish regions were screened for HLA DQ2/DQ8 as part of routine screening. Data collected included the frequency of DQ2/DQ8 genotypes and the additional cost of HLA screening.

Results Overall, DQ2/DQ8 alleles were identified in 94% of patients. The additional cost of HLA typing was £3699.52 (£21.02 per patient). All patients with known CD (11/176) were positive for DQ2/DQ8 and all were diagnosed with CD within 5 years of T1DM diagnosis.

Conclusions The vast majority of children with T1DM have CD-predisposing HLA genotypes limiting the number of patients that can be excluded from further screening. We conclude that HLA genotyping is not currently indicated for CD screening in this population.

What is already known on this topic

- Coeliac disease is relatively common in children with type 1 diabetes compared with the general population.
- HLA genotyping may be useful in determining the risk of developing coeliac disease.
- Screening for coeliac disease, including HLA genotyping, is recommended for children with type 1 diabetes.

What this study adds

- We demonstrate that coeliac predisposing genotypes are present in the vast majority of patients with type 1 diabetes in a UK cohort.
- Screening for HLA genotypes is not currently cost-effective for coeliac screening in patients with type 1 diabetes.
- Clarification of coeliac disease risk for specific HLA genotypes is urgently required for implementing a screening strategy in patients with type 1 diabetes.

INTRODUCTION

Children with type 1 diabetes mellitus (T1DM) are at increased risk of coeliac disease (CD) compared with

COELIAC SCREENING IN TYPE 1 DIABETES – IS HLA GENOTYPING THE WAY FORWARD?

Rod Mitchell*[1], Amaila Mayo[2], Angela Sun[3], Maureen Forgan[4], Alan Comrie[4], Peter Gillett[1]

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[3]Dr Grays Hospital, Elgin
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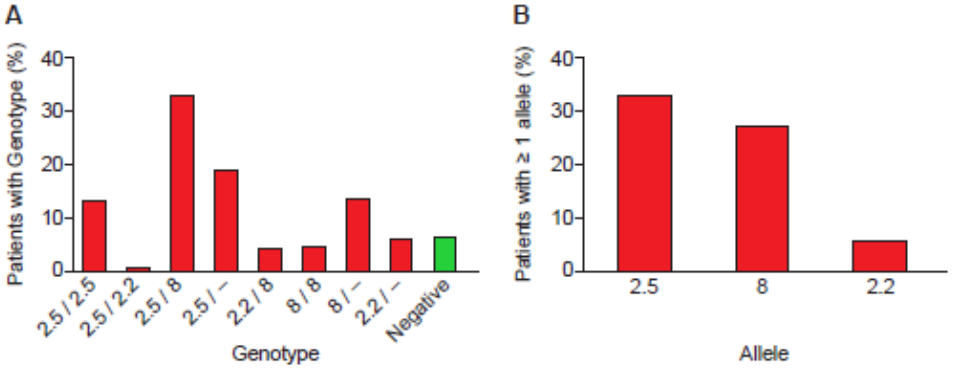
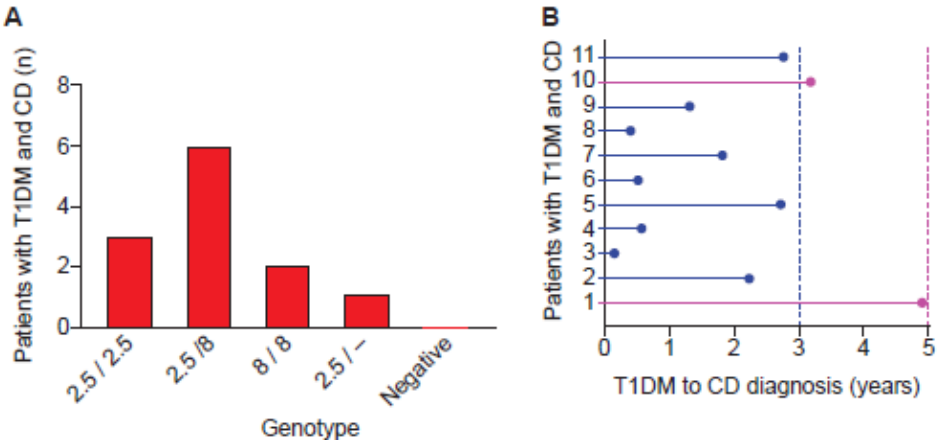


Figure 2 - A) Frequency of individual haplotypes in the whol
Numbers of patients in the whole cohort with at least a singl
DQ2.5, DQ8 or DQ2.2.



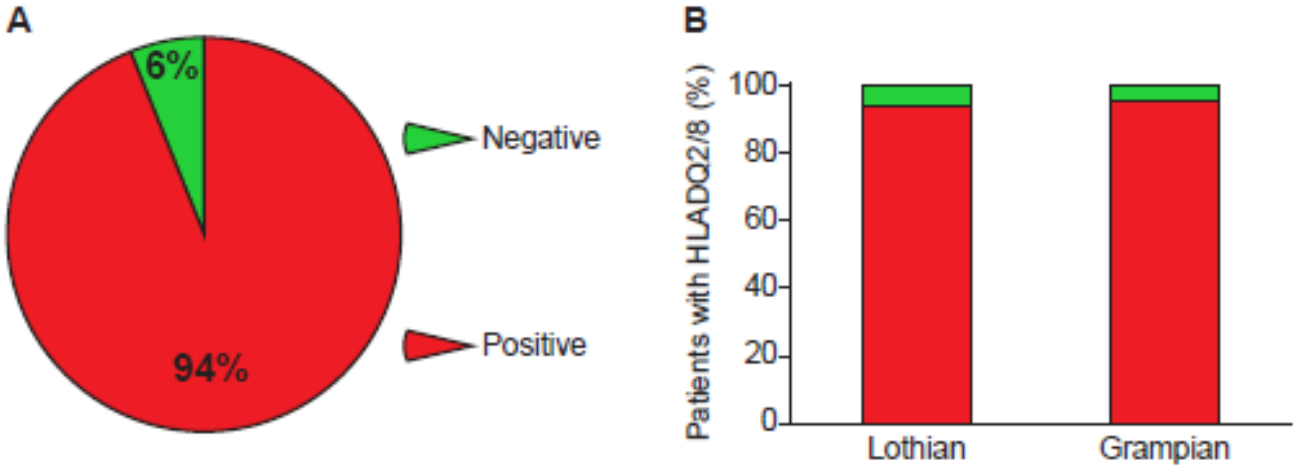
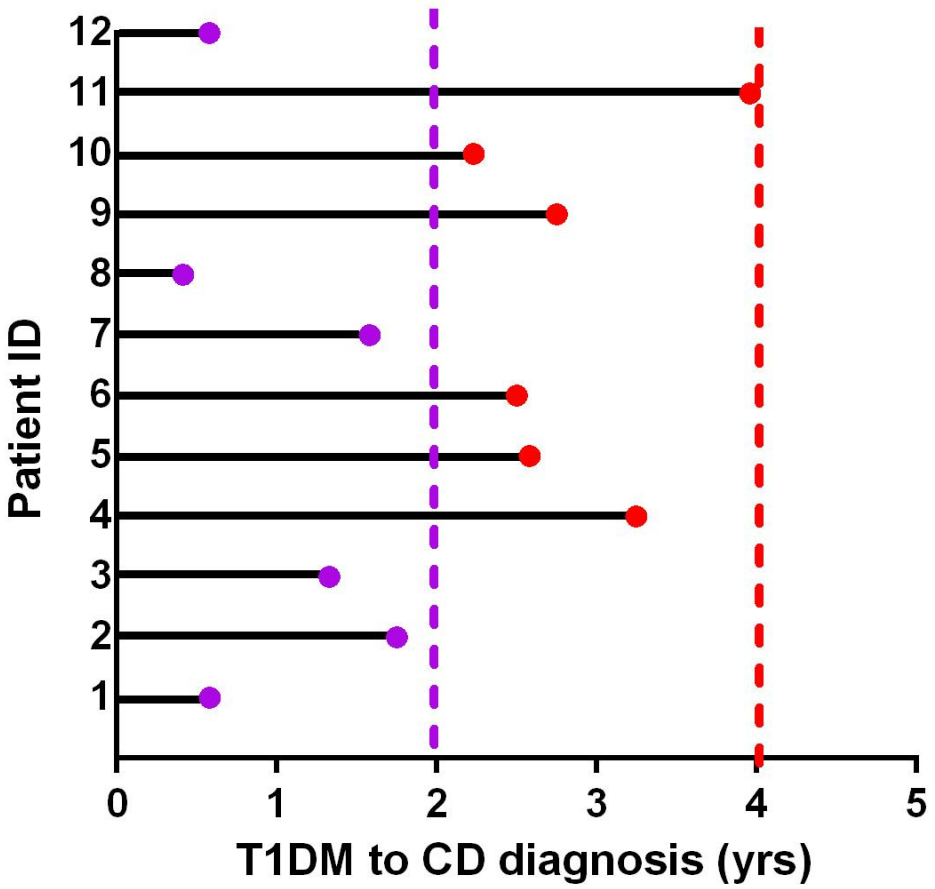


Figure 1 - A) Frequency of CD–predisposing HLA (DQ2 and/or DQ8) genotypes in children with T1DM. **B)** Frequency of HLADQ2 and/or DQ8 by region.

Conclusion

CD predisposing HLA genotypes are present in the majority (94%) of our paediatric T1DM population and the benefit of implementing HLA screening appears marginal. Further research aimed at determining the absolute risks of specific HLA genotypes may help to stratify risk for the development of more effective screening strategies in this patient population.

Time from T1DM Onset to CD Diagnosis



1st degree relatives

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Risk of Pediatric Celiac Disease According to HLA Haplotype and Country

Edwin Liu, M.D., Hye-Seung Lee, Ph.D., Carin A. Aronsson, M.Sc.,
William A. Hagopian, M.D., Ph.D., Sibylle Koletzko, M.D., Ph.D.,
senbarth, M.D., Ph.D.,*
., Ville Simell, M.Sc.,
DY Study Group†

RESULTS

The median follow-up was 60 months (interquartile range, 46 to 77). Celiac disease autoimmunity developed in 786 children (12%). Of the 350 children who underwent biopsy, 291 had confirmed celiac disease; an additional 21 children who did not undergo biopsy had persistently high levels of tTG antibodies. The risks of celiac disease autoimmunity and celiac disease by the age of 5 years were 11% and 3%, respectively, among children with a single DR3–DQ2 haplotype, and 26% and 11%, respectively, among those with two copies (DR3–DQ2 homozygosity). In the adjusted model, the hazard ratios for celiac disease autoimmunity were 2.09 (95% confidence interval [CI], 1.70 to 2.56) among heterozygotes and 5.70 (95% CI, 4.66 to 6.97) among homozygotes, as compared with children who had the lowest-risk genotypes (DR4–DQ8 heterozygotes or homozygotes). Residence in Sweden was also independently associated with an increased risk of celiac disease autoimmunity (hazard ratio, 1.90; 95% CI, 1.61 to 2.25).

DQ8 is associated with an in-
ildren with celiac disease have
TG).

Journal of Pediatric Gastroenterology and Nutrition
42:150–154 © February 2006 Lippincott Williams & Wilkins, Philadelphia

Serologic and Genetic Markers of Celiac Disease: A Sequential Study in the Screening of First Degree Relatives

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ABSTRACT

Objectives: The prevalence of celiac disease (CD) among the relatives and the complications of an undiagnosed CD prompted us to identify a useful disease screening strategy.

Methods: We studied 441 first degree relatives of 208 CD patients by immunoglobulin (Ig)A antiendomysium antibodies (EMA) and radioimmunoprecipitation assay (RIA) IgA anti-transglutaminase autoantibodies (TGAA). Of these, 364 were

CD prevalence resulted 9.5%, the enlarged prevalence 10.9%. The DQ2/DQ8 heterodimers were carried in 231 of 364 subjects and in 38 of 40 biopsy-proven celiac patients. Three DQ2-positive parents became positive to the serology during a long-lasting follow-up.

Conclusions: On the basis of a carefully conducted study, CD prevalence in our series was seen as very high. These data suggest an accurate algorithm to select candidates for intesti-

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JGHF

doi:10.1111/j.1440-1746.2009.06044.x

GASTROENTEROLOGY

Prevalence, human leukocyte antigen typing and strategy for screening among Asian first-degree relatives of children with celiac disease

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Key words
celiac, first-degree relative, histology, HLA, screening, serology.

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Abstract

Background and Aim: Data on prevalence, human leukocyte antigen (HLA) typing and small bowel histology among first-degree relatives of subjects with celiac disease (CD) is scarce. This prospective study evaluated the prevalence and role of HLA DQ2/8 testing in screening of first-degree relatives of children with CD.

Methods: Thirty confirmed children with CD and 91/94 first-degree relatives (parents and siblings) were enrolled. HLA DQ2/8 testing was carried out in all index CD cases. Clinical evaluation with a questionnaire, total serum immunoglobulin A (IgA), human IgA-tissue transglutaminase (IgA-tTGA) and HLA DQ2/8 testing was carried out in all first-degree relatives. Subjects who were positive for IgA-tTGA were recommended endoscopic duodenal biopsy to document histological changes of CD.

Results: Nine first-degree relatives were positive for IgA-tTGA, seven underwent duodenal biopsy and four subjects had Marsh IIIa changes suggestive of CD. The prevalence of histologically confirmed CD in first-degree relatives was 4.4%. The prevalence of potential CD was 9.8%. IgA-tTGA-positive subjects (4/9) were significantly more often symptomatic than IgA-tTGA-negative first-degree relatives (2/82). Twenty-nine (96.6%) index cases of CD and all IgA-tTGA-positive first-degree relatives were positive for HLA DQ2. None of the index CD cases or first-degree relatives were HLA DQ8-positive. A total of 85% of the first-degree relatives were positive for HLA DQ2 and thus at risk of developing CD.

Conclusions: In this first Asian study on a limited number of families of children with CD, 4.4% of the first-degree relatives had CD. Only 15% of the first-degree relatives were negative for HLA DQ2/DQ8. Initial evaluation with HLA and serology followed by only serial serology in HLA-positive relatives is recommended.

European Journal of Human Genetics (2015) 23, 405–408

www.nature.com/ejhg

SHORT REPORT

Impact on parents of HLA-DQ2/DQ8 genotyping in healthy children from coeliac families

Margreet MS Wessels*,[1], Sabine L Vriezinga[1], Sybille Koletzko[2], Katharina Werkstetter[2], Gemma Castillejo-De Villasante[3], Raanan Shamir[4], Corina Hartman[4], Hein Putter[5], Sylvia M van der Pal[6], Cisca Wijmenga[7], Enzo Bravi[8] and M Luisa Mearin[1] on behalf of the PreventCD study group

Due to the association of coeliac disease and HLA-specificities DQ2 and DQ8, HLA-typing can be used for risk determination of the disease. This study was designed to evaluate the knowledge of parents from coeliac families regarding HLA-typing and the impact of HLA-typing on the perception of the health of their children. A structured questionnaire was sent to the Dutch, Spanish and German parents participating with their child in the European PreventCD study on disease prevention in high-risk families, addressing parents' understanding of and attitude towards HLA-typing, distress related to HLA typing and perceived health and health-related quality of life of their children. Sixty-eight percent of p questionnaires, with 85% of children being DQ2/DQ8 positive. The majority of a correctly. Forty-eight percent of parents of DQ2/DQ8-negative children thought th distress was reported by parents of DQ2/DQ8-positive children ($P<0.001$). All p HLA-typing in future children. Perceived health and health-related quality of life misinterpretation of DQ2/DQ8-negative results by parents is frequent. DQ2/DQ8- and health-related quality of life of children but may cause temporary negative f families seem to support HLA-typing.

European Journal of Human Genetics (2015) **23**, 405–408; doi:10.1038/ejhg.20

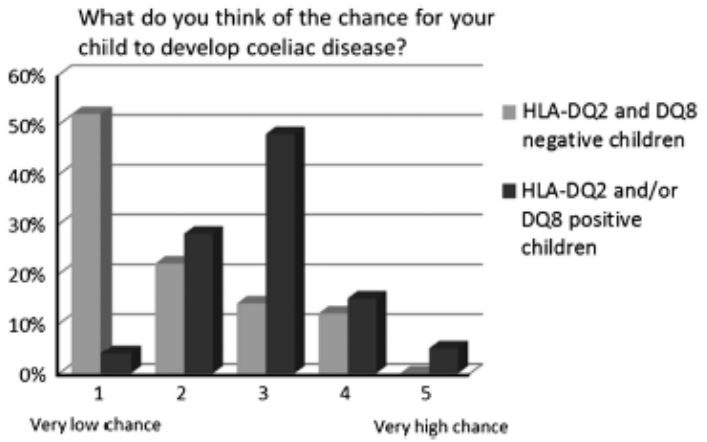

Figure 1 Parental assessment of risk of developing coeliac disease in their child according to HLA-typing results.

So who is it helpful for?

DQ TYPING IS EFFECTIVE IN COELIAC DISEASE SCREENING IN DOWN SYNDROME IN SOUTHEAST SCOTLAND

Claire Sumner[1], Geetha Veerasamy[1], Sarah Clegg[1], Helen Barlow[2], Maureen Forgan[3], Alan Comrie[3], Rod Mitchell[1,4], Peter Gillett[1]

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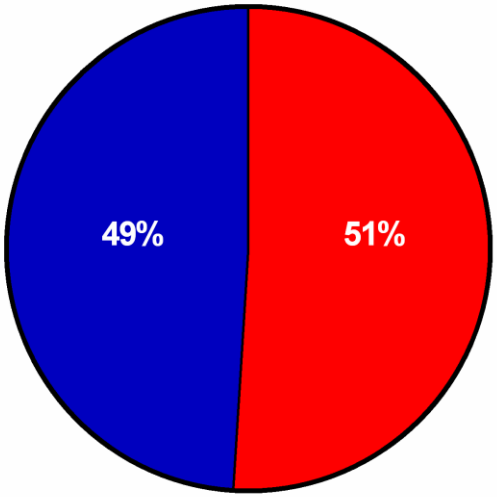
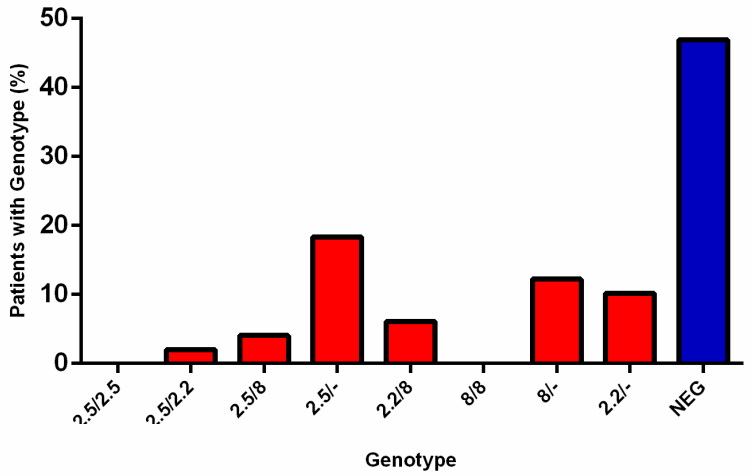
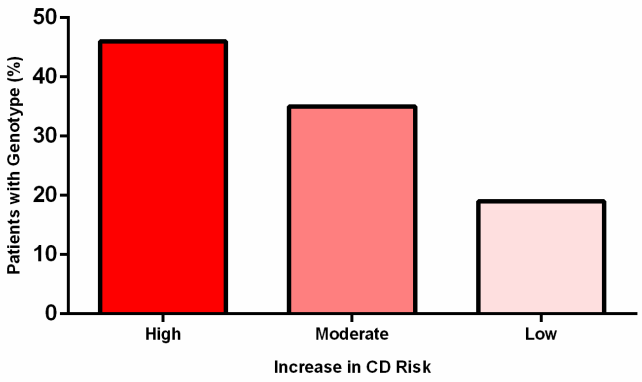
[4]University of Edinburgh







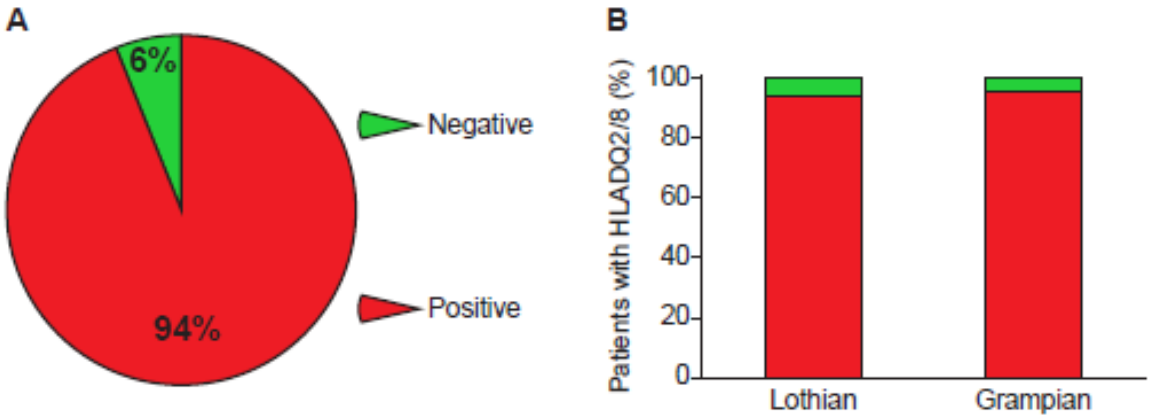


Figure 1 - A) Frequency of CD–predisposing HLA (DQ2 and/or DQ8) genotypes in children with T1DM. **B)** Frequency of HLADQ2 and/or DQ8 by region.

Conclusion

CD predisposing HLA genotypes are present in the majority (94%) of our paediatric T1DM population and the benefit of implementing HLA screening appears marginal. Further research aimed at determining the absolute risks of specific HLA genotypes may help to stratify risk for the development of more effective screening strategies in this patient population.

Conclusions

- CD predisposing HLA haplotypes are only present in approximately half of patients with DS tested in South East Scotland

- DQ typing is effective in excluding nearly 50% of children with DS from ongoing screening for CD. This is in contrast to only 6% in TIDM[5]

- The test can be performed at the earliest opportunity in any child (even prior to gluten exposure) and should be accepted as a standard of care across the UK

- It reduces the burden of repeated venepuncture for the child, and the financial cost of repeated anti-tTG screening

- A positive haplotype allows risk stratification, with DQ2.2 being very low risk and two copies of DQ2.5 being the highest risk[6]

- Future targeted therapy (Nexvax 2) will require identification of the DQ type in CD patients, as it is specific for those with DQ2.5[7]

A DIAGNOSTIC NIGHTMARE ? DQ TYPING and NCGS

- 3 year old on holiday, preceding abdo distension and loose stools for a year then summer 2015- all inclusive GF resort, better on holiday, gran coeliac, went to GP, referred – suggested anti TTG IgA – normal three weeks into GFD. Rechallenged – 'terrible' – urgent scope – normal, biopsies normal. DQ2 and DQ8 negative from original bloods. NCGS

- 14 year old with loose stools and abdo pain, attributed to wheat barley and rye, better off these. Referred and again bloods performed, with normal anti-TTG. Back on gluten – terrible – scoped urgently – normal. DQ2 and DQ8 negative from original bloods. NCGS

Who would be eligible for no Bx ?

RHSC audit of results 2011 -2014

Audit results

BSPGHAN Guidelines:	Standard	Result N=165	
If tTG raised – but **less than 10 x upper limit of normal** for assay *duodenal biopsy required.*	Initial tTG < 50	**Total (n=74)**	**45%**
		2011 (n=13)	8%
		2012 (n=22)	13%
		2013 (n=18)	10%
		2014 (n=21)	12%
If tTG raised –and **greater than 10 x upper limit of normal** assay *either:* *a)Perform duodenal biopsy, or* *b)Further blood sample to check IgA-EMA and HLA-DQ2/DQ8* typing.	Initial tTG >50	**Total (n=91)**	**55%**
		2011 (n=25)	15%
		2012 (n=30)	18%
		2013 (n=22)	13%
		2014 (n=14)	8%

New guidelines in prospective practice

Coeliac disease in the ERA of the new ESPGHAN and BSPGHAN guidelines: a prospective cohort study

Elisa Benelli,[1] Valentina Carrato,[1] Stefano Martelossi,[2] Luca Ronfani,[2] Tarcisio Not,[1,2] Alessandro Ventura[1,2]

rial is nly. To view please visit the journal online (http://dx.doi.org/10.1136/archdischild-2015-309259).

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ABSTRACT

Objective To evaluate the consequences of the last European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN) guidelines for the diagnosis of coeliac disease (CD) by means of a prospective study.

Design Prospective cohort study.

Setting Institute for Maternal and Child Health IRCCS Burlo Garofolo (Trieste, Italy).

Patients Children diagnosed with CD without a duodenal biopsy (group 1), following the last ESPGHAN and BSPGHAN guidelines, and children diagnosed with a duodenal biopsy, matched for sex, age and year of diagnosis (group 2), were prospectively enrolled over a 3-year period. All patients were put on a gluten-free diet (GFD) and were followed up for clinical conditions and laboratory testing at 6 months every year since diagnosis (median follow up: 1.9 years).

Outcome measures Resolution of symptoms, body mass index, laboratory testing (haemoglobin, anti-transglutaminase IgA), adherence to a GFD, quality of life, and supplementary post-diagnosis medical consultations.

Results 51 out of 468 (11%) patients were diagnosed without a duodenal biopsy (group 1; median age 2.1 years) and matched to 92 patients diagnosed with a biopsy (group 2; median age 2.4 years). At the end of follow-up the two groups were statistically comparable in terms of clinical and nutritional status, anti-transglutaminase IgA antibody titres, quality of life, adherence to a GFD, and number of supplementary medical consultations.

Conclusions On the basis of this prospective study, diagnosis of CD can be reliably performed without a

What is already known on this topic

- According to the latest European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)/British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN) guidelines, coeliac disease may be diagnosed without duodenal biopsy in symptomatic patients with high titres of anti-transglutaminase IgA.
- Prospective data on the consequences of the application of the latest ESPGHAN and BSPGHAN guidelines are still lacking in clinical practice.

What this study adds

- Coeliac disease can be reliably diagnosed without biopsy in at least 11% of all cases and in 37% of children younger than 2 years.
- After 2 years, there are no differences, between patients diagnosed with and without biopsy, in clinical improvement, adherence to diet and quality of life.
- This is the first prospective study that validates the safety and effectiveness of the new ESPGHAN/BPSGHAN guidelines for the diagnosis of coeliac disease in children, at least in a short follow-up.

DISCUSSION

This study demonstrates in a prospective manner that the new ESPGHAN and BSPGHAN guidelines, diagn may be reliably done without a duodenal biopsy in at of cases. At the end of the follow-up children without a biopsy were statistically comparable to t nosed with a biopsy in terms of clinical and nutriti serum anti-tTg IgA antibody titres, quality of life, ad a GFD and number of post-diagnosis medical consult

The number of spared biopsies seems to be lowe predicted by previous studies,[5 11] probably because the new ESPGHAN/BSPGHAN guidelines in a rest considering as symptomatic only those cases with weight loss, failure to thrive, and/or iron deficient ana cautiousness in the application of the new E BSPGHAN guidelines was motivated by a lack of va the new diagnostic algorithm by prospective studies. applied the new algorithm to the letter (including o toms possibly suggestive of CD), we would have avoided 165 biopsies of the 468 new CD diagnoses (35.2%).

Children diagnosed without a biopsy were largely under the age of 5 years (88%) and presented a BMI below the third centile in a higher percentage of cases (22%) than those diag nosed with a biopsy. This is not surprising because it is known that CD occurs with more severe symptoms, such as malabsorp tion syndrome, under 2 years of age.[12] Therefore, in this age group, it was possible to spare biopsies more frequently. If we limit the analysis to cases diagnosed under the age of 2 years, the percentage of cases diagnosed without a biopsy following the ESPGHAN/BSPGHAN guidelines would be 37% (22/60).

What this study adds

- Coeliac disease can be reliably diagnosed without biopsy in at least 11% of all cases and in 37% of children younger than 2 years.
- After 2 years, there are no differences, between patients diagnosed with and without biopsy, in clinical improvement, adherence to diet and quality of life.
- This is the first prospective study that validates the safety and effectiveness of the new ESPGHAN/BPSGHAN guidelines for the diagnosis of coeliac disease in children, at least in a short follow-up.

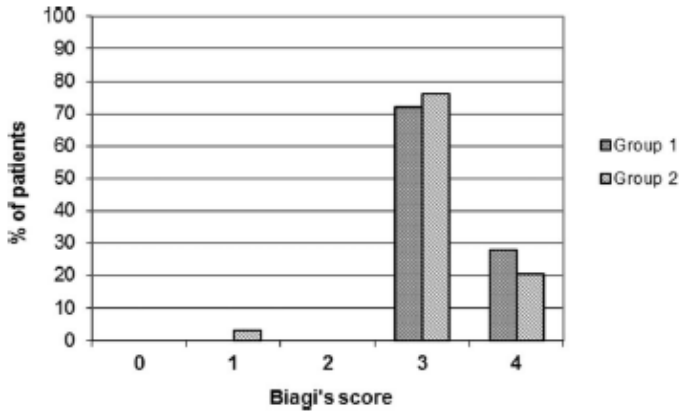

Figure 4 Adherence to a gluten-free diet according to Biagi's score (0, 1, 2=low; 3, 4=high).

Confession session ? Eurosceptic??

What’s going to really convince me?

ProCeDE

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The Project

The Study Group

For Study Centers

Contact

Welcome to ProCeDE!

ProCeDE = Prospective **Ce**liac Disease **D**iagnostic **E**valuation

German Registry for Clinical Trials: Reg-No DRKS00003555

Link to WHO website

********** **NEWS and PROGRESS** **********

June 2014: The main database is now complete for the baseline data of the clinical centers. Two third of the samples are processed and analysed in the central labs. During the annual meeting of the ESPGHAN (European Society of Pediatric Gastroenterology, Hepatology and Nutrition) in Jerusalem, a ProCeDE presentation was given by Sibylle Koletzko during the Parallel Symposia: The Diagnosis of Coeliac Disease, 11th June, 16:20, Location: Teddy A.

Dec 2013: Finally more than 750 patients are already included in the study and recruitment will be finished by 31 Dec 2013. The central analysis of several CD specific antibodies, HLA-typing of DNA and histopathology review are ongoing.

Sept 2013: During the ICDS (International Celiac Disease Symposium) in Chicago, a poster about the clinical presentation at diagnosis of patients in the ProCeDE study was presented. Currently, about 650 patients have been included and another 100 patients are still being recruited. Central lab analysis are proceeding.

May 2013: During the 46th annual meeting of the European Society for

ProCeDE

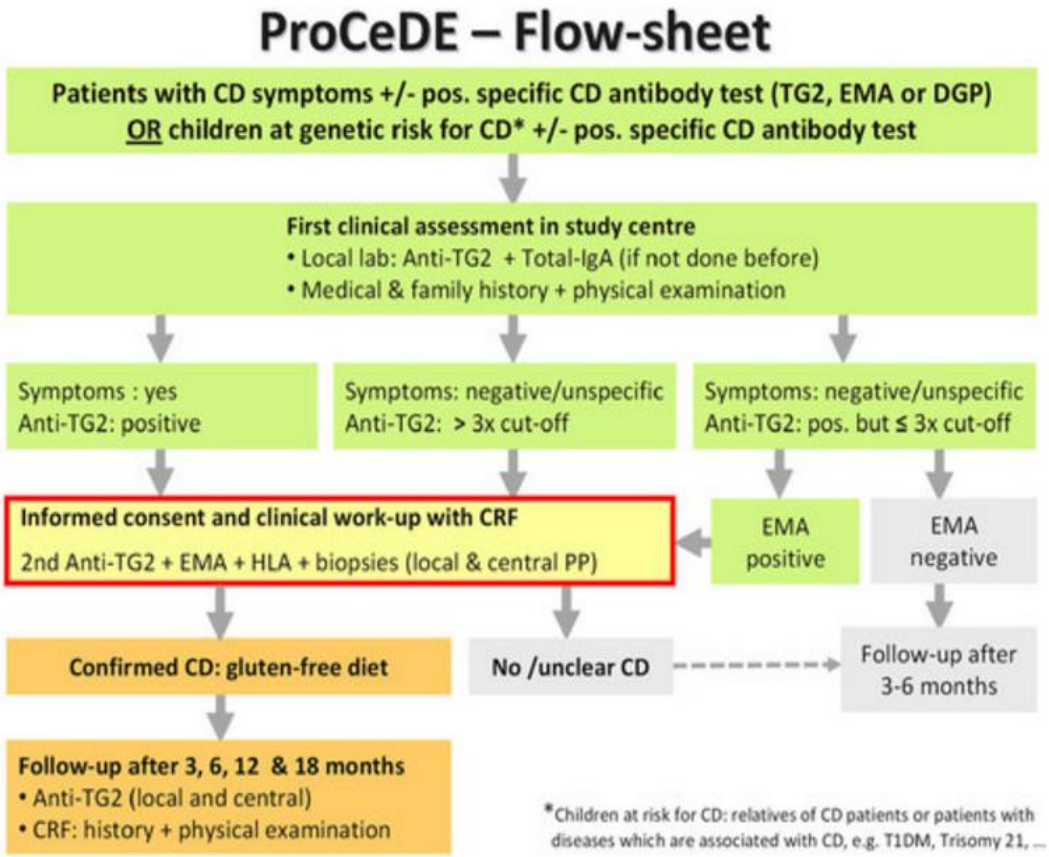
Study design

The Study Group

For Study Centers

Contact

The children will be followed for 18 months after diagnosis.



Viewable in full size - click on illustration

Still to report !


MONTH DAY YEAR PM HOUR MIN
OCT 26 1985 • 09:00
DESTINATION TIME
MONTH DAY YEAR PM HOUR MIN
OCT 21 2015 • 07:28
PRESENT TIME
MONTH DAY YEAR PM HOUR MIN
NOV 12 1955 • 06:38


BACK TO THE FUTURE

Constant question in clinic
Nexvax 2 for children !

Gastroenterology 2015;149:1541–1552

Consistency in Polyclonal T-cell Responses to Gluten Between Children and Adults With Celiac Disease

Melinda Y. Hardy,[1,2] Adam Girardin,[1,2] Catherine Pizzey,[3,4] Donald J. Cameron,[3,5] Katherine A. Watson,[6] Stefania Picascia,[7] Renata Auricchio,[8] Luigi Greco,[8] Carmen Gianfrani,[7] Nicole L. La Gruta,[6] Robert P. Anderson,[9] and Jason A. Tye-Din[1,2,3,4]

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recognition was similar between T-cell clones from children and adults. **RESULTS:** We detected gluten-specific responses by T cells from 30 of the children with celiac disease (73%). T cells from the children recognized the same peptides that were immunogenic to adults with celiac disease; deamidation of peptides increased these responses. Age and time since diagnosis did not affect the magnitude of T-cell responses to dominant peptides. T-cell clones specific for dominant α- or ω-gliadin peptides from children with celiac disease had comparable levels of reactivity to wheat, rye, and barley peptides as T-cell clones from adults with celiac disease. The α-gliadin–specific T cells from children had biases in T-cell receptor usage similar to those in adults. **CONCLUSIONS:** T cells from children with celiac disease recognize similar gluten peptides as T cells from adults with celiac disease. The findings indicate that peptide-based diagnostics and therapeutics for adults may also be used for children.

Good and not so good?

- Collaborative work
- Multiple practical questions to answer
- Registry – national data collection – pilot
- Referrals, numbers of test – capturing them all
- Endoscopy- what are we going to miss?
- ESPGHAN/BSPGHAN guidelines – all uniform in UK or big regional variations
- Microbiome and genetics, bio-banking? Is this the death knell for pure science research?

New guidance Conclusions

- Reconfiguration required on utility but it does work and families
- Attractive option for SOME at risk groups?
  - Frequency of DQ2/8 - families & A I conditions?
  - Is it cost effective? NOT FOR ALL
- Local assay accuracy has to be known and how it relates to histology Sensitivity and specificity of local assay
- HLA DQ typing – reporting NEEDS STANDARDISED
- Specialist gastroenterologist / paediatrician / dietitian must be involved – education really important?
- Consequences of getting it wrong ! Threshold for Bx

The future for adult practice - ESPGHAN leads the way again?

Questions?