Lewis phenotype, secretor status, and coeliac disease

W Dickey, J D C Wylie, J S A Collins, K G Porter, R G P Watson, J C McLoughlin

Abstract

Patients who cannot secrete ABO and Lewis blood group antigens into body fluids, an ability controlled by a single gene on chromosome 19, are known to be at increased risk of certain autoimmune diseases associated with human leucocyte antigen (HLA) markers. This study investigated the possibility of an association with coeliac disease using red cell Lewis (Le) blood group phenotype to infer secretor status. Among 73 patients with coeliac disease who had Le a or b antigen, 48% were non-secretors (Le a+ b-) compared with 27% of 137 blood donors (p=0.004: odds ratio 2.49, 95% confidence intervals 1.37 to 4.51) and 26% of 62 medical and nursing staff controls (p=0.014: odds ratio 2.65, 95% confidence intervals 1.27 to 5.50). Clinical characteristics did not differ between secretors and non-secretors with coeliac disease. Thus, the non-secretor state is significantly associated with coeliac disease, suggesting that genes on chromosome 19 may directly or indirectly participate in conferring susceptibility.

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The ability to secrete ABO blood group antigens into saliva and other body fluids is a dominantly inherited characteristic controlled by a single gene on chromosome 19. Patients who cannot secrete these antigens (non-secretors) are at greater risk of various bacterial and fungal infections,¹ of gastroduodenal disease,² and of some autoimmune conditions, notably ankylosing spondylitis, non-insulin dependent diabetes mellitus, and Graves' disease.³⁻⁵ The mechanisms underlying these associations are not understood.

Coeliac disease arises after immunological sensitisation of the small bowel to dietary gluten and is associated with certain genes of the major histocompatibility complex on chromosome 6: environmental factors are important in the development of overt disease and non-HLA associated genes probably also confer susceptibility.⁶

As secretor status is closely associated with expression of Lewis antigens both in secretions and on erythrocytes, determination of red cell Lewis phenotype provides a simple method for measuring the prevalence of non-secretors within populations. We used this method to discover if there is a link between secretor status and coeliac disease.

Patients and methods

We studied patients with coeliac disease attending our gastroenterology clinics over a four month period. At initial presentation, all had had biopsy specimens of jejunum obtained by Crosby

capsule or of distal duodenum by forceps, which had shown villous atrophy and increased numbers of intraepithelial lymphocytes and of inflammatory cells in the lamina propria.

Two control populations were studied: blood donors attending a centre in Belfast, and nursing and medical staff of our hospitals who had never been diagnosed as having coeliac disease or dermatitis herpetiformis and had no history of anaemia or of gastrointestinal symptoms.

Red cell Lewis phenotype was determined by standard haemagglutination techniques using commercially available anti-Lewis a and anti-Lewis b blood grouping reagents (Organon Teknika, Durham, North Carolina).

Results were analysed using χ^2 with Yates's correction for 2x2 tables and the crossed odds ratio with 95% confidence intervals to estimate the comparative risk of coeliac disease associated with the non-secretor state.

Results

We tested 75 patients with coeliac disease, 145 blood donors, and 67 staff controls for Lewis phenotype. Of these, two patients (3%), eight blood donors (6%), and five staff controls (7%) were both Lewis a and b antigen negative. As secretor status cannot be inferred from this phenotype, they were excluded from further study. The Table shows the prevalence of non-secretors among the remaining members of each group.

There was a significant excess of non-secretors among patients with coeliac disease compared with both blood donors ($\chi^2=8.36$, df=1, p=0.004) and staff controls ($\chi^2=6.08$, df=1, p=0.014). The odds ratio for coeliac disease with non-secretors was 2.49 (95% confidence intervals 1.37 to 4.51) using blood donors as controls and 2.65 (1.27 to 5.50) when compared with staff controls.

A number of clinical characteristics was compared between secretors and non-secretors with coeliac disease. There was no association between patient sex, childhood (age <16 years) v adult onset of symptoms, age of onset of symptoms, age at diagnosis, presenting symptoms (presence of diarrhoea/steatorrhoea v absence), or haemoglobin concentration at presentation, and secretor status.

Prevalence of non-secretors among patients with coeliac disease, blood donors, and staff controls

Group	Total	Non-secretors (Le a+b-) (%)	Secretors (Le a-b+) (%)
Coeliac disease	73	35 (48)	38 (52)
Blood donors	137	37 (27)	100 (73)
Staff controls	62	16 (26)	46 (74)

Le=Lewis blood group phenotype.

Department of Medicine,
Queen's University of
Belfast
W Dickey
K G Porter
R G P Watson

The Royal Victoria
Hospital, Belfast
J D C Wylie
J S A Collins

Mater Infirmary
Hospital, Belfast
J C McLoughlin

Correspondence to:
Dr W Dickey, Department of
Medicine, Institute of Clinical
Science, Grosvenor Road,
Belfast BT12 6BJ.

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Discussion

Secretors usually possess the red cell Lewis phenotype Le (a-b+). A minority have Le (a-b-) red cells. Conversely, non-secretors have Le (a+b-) or Le (a-b-) phenotypes as determined by erythrocyte markers. Thus, secretor status cannot be inferred by this method in patients with the Le (a-b-) phenotype but as they are uncommon, determination of red cell Lewis phenotype permits inference of secretor status in most subjects. This method avoids the potential problem of false positive secretors when saliva is tested for ABO and Lewis group antigens, as a result of contamination by blood from poor oral hygiene, periodontal disease or over vigorous brushing of teeth.⁷ The prevalence of non-secretors among our control groups is comparable with control populations elsewhere in the British Isles.¹

The genetic factors participating in the inheritance of coeliac disease are not fully understood. The importance of the HLA genes of the major histocompatibility complex on chromosome 6 is well recognised, but this association merely confers an increased susceptibility and other genes may also be important. The possibility that a second gene located on chromosome 14 in or near the region coding for immunoglobulin heavy chain allotypes (Gm types) might be implicated has been explored. Kagnoff *et al*⁸ reported an association of the phenotype Gm (f;n;b) with coeliac disease in patients lacking HLA-B8 and HLA-DR3, but others failed to confirm this.⁹

The hypothesis that secretor status, controlled by a single gene on chromosome 19, is linked to susceptibility to coeliac disease is an attractive one. An association with the non-secretor state and a number of immunologically mediated diseases associated with HLA markers has been shown by Blackwell and others in Edinburgh. Compared with a prevalence of non-secretors in healthy controls of 27%, that among patients with ankylosing spondylitis was 49%,³ with non-insulin dependent diabetes mellitus 40%,⁴ and with Graves' disease 44%.⁵

To our knowledge, only one previous study has compared the prevalence of non-secretors among patients with coeliac disease with that of controls. Using saliva samples to determine secretor status, Langman *et al*¹⁰ reported that only 14% of 50 patients with coeliac disease in Birmingham were non-secretors, compared with 27% of 92 coeliac patients in London and 22% of 591 healthy controls: there was no statistical difference between the groups. There may be considerable discrepancy between the non-secretor prevalence assessed by saliva testing and by determination of Lewis phenotype, because of contamination of saliva by blood: Blackwell *et al* obtained figures of 25 and 38% respectively in one area.⁷ In addition, patients with coeliac disease are more likely to have mouth ulcers and other oral lesions, and we postulate that a higher risk of blood contamination of saliva as a result among coeliac patients may have led to an underestimation of non-secretor prevalence in this group when tested by Langman *et al*. This would at least partly explain the discrepancy with our study's outcome.

Our results suggest that the occurrence of

coeliac disease is indeed significantly associated with the non-secretor state. Predisposition to coeliac disease may be related to some aspect of immune function that is changed in non-secretors, although the exact mechanism is unclear.¹ Reports of reduced concentrations of salivary and serum IgA in non-secretors, suggesting an abnormality in mucosal protection,¹¹ have not been substantiated by other workers.¹² The increased susceptibility of non-secretors to various infections had led Blackwell to propose that association with the non-secretor state in certain autoimmune conditions is evidence for an infective aetiology.¹ While prior adenovirus 12 infection has been considered in the pathogenesis of coeliac disease,¹³ this has not been substantiated¹⁴ and some virus infections seem to be associated with the secretor rather than the non-secretor state.¹⁵ Alternatively, linked genes on chromosome 19 may determine independently secretor status and the risk of developing coeliac disease.

Assessment of HLA phenotype in combination with secretor status may identify those first degree relatives of patients with coeliac disease at greatest risk of developing the condition, but family studies will be required to confirm this. Secretor status, however, like the HLA phenotypes associated with coeliac disease, is common in the general population and therefore confers susceptibility and not disease. Other genes may well be implicated in the pathogenesis.

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