Down’s syndrome is strongly associated with coeliac disease

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Abstract

Background—There is evidence of an increased prevalence of coeliac disease in Down’s syndrome.

Aims—To investigate the association, patients with Down’s syndrome and matched controls were examined.

Methods—Fifty nine patients with Down’s syndrome residing in government institutions in the Hunter region of New South Wales were studied. Four were excluded (terminally ill=1, uncooperative=3). Each of 55 patients was matched for age, sex, and residence with a control patient. Patients with both positive IgA and IgG antigliadin antibodies were considered for endoscopy due to endoscopy biopsy.

Results—Twenty one patients and two controls had raised IgA and IgG antigliadin antibodies (χ2=19.4; p<0.001). Tissue was obtained in 18 patients. Two had characteristic flat, five pronounced lymphocytic infiltration not diagnostic of coeliac disease, two giardiasis, and eight were normal. In one the tissue was not suitable for analysis. There were few differences between the subgroups in their anthropomorphic, biochemical, or haematological findings.

Conclusions—The prevalence of coeliac disease in these 51 patients with Down’s syndrome is at least two (3-9%; 95% confidence interval 9%–9–2%) and could be as many as seven (13-7%; 95% CI 4-3%/23-2%). In this community the prevalence of coeliac disease in Down’s syndrome is increased more than 100-fold (X=135–473).

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Keywords: coeliac disease, Down’s syndrome, antigliadin antibodies, biopsy of the small bowel, T-cells.

The association between coeliac disease and Down’s syndrome is now well established. The earliest reports were case study approaches which described the coexistence of the two conditions in a few patients.1-7 As this association could occur by chance, of more relevance were studies which retrospectively surveyed larger populations, either of known cases of coeliac disease or known cases of Down’s syndrome in an effort to estimate prevalence of the combined conditions. One study suggested an increased prevalence of coeliac disease in Down’s syndrome of 43 times that of other children; another suggested a 20-fold increase.

The next progression has been to prospectively survey populations of patients with Down’s syndrome, using antibody screening tests to determine eligibility for biopsy.11–16 It is difficult to draw conclusions about the strength of the association between coeliac disease and Down’s syndrome from these studies because of the lack of comparability in the findings (Table 1). The patients have differed in age; the representativeness of the sample is not always clear; not all studies have control groups; there are differences in screening methods and criteria for biopsy selection; and most studies have failed to biopsy all those identified by the screening process. Prevalence figures have ranged from 3% to 7% and would seem to be an underestimate in most cases.

These studies have also raised the question of the reliability of antibody testing, particularly antigliadin antibodies. Between 24% and 50% of those biopsied were found to have coeliac disease, indicating that most antibody results were "false positives". The more recent studies have indicated that the antiendomysial antibodies are more accurate than antigliadin antibodies in determining selection for biopsy.

The present study was undertaken to examine these issues in more detail. The questions of concern were:

• Is there an increased frequency of antigliadin antibodies in those with Down’s syndrome?
• Is there an increased incidence of coeliac disease in those with Down’s syndrome?
• Is the antigliadin antibody test a reliable screening device for this group of people?

The study focuses on the serological and biopsy findings in an institutionalised population of adults with Down’s syndrome.

Methods

Patients

The patients were 59 adults with Down’s syndrome who resided in the three campuses of the Hunter Region Developmental Disability Service, the largest government institution for people with intellectual disability in New South Wales, Australia. The diagnosis was confirmed by chromosome analysis. The patients, severely disabled and institutionalised for most of their lives, ranged in age from 25 to 62 (mean 37) years; 28 were women. A control group was matched with the Down’s
syndrome group on the basis of age (within five years), sex, and residential unit within each campus. Consent to the procedures was given by the person or bodies responsible for the patients under the Disability Services and Guardianship Act, 1987 (natural guardian, Guardianship Board, or the Public Guardian).

**METHODS**

**Blood collection**

Blood samples were collected from 55 of the 59 in the Down’s syndrome group and their 55 matched controls. Three patients with Down’s syndrome were uncooperative and would not allow venepuncture and one with a terminal illness was excluded. The samples were sent to two different laboratories as each campus did not use the same pathology provider. The two laboratories used different kits for the determination of antigliadin antibodies (Kabi-Pharmacia Uppsala, Sweden and Coeliac Screening kit, Medical Innovations, Artarmon, NSW). As well as antigliadin antibodies, haematological and biochemical tests were carried out on the Down’s syndrome group using standard techniques.

**Biopsies**

Those patients with a positive antigliadin test (defined as above normal concentrations on both antigliadin IgA and antigliadin IgG after excluding IgA deficiency) were examined further. Case histories were prepared including history of diarrhoea, anaemia, and weight loss as well as behavioural characteristics (for example, disturbances of mood and behaviour). All those with a positive test result were considered for biopsy whether or not the history and findings suggested coeliac disease. Endoscopic biopsy specimens were taken from as far distal as possible in the duodenum.

**Statistical methods**

$\chi^2$ Tests were used for categorical data with Yates’s correction as appropriate. For normally distributed data $t$ tests with a two-tailed test of significance were used.

**Results**

**ANTIGLIADIN ANTIBODY TEST**

Of the 55 patients with Down’s syndrome, 21 had an increase in both IgA and IgG antibodies and another one had IgA deficiency and raised IgG antibodies compared with only two controls ($\chi^2=19.4, p<0.001$; Table II). The patient with IgG antibodies and IgA deficiency was included in the positive group for further investigation and analysis. More male (15 of 31) than female (six of 24) patients with Down’s syndrome had an increase in both IgA and IgG antibodies ($\chi^2=4.0, p<0.05$; Figure).

**HAEMATOLOGY AND BIOCHEMISTRY (PATIENTS WITH DOWN’S SYNDROME)**

Although a few patients had below normal values for haemoglobin, ferritin, and calcium, most results were within reference values. The exception was albumin: 16 of 54 patients with Down’s syndrome tested had low concentrations of albumin. Mean concentrations of albumin in the positive antibody group were 37.6 g/l and in the negative antibody group 41.9 g/l ($r=4.3, p<0.0001$). Mean values of haemoglobin were significantly lower in antibody positive men but not women ($r=2.61, p<0.015$; Table III).

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**TABLE I** Major findings of studies which have screened for coeliac disease in populations of patients with Down’s syndrome

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Age group</th>
<th>Selection criteria</th>
<th>Control group</th>
<th>Test</th>
<th>Positive (%)</th>
<th>Biopsy selection criteria</th>
<th>Biopsies able to be done (%)</th>
<th>Biopsy specimens positive for CD (%)</th>
<th>CD in whole sample (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reading 1984</td>
<td>17</td>
<td>?</td>
<td>?</td>
<td>No</td>
<td>Gluten antibodies</td>
<td>47</td>
<td>No biopsies performed</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kanavin et al</td>
<td>38</td>
<td>Mostly adults</td>
<td>All DS patients in local institutions</td>
<td>Yes</td>
<td>Antigliadin IgA, Antigliadin IgG</td>
<td>58</td>
<td>Those &quot;with the highest&quot; IgA n=7</td>
<td>32</td>
<td>29</td>
<td>5</td>
</tr>
<tr>
<td>Storm 1990</td>
<td>78</td>
<td>Children</td>
<td>?</td>
<td>Yes</td>
<td>Antigliadin IgA, Antigliadin IgG</td>
<td>3</td>
<td>Positive results on both tests n=6</td>
<td>67</td>
<td>50</td>
<td>3</td>
</tr>
<tr>
<td>Castro et al</td>
<td>155</td>
<td>Children</td>
<td>?</td>
<td>Yes</td>
<td>Antigliadin IgA</td>
<td>26</td>
<td>Positive IgA n=41</td>
<td>51</td>
<td>33</td>
<td>5</td>
</tr>
<tr>
<td>Zubillaga et al</td>
<td>70</td>
<td>Children</td>
<td>Attending a local child health clinic</td>
<td>No</td>
<td>Antigliadin IgA (if +, then antitissue)</td>
<td>13</td>
<td>Positive IgA n=9</td>
<td>89</td>
<td>36</td>
<td>4</td>
</tr>
<tr>
<td>George et al</td>
<td>115</td>
<td>Children</td>
<td>?</td>
<td>No</td>
<td>Antigliadin IgA, Antigliadin IgG</td>
<td>29</td>
<td>Positive result on any one of the four tests n=43</td>
<td>79</td>
<td>(100%)</td>
<td>7</td>
</tr>
</tbody>
</table>

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**TABLE II** Antigliadin antibody results for patients with Down’s syndrome and control patients

<table>
<thead>
<tr>
<th></th>
<th>Negative IgA and IgG (n (%))</th>
<th>Positive IgA only (n (%))</th>
<th>Positive IgG only (n (%))</th>
<th>Positive IgA and IgG (n (%))</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>DS</td>
<td>17 (30.9)</td>
<td>3 (5.5)</td>
<td>14 (25.5)</td>
<td>21 (38)</td>
<td>55</td>
</tr>
<tr>
<td>Control</td>
<td>43 (78.2)</td>
<td>2 (3.6)</td>
<td>8 (14.5)</td>
<td>2 (3.6)</td>
<td>55</td>
</tr>
</tbody>
</table>

DS=Down’s syndrome.
BIOPSY SPECIMENS
Biopsy specimens were obtained from 18 of 22 patients and 17 were interpretable (Figure). Two had unequivocal appearances of coeliac disease, two had giardiasis, in five there was evidence of lymphocytic infiltration of the lamina propria, and eight were histologically normal. The two patients who had coeliac disease diagnosed were placed on gluten-free diets.

OTHER MEASURES
There was a significant difference between patients with Down’s syndrome and control patients in height and weight. Patients with Down’s syndrome were significantly shorter ($r=5.42$, $p<0.001$) and lighter ($r=3.82$, $p<0.001$) than their matched controls. In the Down’s syndrome group there was no difference between those with a positive and those with a negative antigliadin antibody test on measures of age, height, or weight, or clinical indications of coeliac disease. Histories of diarrhoea, anaemia, and weight loss were common for the Down’s syndrome group as a whole (Table III).

Discussion
We may now attempt to answer the questions put earlier. Firstly, there is unquestionably an increased prevalence of antigliadin antibodies in Down’s syndrome.

The second question, that of the prevalence of coeliac disease in Down’s syndrome, requires some exploration. Two patients had unequivocal changes – the classic “flat” biopsy specimen. Seven patients had abnormal biopsy specimens; in two of these giardia organisms were seen and provided adequate explanation for the cellular infiltrate, and in five it is possible but unlikely that they were a response to giardia infestation with a scant population not recognised on microscopy. A much more likely explanation is that they represent the infiltrative lesion described by Marsh, who has vigorously promoted the view that this infiltrative stage represents a response to antigens such as gluten products and which is much more frequent than the classic “flat” biopsy sample. Many years before, Weinstein noted similar infiltrative appearances in patients with dermatitis herpetiformis culminating in a “flat” biopsy sample in patients given a 20 g gluten supplement daily for 20 weeks. This represents a large dose of gluten,
being equivalent to eating almost a 500 g loaf of bread daily (Bread Research Institute of Australia, personal communication). Given that the five patients had raised antigliadin antibodies and lymphocytic infiltrates in their lamina propria, and three of them had lowered serum albumin concentrations, it is difficult to escape the conclusion that they, or most of them, had gluten intolerance. If this is so then up to seven of the 18 patients biopsied out of 51 patients adequately examined had coeliac disease. There are strategies to consider to confirm the gluten intolerance of patients such as these. A rebiopsy after a period of gluten-free diet or, after a period of high gluten diet such as that used by Weinstein might well settle the issue. The caregivers of one of these five have attempted to implement a gluten-free diet, with equivocal results. Compliance with the diet by a severely disabled patient and his multiple caregivers has presented major logistical problems and it is difficult to justify rebiopsy when withdrawal has not been complete. The patient also has cardiac problems which have worsened since the initial biopsy, placing him at risk for procedures requiring sedation. Many of the biopsies were carried out in difficult circumstances, with sedation being difficult to achieve at the usual dosages. It needs to be recognised that endoscopic biopsy on uncooperative adults presented major challenges and pulse oximetry showed, at times, appreciable hypoxaemia. Equally, general anaesthesia was not a feasible alternative.

In summary, the prevalence of coeliac disease in our patients with Down’s syndrome is at least two and probably seven of 18 patients biopsied and of 51 of the entry cohort giving a prevalence of at least 3-9% (95% CI = 0-9-2%) and as much as 13-7% (95% CI = 4-3-23-2%). The prevalence of coeliac disease in the Hunter region is about 29/105, so the prevalence in Down’s syndrome is increased more than 100-fold (135-473).

The third question, that of the utility of the search for antigliadin antibodies, can be answered with some reservations. The antigliadin IgG test is too sensitive and the antigliadin IgA test a better discriminant.

Our study, like others reported earlier, found many “false positive” antibody results; that is, almost 50% of antibody positive patients with Down’s syndrome had a normal biopsy result. As the control group did not show such a high rate of positivity this is a response specific to the Down’s syndrome group. There was little correlation between actual antibody titre and biopsy result; some of the patients with Down’s syndrome had very high antibody titres and a normal biopsy specimen. Given the higher number of “false positives” when using antigliadin antibodies with the patients with Down’s syndrome compared with controls, we think that antiendoymal antibody is preferable.

11 No value in screening patients was seen in standard full blood count, 20 item biochemistry, or serum zinc, carotene, ferritin, folate, and vitamin B12 estimation. None of this explains why gluten intolerance should have an increased prevalence in Down’s syndrome. The modern view is that the basic defect in coeliac disease is the presence in gluten of specific amino acid sequences which are processed within the lamina propria and presented by macrophages of specific affinities to coeliac disease to CD4 lymphocytes with a resultant upregulation of cytokine production. This would explain much of the resulting anatomical and physiological changes seen. A synthetic peptide corresponding to amino acids 31-49 of A gliadin or amino acids 31-47 produces changes in coeliac tissues. Moreover, patients with coeliac disease have a cell surface molecule DQw2 and many have DR17. However, a genetic basis for coeliac disease is inadequate – for example, identical twins only show 70% concordance in coeliac disease and 25% of northern European white people exhibit DQw2. A key issue then is the mechanism preventing the development of coeliac disease in nearly all those with the appropriate MHC2 phenotype and why the mechanism is suboptimal in Down’s syndrome. Three potential explanations appear. Firstly, there is evidence of premature aging and loss of T cell function in Down’s syndrome and there is a higher prevalence of immunological disturbances in the condition. A second consideration is early weaning, characteristic of the condition and associated with a five-fold increase in the incidence of coeliac disease. Thirdly, it is possible that the frequent gastrointestinal infections in such institutionalised patients may lead to an impairment of integrity of the small bowel. In summary, there are no data to explain the high prevalence of coeliac disease in Down’s syndrome. Whether the solution lies in more intensive epidemiological studies or in events at a molecular level must remain speculative. Further investigations along these lines are warranted.

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