**Inflammatory bowel disease**

**T59-T70**

**CHILDHOOD RISK FACTORS FOR IBD USING A TWIN CASE-CONTROL METHOD**

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Previous case-control studies of IBD have used hospital or community derived controls. There are obvious inherent biases in both methods, which also fail to control for genetic factors. Same-sex twin studies overcome both these flaws and are statistically more powerful.

**Methods:** Each member of a registry of 175 twins-pairs, at least one of which had IBD, was independently sent validated questionnaires confirming their disease, zygosity and asking about childhood (age <16 years) risk factors.

**Results:** In 130 cases both twins replied, 116 discordant for the disease, 80 of which were the same gender (47 monogygotic). These 80 pairs formed the case-control study.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Case</th>
<th>Control</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td>64</td>
<td>56</td>
<td>1.71 (0.8 - 3.8)</td>
</tr>
<tr>
<td>Mumps</td>
<td>38</td>
<td>43</td>
<td>0.78 (0.4 - 1.5)</td>
</tr>
<tr>
<td>Chickenpox</td>
<td>64</td>
<td>65</td>
<td>0.94 (0.4 - 2.2)</td>
</tr>
<tr>
<td>Asthma &amp; Hayfever</td>
<td>8</td>
<td>13</td>
<td>0.57 (0.2 - 1.6)</td>
</tr>
<tr>
<td>Tonsillitis</td>
<td>17</td>
<td>17</td>
<td>1.0 (0.4 - 2.3)</td>
</tr>
<tr>
<td>Appendectomy</td>
<td>0</td>
<td>4</td>
<td>p=0.12</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3</td>
<td>7</td>
<td>0.41 (0.1 - 1.9)</td>
</tr>
<tr>
<td>Gastroenteritis &gt; twin</td>
<td>22</td>
<td>5</td>
<td>5.69 (1.9 - 20)</td>
</tr>
<tr>
<td>Exposure to animals &gt; twin</td>
<td>16</td>
<td>3</td>
<td>6.42 (1.7 - 35)</td>
</tr>
</tbody>
</table>

\* \* \* p < 0.0007

**Conclusions:** These preliminary results confirms the increased frequency of episodes of "gastroenteritis" and reveals an increased exposure to animals. This method overcomes many of the traditional problems of case control studies. The greater degree of matching increases the statistical power and comparing answers provides an internal validation of the data.

**FAMILIAL AGGREGATION AND CONCORDANCE IN CLINICAL CHARACTERISTICS IN CROHN'S DISEASE**

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**Background:** Age adjusted risks are important for genetic counselling and modelling in Crohn's disease. Moreover, knowledge of concordance in disease characteristics is important to define phenotypic subtypes.

**Aims:** First, to determine familial occurrence and age adjusted risks in first degree relatives of Crohn's patients compared to controls. Second, to evaluate the agreement in disease characteristics within Crohn's families.

**Methods:** Crohn's patients (n=640) and controls (n=800) were questioned about familial occurrence of IBD in their first degree relatives. In addition agreement for age at diagnosis, initial disease location, disease behaviour and number of bowel resections was determined in 68 multiply-affected families and 100 unrelated Crohn's patients.

**Results:** Crohn's probands had a more frequent (p<0.001) positive family history for Crohn's disease (13.6%) than controls (1.1%). Risk estimates were significantly higher in relatives of patients compared to controls. The highest age adjusted risk for IBD was found in offspring (10.4%). Especially daughters of Crohn's patients showed an important IBD risk (12.6%). Parents were significantly (p<0.001) older at diagnosis than their offspring. Within generation age at diagnosis was very similar (p=0.69, p<0.001). The initial disease location showed a significant agreement within familial cases (k=0.285, 0.057-0.512). Especially between siblings the agreement was striking (k=0.372, 0.119-0.626).

**Conclusions:** Our large family study provides for the first time age adjusted risks for a European population. The clinical impression of familiality in disease characteristics was confirmed by using an objective measure of agreement, namely the k-value.
SOCIAL CLASS, ETHNICITY & SMOKING IN A NATIONALLY REPRESENTATIVE COHORT WITH CROHN'S DISEASE.

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Introduction: There are few studies concerning the frequency of Crohn's disease (CD) among different ethnic groups within the UK. Likewise, there are few reports concerning the relevance or not of social class. Smoking has been shown to be a risk factor for CD. The fourth Morbidity Study, a General Practice (MSP4) represents a study of why patients in England or Wales visit their GP. It was conducted in 1991-92 and covered a population of 468,042. Data concerning ethnicity, social class, economic activity, smoking status (in the last week) and living in an urban or rural environment had been collected in MSP4.

Methods: We have previously identified 291 patients reported to have CD and in whom the diagnosis was not refuted subsequently. Controls were selected from the same practice as the case and matched for gender and age. Data were analysed in conditional logistic regression models using the GLIM4 program. Odds ratios (OR) for individual factors were obtained with 95% confidence intervals.

Results: 1682 controls were selected. The OR for afro-caribbean's was 3.19 (95% confidence interval 2.86-3.53) and for Indians 1.03 (1.00-1.08). Compared with social classes 1 & 2 the OR for social class 3-non-manual was 1.21 (0.79-1.85), 3-manual 0.70 (0.48-1.03) and 4.65 1.08 (0.72-1.64). There was no significantly increased risk of being unemployed, or 0.63 (0.29-1.36) but there was an increased risk of being registered as a pensioner (r=0.27-7.29). The OR with Crohn's disease were more likely to smoke, OR 1.29 (0.95-1.75) and less likely to live in a rural environment, OR 0.75 (0.44-1.28).

Conclusion: This confirms that CD is more likely to occur in those who smoke and live in an urban environment. Social class is not a significant factor for CD. It may be more common in those of afro-caribbean but not Indian origin.

THE ASSESSMENT OF QUALITY OF LIFE IN INFLAMMATORY BOWEL DISEASE PATIENTS: A FIVE ITEM SCALE FOR OUTPATIENT USE.

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Quality of life (QOL) has been identified as an important measure in the evaluation of patient response to treatment in IBD patients. QOL or well-being has also been shown to be a strong determinant of clinical course (e.g., outpatient visits, subjective pain or symptom complaints & patient satisfaction). Previous studies by our group have suggested that QOL in IBD is complex and is influenced by disease activity and psychosocial factors. The purpose of this study was to develop a brief easily administered self-report scale to assess QOL in an outpatient clinic. Recent data by our group indicates that in the IBD, a disease specific measure of QOL can be predicted by five questions from the entire 32 item questionnaire (Gastroenterol 1995; 108: A931). We enrolled 123 consecutive patients with IBD (94 Crohn's, 29 U.C.) who completed the IBDQ and the five item questionnaire (IBDQ-SF). Disease activity was recorded in 69 Crohn's (Dutch AI and CDAI) and 10 UC patients.

Results: There was a strong correlation between the IBDQ-SF and the total score of the IBDQ (r=0.91, p<0.001). The IBDQ-SF score also correlated with the 4 subscales of the IBDQ (ie) bowel symptoms, r=0.79 p<0.001; Emotional functioning, r=0.88 p<0.001; Psychosocial symptoms, r=0.88 p<0.001; Social symptoms, r=0.77 p<0.001. For the Crohn's patients the CDAI was strongly r=0.72 to 0.75 (ie, r=0.71, p<0.001 with the IBDQ total, with significant correlations [r<0.001] with the four subscales as well), whereas the relationship between the Dutch AI and IBDQ (ie, r=0.27 ±0.05 for the IBDQ total).

Conclusion: The five item questionnaire, the IBDQ-SF is a quick and easy means to measure QOL in an IBD Clinic setting. This scale will allow clinicians to identify patients whose disease-specific QOL is impaired and who may need specialized care addressing psychological issues which will facilitate clinical care. The CDAI also correlates with measured QOL in Crohn's disease whereas the Dutch AI, a more objective measure of disease activity does not.

LOW APPENDICECTOMY RATES IN PATIENTS WITH ULCERATIVE COLITIS: EFFECT IS INDEPENDENT OF SMOKING.

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It has recently been noted that there is an inverse relationship between appendicectomy and ulcerative colitis (UC) in a Belgian study. This has not yet been confirmed in the U.K. There is also a possibility that this relationship may be linked with smoking. This case-controlled, prospective study examines the frequency of appendicectomy and smoking in a stable U.K. population.

Methods: A total of 228 patients with a definitive diagnosis of inflammatory bowel disease were prospectively interviewed by a standardised questionnaire. There were 112 patients with a diagnosis of ulcerative colitis and 116 patients with Crohn's disease. 112 controls were recruited from accident and emergency department and were matched for age and sex.

Results: The appendicectomy rates amongst patients with UC was 2.7% (3/112) which was significantly lower compared to 16.1% (18/112) amongst controls (p<0.005, Odds ratio: 6.96, 95% C.I. 3.77-19.3). 2 patients with UC had their appendicectomy performed after diagnosis. Appendicectomy rates amongst patients with Crohn's disease was significantly greater than controls: 34% (18/112) vs. 16.1% (39/116), (P<0.01); OR: 2.65, 95% C.I. 5.31-13.4) but includes 9 patients who had appendicectomy as part of surgical intervention for Crohn's disease. The strong association of UC with non-smoking is confirmed (2% v 42%, P<0.001, OR: 35.6; 95% C.I. 308-868).

However there appears to be no association between smoking and appendicectomy in all three groups.

Conclusion: UC is associated with significantly lower appendicectomy rates than controls while appendicectomy rates in Crohn's disease is higher. This finding is independent of smoking. This intriguing finding may have implications in the aetiology of inflammatory bowel disease.

THE ARTICULAR DISTRIBUTION AND CLINICAL COURSE OF THE PERIPHERAL ARTHROPATHIES IN ULCERATIVE COLITIS (UC) ORCHARD T.R., Wordsworth B.P., Jewell D.P. Nuffield Department of Medicine, John Radcliffe Hospital, Oxford. UK.

The association between UC and peripheral arthropathy is well recognised, but there are no diagnostic criteria and no information on their long term outcome. We have reviewed the records of patients with UC currently under review in Oxford and by subdividing them into 'reactive' (ReA), peripheral (PeA) and arthralgia have assessed the frequency and clinical course of the arthropathies.

The case notes were reviewed for the presence of arthritic symptoms and signs. Reactive arthropathies involved less than 5 joints including a weightbearing joint with recorded evidence of joint swelling or effusion. Peripheral arthropathies involved 5 or more joints with evidence of swelling or effusion. Poorly defined joint symptoms and complaints without joint swelling were classified as arthralgia. Coincident rheumatic complaints, general features of UC and other extraintestinal manifestations were also recorded.

There were 860 patients under active review, of which 117 (13.6%) complained of peripheral joint problems. 43 (5.0%) had arthralgia, 27 (3.3%)ReA and 22 (2.6%) PeA. In addition 6 patients had known rheumatoid arthritis and 39 had osteoarthritis. 23 of 27 patients (85.2%) with ReA had an episodic course, of which 7 (30.4%) had more than one episode, and 4 (14.8%) had a continuous course. The most commonly affected joint was the ankle. Peripheral arthritis was affected in 33/27 cases with an effusion present in 10. Of 22 patients with peripheral arthritis 18 (82.8%) had a continuous course from 10-180 months, 2 (9.1%) were episodic, and 2 (9.1%) had only a single attack. The metacarpophalangeal joints were the most commonly involved (14/18) and there were no joint effusions recorded.

We have demonstrated two distinct forms of peripheral arthropathy in UC with different distributions and natural histories, ReA, which occurs as a single episode in 59.3% of cases and pursues a continuous course in only 14.8%, and PeA which pursues a continuous course in 82.8% of cases and only occurs as a single episode in 9.1%.

Patients with Crohn’s disease (CD) are at risk of osteoporosis but the underlying pathophysiology is unclear. The aim of this cross-sectional study was to assess bone mineral density (BMD) in CD and use bone turnover markers to investigate the possible mechanisms of bone loss.

Methods: 140 patients with Crohn’s disease (122 premenopausal females, 48 males, mean age 38.7 (13.2) had BMD measured at the hip and lumbar spine by dual energy x-ray absorptiometry (Osteoporosis: BMD > 2.5 SD below young adult, osteopenia: BMD >1 STI below young adult). Bone formation markers were osteocalcin (Bone gl protein, BGP), bone specific alkaline phosphatase (BAP) and pro-collagen carboxy-terminal propeptide (PICP). Urinary deoxyypyridinoline (dPYR) was measured to assess bone resorption. Results are presented as mean (SD) (normal range).

Total alkaline phosphatase increased in 35% (17.5 (13.5) normal range 11.6-43.3 U/L). 2% (2 patients) had increased BAP, and in 21 (23%) BALP was lower than normal. Mean PICP was 98.1 (47.6) (normal range 69-163 ng/ml). PICP was high in 7 (7%) patients with 24 (24%) patients recording values below the normal range. Mean dPYR was 10.2 (6.7) (normal range 2.5-6.5 nmol/dm Creat); 73 (73%) of the 98 patients had elevated dPYR. Bone formation markers were significantly different in patients with low bone density but dPYR was significantly reduced (43.4 when BMD 0.5SD below young adult).

Association with disease activity was not found, although a trend towards increasing dPYR was observed with increasing age and BMD. It was proposed that the increase in dPYR may be a result of osteoclast activation, and not of bone loss.


This study compared the tolerability and efficacy of balsalazide (mesalazine produrg) and mesalazine (84-hour delayed-release) in acute UC. Patients (101 total, 99 evaluable) (62 male) aged 41 ± 13 years (mean ±SD) with grade 2 (erythema and/or edema <1 cm), plus bleeding: (55%) patients, 3 (3 spontaneous bleed) or >12 cm; 32% of patients) or 4 (+s) (severe inflammation: 3% of patients) (extent >12 cm; left-sided disease 8%) morphologically verified, symptomatic (moderate 69% or severe 31%) UC were randomised, double blind, to receive balsalazide 2.25g t.d.s. (equivalent to 0.7g mesalazine) (n=50) or mesalazine 0.8g t.d.s. (n=49) for 4 to 8 weeks, respectively. Recital hydrocortisone p.r.n. was provided as relief medication. Both groups were comparable at entry.

A greater proportion of patients achieved symptomatic remission (none/mild symptoms) at 2 (64% vs 43%, p<0.05), 4 (70% vs 51%, p<0.05), 8 (78% vs 45%, p<0.001) and 12 weeks (88% vs 57%, p<0.001) after balsalazide treatment compared to mesalazine. Similarly, more patients achieved complete remission (none/mild symptoms, sigmoidoscope grade 0 (normal) or 1 (erythema with loss of vascular pattern) with no steroid use in previous 4 days) in the balsalazide group after 4 (38% vs 12%, p<0.01), 8 (54% vs 22%, p<0.005) and 12 weeks (62% vs 37%, p<0.05) with greater patient satisfaction (12 weeks: 91% vs 63%, p<0.005). Diary card analysis showed that patients taking balsalazide experienced more days with complete symptom relief (missing no steroid during the first 4 weeks of treatment (24% vs 14%, p<0.01) and took less time to achieve their first complete symptom free day (median: 10 vs 25 days, p<0.005) compared to those taking mesalazine. One patient in each group discontinued due to an unacceptable adverse event (AE) however, all 4 serious AEs (complications of UC) occurred in the mesalazine group and fewer patients in the balsalazide group reported AEs (4% vs 71%, p<0.05).

Analysis of prognostic factors identified low ulcerative colitis grade at entry (p<0.05) and treatment with balsalazide (p<0.01) as increasing the probability of complete remission after 12 weeks.

In conclusion, balsalazide 2.25g t.d.s. was more effective than mesalazine 0.8g t.d.s. in achieving both symptomatic and sigmoidoscopic remission of acute ulcerative colitis and was associated with a better adverse event profile.

NON-STERoidal ANTI-INFLAMMATORY Drugs (NSAID’S) SALICYLCATED AND COLITIS - A STRONG ASSOCIATION. Gleeson M W, Hardman J, Clinton C, Spencer D. The General Hospital, Jersey, Channel Islands, UK.

In a prospective study of 62 consecutive new cases of colitis from November 1993 to May 1996, a careful drug history revealed 45 patients who had been taking NSAID’s or salicylates. The mean age of patients with NSAID-associated colitis was 40.5 years (range 20-77) and of others (idiopathic colitis) was 49.9 (range 23-90). No patients had a previous history of colitis, faecal cultures were negative and diagnosis was always established by colonoscopy. Patients with NSAID-associated colitis had either; (1) distal disease, identical in endoscopic appearances to ulcerative colitis (55%) or (2) proximal disease with rectal sparing and discontinuous disease, similar to Crohn’s colitis.

Histology revealed crypt abscesses, ulceration and a mixed inflammatory infiltrate but no granulomas. All patients received standard medical treatment for inflammatory bowel disease and 18 (36.9%) of the NSAID group required systemic steroids compared to 8 (47.1%) of the idiopathic group. One patient in the NSAID group required proctocolectomy, and 3 patients with NSAID-associated colitis have relapsed (the majority being in the distal colitis group). Relapses have occurred without further exposure to NSAID’s or salicylates, and this group of patients appear to be developing a chronic colitis.

It could be argued that these observations were a coincidence due to the high level of exposure of the general population to NSAID’s and salicylates. However, carried out a control study. A drug history was obtained from 45 attenders at a minor injuries clinic. The age range of this series was 18 – 90 (mean 38) years, 38 (8%) were taking NSAID’s or salicylates. This compares to 45 (72%) of 62 patients taking NSAID’s or salicylates in the colitis group. This gives an odds ratio of 33.1 (95% confidence interval), significantly supporting a causal association between these agents and colitis. They appear to be an important aetiological trigger factor in inflammatory bowel disease.

IMPRESSIVE HISTOLOGIC IMPROVEMENT AFTER TNF-α ANTIBODY (cA2) THERAPY IN ACTIVE CROHN’S DISEASE. Baert F, Peeters M, D’Haens G, Geboes K*, Ectors N*, Rutgeerts P. Dept of Gastroenterology and Pathology* University of Leuven, Belgium.

TNF-α is an important mediator of inflammation in Crohn’s disease (CD). We studied the histologic effects of cA2 therapy in a systematic way. Biopsies of 13 patients with active CD before and 4 weeks after a single placebo or cA2 infusion (5, 10 or 20 mg/kg) were reviewed by one blinded pathologist. Six biopsies were taken per patient at every occasion in the most inflamed areas. If ulcers were present, biopsies were taken in the vicinity. Seven pts had colitis, four ileitis and two colitis. Assessment of the severity of inflammation was based on epithelial alterations, inflammatory changes, the presence of ulcerations and/or granulomas and the number of biopsies affected. A score from 0-3 was given for each item according to severity. The minimal score was 0, the maximum 16.

In addition to classical H&E, immunohistochemical stainings for HLA-DR, CD68 (activated macrophages), ICAM-1 and LFA-1 were performed using an indirect immunoperoxidase method.

Results: The mean total activity score in the cA2 treated group dropped from 6.7 (2.1-12) to 3.0 (0-7) in ileitis and from 7.6 (2.1-12) to 3.0 (0-8) in colitis compared to 11 (10-12) before and 9 (6-12) after placebo. There were differences in the inflammatory components of the score for most pronounced. The enhanced epithelial HLA-Dr and endothelial ICAM-1 expression were more pronounced in most patients. LFA-1 lymphocytes observed at week 0 markedly declined in CD pts treated with cA2 but not in the placebo group.

Conclusion: Monoclonal TNF-α antibody therapy significantly improves histologic disease activity in active Crohn’s ileitis and colitis. The improvement is mainly due to a dramatic decrease of the inflammatory infiltrate parallel to a reduction of HDL-Dr expression and the number of CD68+ and LFA1+ cells.
LIVER T71–T85

GRAFT INFILTRATING LYMPHOCYTES IN LONG TERM LIVER TRANSPLANTS. A MARKER OF TOLERANCE?

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Clinical tolerance is present in a significant proportion of long term liver transplant recipients, although to date it has not been possible to reliably identify these recipients by conventional clinical, or biochemical, parameters. The present study examined whether immunohistochemical analysis of pre-weaning liver biopsies could discriminate unique patterns in patients subsequently found to be tolerant.

Methods: 37 biopsies: 27 from patients with stable graft function 5 years, or more post transplant, and 10 from patients experiencing acute rejection were studied. Anti-C3D, C4D, C4DSRO, CDSRA, CDSK6, and CD68 staining was performed.

Results: Of the 27 long term patients, 20 subsequently underwent weaning of their immunosuppression; 6 were tolerant, 5 achieved substantial reductions in their immunosuppression (partially tolerant), and 9 were unable to achieve any substantial reduction (intolerant).

Reduced numbers of lobular CD8+ and CD3+ cells were present in the tolerant as compared to the intolerant grafts (median 15 vs 22 p<0.01, 15 vs 26 cells/high powered field [hpf] respectively, p<0.03). Similarly, there were fewer numbers of lobular CD3, CD8, CD45RO+ cells in tolerant grafts when compared with acute rejection (16 vs 32 p<0.01, 15 vs 31 p<0.01, 17 vs 24 p=0.03 median cells/hpf respectively).

Conclusions: In all long term liver grafts, infiltrating lymphocytes are present, and with those grafts from patients intolerant of immunosuppression withdrawal they are phenotypically similar to those during acute cellular rejection. Fewer CD8 positive cells correlate with graft tolerance, and may aid in the identification of patients in whom successful withdrawal of immunosuppression may be undertaken.

T70

TWO-STAGE GENOME-WIDE SEARCH IN INFLAMMATORY BOWEL DISEASE: STRONG EVIDENCE FOR SUSTAINABILITY LOCi ON CHROMOSOMES 3, 7 AND 12

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Concordance rates in siblings and twin pairs have provided strong evidence that genetic predisposition is important in the pathogenesis of the inflammatory bowel diseases (IBD). However, neither Crohn’s disease (CD) nor ulcerative colitis (UC) has a simple Mendelian pattern of inheritance; the model which seems most pertinent to inflammatory bowel disease is that of a heterogeneous group of polygenic disorders. In the present study, a systematic two-stage search of the human genome for susceptibility genes in inflammatory bowel disease was performed, involving 186 affected sibling pairs.

In the first stage, 89 sibling pairs with IBD were genotyped at 260 microsatellite markers spanning the 22 autosomes, using fluorescence labelled primers for polymerase chain reaction, and semi-automated DNA fragment sizing technology. Allele sharing in affected sibling pairs provided evidence for linkage with 12 markers in 5 distinct regions of chromosomes 2, 3, 7, 12 and 15 (p<0.001 for an individual marker, or adjacent markers each with p<0.01).

In the second stage, a further 97 affected sibling pairs with IBD were genotyped; linkage for the clustered markers on chromosomes 3, 7 and 12 was confirmed.

Combining data from the first and second stages provided striking evidence for linkage with 3 adjacent markers on chromosome 3 with HLOD score of 2.66 x 10^4 (CD3=3.05 and D3S524=2.95) (p=2.14 x 10^-4), lod score 4.59 and D12S368 (p=5.03 x 10^-4); lod score 3.29) - and three adjacent markers on chromosome 7 - D7S519 (p=1.33 x 10^-4), lod score 2.89), D7S866 (p=8.20 x 10^-4), lod score 3.08) and D7S524 (p=8.45 x 10^-4), lod score 2.14). Individual markers on chromosome 2 (D2S142) and chromosome 12 (D12S368) were linked with susceptibility to UC (p=0.0071) and CD (p=0.009), respectively.

These data provide compelling evidence for the chromosomal location of IBD susceptibility genes. Strong candidate genes are present in each of the regions which have been implicated, and are currently being studied.