SHORT REPORTS

Familial prevalence of inflammatory bowel disease in relatives of patients with Crohn's disease

The current incidence of Crohn's disease in Cardiff is about $5/10^5/\text{year}^1$ and relatives of patients develop the disease more often than the rest of the population. We have examined the prevalence of inflammatory bowel disease in first-degree relatives and spouses of 139 patients with Crohn's disease in Cardiff and have reviewed the case notes of those relatives who were thought to be affected.

Patients, methods, and results

In 1977 156 patients with Crohn's disease were living in the City of Cardiff (prevalence = $55.7/10^5$ population). This was established from data collected in a study of incidence between 1934 and 1977 based on a diagnostic index kept by hospitals in Cardiff.¹ One hundred and forty-seven patients alive in 1979 were asked to complete a questionnaire which related to family size and the occurrence of ulcerative colitis or Crohn's disease in the family. Questions related to the spouse and first-degree relatives, who included parents, siblings, and children over 15 years. The diagnosis in both patients and relatives was confirmed from hospital case notes using histological and radiological criteria.

Completed questionnaires were returned by 139 of the 147 patients. Thirteen patients had at least one first-degree relative with either Crohn's disease or ulcerative colitis. The diagnosis in the parents of two other patients was not confirmed, because one had diverticular disease and the other carcinoma of the colon. Eleven of the 437 siblings at risk had either ulcerative colitis or Crohn's disease, two of the 278 parents had ulcerative colitis, and one of the 152 children at risk also had colitis (table). Out of

Inflammatory bowel disease in Cardiff in 1977

	No at risk	No of cases of ulcerative colitis	No of cases of Crohn's disease	Prevalence of Crohn's disease (cases/ 10^5 population)
Cardiff residents	280 100	—	156	55.7
Relatives of patients with Crohn's disease:				
Parents	278	2	0	0
Siblings	437	4	7	1601.8
Children over 15 years old	152	1	0	0
Spouses	87	1	0	0

The number of residents with ulcerative colitis is unknown as it has not been measured. The prevalence of Crohn's disease in relatives is 13 times greater than that in non-relatives.

the 156 cases of Crohn's disease only one pair of brothers were both resident in the city at the time of diagnosis; the five other affected siblings were resident elsewhere. The expected number of cases of Crohn's disease in 869 first-degree relatives is 0.49. If one avoids counting the sibling pair twice then there were six cases recognised ($P < 0.0002$, based on a Poisson distribution). If the number of affected relatives is considered as seven, or attention is restricted to siblings only, much higher levels of significance are obtained.

Comment

Nine per cent of patients with Crohn's disease have a first-degree relative with either Crohn's disease or ulcerative colitis. The risk of siblings developing the disease is almost 30 times that in the total population of Cardiff, which has a high prevalence compared with the rest of Wales. While such a relative risk attains a high degree of statistical significance, the prevalence in first-degree relatives is not high enough to indicate a disease of simple Mendelian inheritance with high penetrance.² It is more likely that an external factor is responsible for the development of the condition in susceptible individuals. Not surprisingly, only two married couples with Crohn's disease have been reported.^{3,4} If the condition occurred with the same frequency in spouses as in siblings only one case in the 87 spouses at risk would have been expected in this study.

Siblings and spouses experience similar diagnostic facilities and are

of a comparable age, whereas many parents lived before Crohn's disease was widely recognised and many children may be too young to have developed the condition. The differential diagnosis between ulcerative colitis and Crohn's disease may be difficult to make, even in specialised centres, but Crohn's disease occurs with much greater frequency in relatives than would be expected by chance. Our study has shown that first-degree relatives have a much greater risk of developing Crohn's disease but the disease is unlikely to be due to a simple genetic effect. An external factor such as infection or diet probably plays a role.

¹ Mayberry JF, Rhodes J, Hughes LE. Incidence of Crohn's disease in Cardiff between 1934 and 1977. *Gut* 1979;20:602-8.

² Almy TP, Sherlock P. Genetic aspects of ulcerative colitis and regional enteritis. *Gastroenterology* 1966; 51:757-63.

³ Whorwell PJ, Eade OE, Hossenbocus A, Bamforth J. Crohn's disease in a husband and wife. *Lancet* 1978;2:186-87.

⁴ Zetzel L. Crohn's disease in a husband and wife. *Lancet* 1978;2:583.

(Accepted 23 October 1979)

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Acute interstitial nephritis and erythroderma associated with diflunisal

Acute interstitial nephritis (AIN) is an uncommon renal disease which may be caused by drugs—for example, sulphonamides, phenindione, ampicillin, and methicillin.^{1,2} Drug-induced interstitial nephritis usually presents as renal failure with haematuria, minimal proteinuria, fever, skin rashes, and eosinophilia. We report here a case of AIN presenting as acute oliguric renal failure, erythroderma, and eosinophilia after a course of diflunisal.

Case report

A 70-year-old woman was referred because of oliguric renal failure. Eight weeks before admission diflunisal 250 mg twice daily for two weeks had been prescribed for mild pain in her fingers. Two weeks after discontinuing the drug she developed urticaria, for which prochlorperazine 5 mg thrice daily, chlorpheniramine 4 mg thrice daily, and, later, prednisolone 15 mg daily were prescribed. The rash cleared but a week after stopping prednisolone it reappeared and she became anuric. Blood urea was 51.5 mmol/l (310 mg/100 ml) and potassium 6.3 mmol(mEq)/l. Peritoneal dialysis was started. There was no history of renal disease or allergy. She had a fever of 37.3°C; oedema of the legs, arms, face, trunk, and vulva; a red, itchy skin with widespread exfoliation; and a blood pressure of 170/90 mm Hg. Laboratory investigations showed haemoglobin 8.5 g/dl; white blood cells $12.4 \times 10^9/\text{l}$ ($12\,400/\text{mm}^3$); eosinophils $1.49 \times 10^9/\text{l}$ ($1490/\text{mm}^3$); platelets $81 \times 10^9/\text{l}$ ($81\,000/\text{mm}^3$); ESR 12 mm in 1st h; total serum protein 51 g/l; albumin 22 g/l; serum aspartate transaminase 15 IU/l; bilirubin 6 $\mu\text{mol/l}$ (0.3 mg/100 ml); antistreptolysin O titre < 125 IU/ml; C3 56 mg/dl. Antinuclear factor, Wassermann reaction, and latex test for rheumatoid arthritis were all negative and Australia antigen was not detected. A catheter specimen of urine contained protein plus, white blood cells $40 \times 10^6/\text{l}$ ($40/\text{mm}^3$), and red blood cells $240 \times 10^6/\text{l}$ ($240/\text{mm}^3$). A high-dose intravenous urogram showed normal-sized kidneys and no obstruction. Renal biopsy showed normal glomeruli but a severe interstitial nephritis. The interstitium contained an intense infiltrate of lymphocytes, plasma cells, and eosinophils with much oedema and fibrosis. The tubules were normal in places but many areas were atrophic. Immunofluorescence showed linear deposition of C3 plus a granular deposition of IgM and IgG

along the tubular basement membranes. Skin biopsy showed a subacute inflammatory cell infiltrate of lymphocytes and neutrophils.

Her rash cleared and renal function slowly improved on prednisolone 60 mg daily. Peritoneal dialysis was discontinued 14 days after her admission. The eosinophil count fell to $130 \times 10^6/l$ ($130/mm^3$). The prednisolone dose was rapidly reduced and stopped after 16 days. Plasma creatinine concentration at that time was $369 \mu mol/l$ ($4.2 \text{ mg}/100 \text{ ml}$). It rose over the next week to $545 \mu mol/l$ ($6.1 \text{ mg}/100 \text{ ml}$). Five weeks after stopping the prednisolone the plasma creatinine was $906 \mu mol/l$ ($10.2 \text{ mg}/100 \text{ ml}$). A mid-stream urine specimen contained leucocytes $168 \times 10^6/l$ ($168/mm^3$), red blood cells $32 \times 10^6/l$ ($32/mm^3$), and 1.0 g/l protein. She was readmitted and given prednisolone 45 mg a day. Her renal function improved: one month after readmission her plasma creatinine was $164 \mu mol/l$ ($1.8 \text{ mg}/100 \text{ ml}$). Seven months after her first admission her creatinine clearance was 30 ml/min and plasma creatinine $196 \mu mol/l$ ($2.2 \text{ mg}/100 \text{ ml}$). Her prednisolone dose had been reduced to 10 mg daily.

Comment

The patient's eosinophilia, rash, fever, acute interstitial infiltrate with plasma cells and eosinophils, and immunoglobulin deposition on the tubular basement membrane suggested a hypersensitivity disease. Diflunisal was the only drug she had taken. No other cases of sensitivity to it have been reported to the Committee on Safety of Medicines. Diflunisal is a new, non-steroidal analgesic related to acetylsalicylic acid. It is usually well tolerated,³ but there have been seven cases of Stevens-Johnson syndrome associated with it.⁴ Our patient responded to corticosteroid treatment and relapsed when it was withdrawn. Although the efficacy of steroids in this condition is not proved their use is recommended.⁵

We thank Dr J Tasker, Northampton General Hospital, for referring this patient.

¹ Méry J-P, Morel-Maroger L. Acute interstitial nephritis: a hypersensitivity reaction to drugs. *Proc 6th Int Congr Nephrol, Florence* 1975:524-9.

² Kleinknecht D, Kanfer A, Morel-Maroger L, Méry J-P. Immunologically mediated drug-induced acute renal failure. *Contrib Nephrol* 1978;10:42-52.

³ Tempero KF, Cirillo VJ, Steelman SL. Diflunisal: a review of pharmacokinetic and pharmacodynamic properties, drug interaction and special tolerability studies in humans. *Br J Clin Pharmacol* 1977; 4:31-6S.

⁴ Committee on Safety of Medicines. *Curr Probl* 1979; No 4.

⁵ Saltissi D, Pusey CD, Rainford DJ. Recurrent acute renal failure due to antibiotic-induced interstitial nephritis. *Br Med J* 1979;1:1182-3.

(Accepted 17 October 1979)

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Tricuspid valve replacement in carcinoid syndrome due to ovarian primary

Carcinoid syndrome with valvular dysfunction due to primary ovarian carcinoid tumour is rare.¹ This case illustrates the importance of recognising this association, since removal of the primary tumour and, if necessary, subsequent valvular surgery can restore health in a potentially lethal condition.

Case report

A 60-year-old woman presented with a six-month history of increasing lassitude, dyspnoea, palpitations, and widespread pains. She had a red face, peripheral cyanosis, and ankle oedema. The apex beat was in the seventh intercostal space in the mid-clavicular line and a harsh pansystolic murmur

was heard over the whole precordium. A tender lower abdominal mass was palpable and ultrasonic scanning suggested a large pelvic mass. Abdominal radiography showed hepatic enlargement. The urinary 5-hydroxyindole acetate (5-HIAA) excretion was $660\text{--}3000 \mu mol/24 \text{ h}$ ($126\text{--}572 \text{ mg}/24 \text{ h}$).

Laparotomy on 30 June 1978 revealed bilateral ovarian masses. The liver appeared free of tumour. Hysterectomy and bilateral salpingo-oophorectomy were performed. The right ovarian lesion was a dermoid cyst. The left ovarian tumour was a yellow-white encapsulated bosselated fibromatous mass $12 \times 9 \times 8 \text{ cm}$ with the typical histological appearance of a carcinoid tumour showing positive diazonium and argentaffin reactions (figure). No

Solid alveolae and trabeculae of fairly uniform polyhedral cells, with ovoid central nuclei, containing argentaffin granules. Masson-Fontana argentaffin reaction $\times 80$ (original magnification).

metastatic tumour was found in liver biopsies. Postoperative recovery was uneventful. Subsequent 5-HIAA excretion was in the normal range. Her dyspnoea, ankle oedema, and pansystolic murmur, however, persisted. Cardiac catheterisation on 25 October 1978 showed a gradient of 5 mm Hg across the tricuspid valve and a peak right atrial pressure of 15 mm Hg . Cardiac surgery on 5 February 1979 confirmed tricuspid regurgitation. The tricuspid valve cusps were thickened but the valve ring was not dilated. The pulmonary valve cusps were thickened but not causing significant stenosis. The tricuspid valve was replaced with a size 27 Carpentier-Edwards pig heterograft. Histologically the thickened valves showed subendothelial hypercellular plaques. She made an uneventful recovery and was discharged after 10 days. She has remained well on mild diuretic therapy.

Comment

Only about 50 primary ovarian carcinoid tumours have been recorded. They are associated with carcinoid syndrome in under half of the cases and even less commonly with valvular dysfunction.¹ The possibility that a woman with the carcinoid syndrome is harbouring an ovarian carcinoid should be considered, however, and a pelvic mass looked for. Primary and intraovarian metastatic carcinoid are indistinguishable on purely morphological grounds, but the exclusion of gastrointestinal carcinoid at laparotomy and the presence of the contralateral dermoid cyst is presumptive evidence that our patient's ovarian carcinoid was primary. The tricuspid valve dysfunction is attributable to the subendothelial plaque-like thickenings noted in the excised valve. We think that such changes result from the healing of repeated endothelial injury initiated by bradykinin release from the carcinoid tumour.² This process appears to favour development of tricuspid incompetence and pulmonary stenosis.³

In some patients with carcinoid heart disease removal of a solitary ovarian carcinoid has resulted in rapid resolution of cardiac failure.⁴ Intractable heart failure, however, has been successfully treated by tricuspid valve replacement.⁵ Our case appears to be only the second such case reported. It affirms the view that if heart failure persists after removal of the ovarian primary valve replacement permits complete restoration of health. Tricuspid and pulmonary valve replacement should perhaps be considered more often in the metastatic carcinoid syndrome to relieve the resultant incapacity of the cardiac lesion.³

¹ Fox H, Langley FA. *Tumours of the Ovary*. London: William Heinemann, 1975.

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