Platelet count/spleen diameter ratio as a predictor of oesophageal varices in alcoholic cirrhosis

We read with great interest the article by Giannini et al (Gut 2003;52:1200–5) regarding platelet count/spleen diameter ratio as a non-invasive parameter to predict the presence of oesophageal varices in patients with liver cirrhosis.1 In patients with liver disease due to alcohol, platelet count is reduced due to the myelotoxic effect of alcohol. In the study, only 16.5% (24/145) of patients had liver cirrhosis due to alcohol. In the UK, alcohol is the commonest cause of liver cirrhosis.

We retrospectively studied endoscopy, haematology, and radiology reports of 40 patients who had been treated for alcohol induced cirrhosis at Homerton Hospital, London. Of these, 30 had oesophageal varices at endoscopy and 10 did not. The platelet count/spleen diameter ratio was calculated within two months of endoscopy.

The median platelet count/spleen diameter ratio in patients with varices was 537 (range 371–670) and with no varices 2229 (range 1542–3174). A platelet count/spleen diameter ratio of <909 had 100% sensitivity and specificity for the prediction of oesophageal varices in patients.

We have shown that this non-invasive method of predicting the presence of oesophageal varices through platelet count/spleen diameter ratio is reproducible in alcoholic cirrhosis patients.

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Reference


Diagnosis of hereditary non-polyposis colorectal cancer (HNPPC)

The paper addressing the role of monogenic inheritance in the aetiology of colorectal cancer highlights the importance of achieving a meaningful working diagnosis of hereditary non-polyposis colorectal cancer (HNPPC) (Gut 2004;53:115–22). The diagnosis of HNPPC may be achieved in two ways:

(1) by equating the Amsterdam criteria with a clinical diagnosis,
(2) by compiling a comprehensive set of clinical, pathological, and molecular features that would together support the diagnosis of a specific condition caused by a germline mutation in a DNA mismatch repair gene such as hMLH1 or hMSH2.

It is clear that there is potential for considerable confusion if the label HNPPC is used in these very different ways.

The original Amsterdam criteria were not developed to serve as the diagnostic criteria for HNPPC but merely to introduce a uniform approach to the selection of families for collaborative studies.1 It was originally considered that the criteria would be relatively specific rather than sensitive. However, colorectal cancer is a common disease, and the finding of three close relatives affected by bowel cancer within a single large family would not necessarily equate with a specific autosomal dominant disorder, even if one were sure that the subjects happened to be aged below 50 years. Ponz de Leon and colleagues (Gut 2004;53:115–22) showed in table 3 that families meeting the Amsterdam criteria but having cancers that are DNA microsatellite stable do not display the clinical features of HNPPC (see below). This is not altogether surprising. In fact it was shown nearly 10 years ago that colorectal cancers in such Amsterdam criteria positive kindreds were often microsatellite stable and that the clinical and pathological features of these families were unlike HNPPC (see below).2 Of course, the latter findings do not preclude a genetic basis for such clustering of colorectal cancer within a family.

The diagnostic features of HNPPC have accumulated and been refined over time. HNPPC is now defined by a set of clinical, pathological, and molecular features that encompass: a family history of colorectal cancer, a particular spectrum of extracolonic neoplasms, multiple colorectal neoplasia, early onset neoplasia, particular histological features among colorectal cancers, the presence of DNA microsatellite instability, loss of expression of DNA mismatch repair proteins as shown by immunohistochemistry, and a germline mutation in a DNA mismatch repair gene.3 It may not be possible to identify the germline mutation in all families, even when cancers show evidence of deficient DNA mismatch repair. This is merely the result of technical limitations which should not preclude a diagnosis when other features are met. Close mimicry of HNPPC may occur when hMLH1 has been methylated, perhaps through a familial predisposition to this chemical modification of DNA.4 In the latter instance colorectal cancers may develop in a background of multiple hyperplastic polyps.5

Now that there is international agreement that the term HNPPC equates to a specific clinicopathological entity,6 there would seem to be little merit in applying the diagnosis when only the limited set of clinical features encompassed by the Amsterdam criteria is met. Reporting of a family history of colorectal cancer has been shown to be unreliable.7 What would we think of a judge who chose to base his verdict only on hearsay and rumour and to ignore all evidence of a scientific nature? Why should a family be burdened unnecessarily with the label HNPPC and all its ramifications and how may epidemiological research be advanced by the application of a vague and unreliable diagnostic label?

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Author’s reply

In reply to the letter of Dr Jass we would like to make the following points.

We agree with Dr Jass that since the new discoveries and advances in our knowledge of hereditary non-polyposis colorectal cancer (HNPPC), the diagnosis of the syndrome has become a matter of conscience. The Amsterdam clinical criteria are useful but not definitive in the diagnosis of the disease, and other parameters (pathological, biological, molecular) must be taken into account. Besides, family history is not reliable in every case. So, what should we do?

We believe that, as a first step, the classical clinical approach of tracing a genealogical tree focused on malignancies in the family should be pursued for each patient. We attempt to estimate the probability of disclosing an hereditary form of colorectal cancer. In doing this, we do not label a family as HNPPC on clinical grounds alone, but we think that such families should be studied and followed with particular attention to obtain other clues and proof of the syndrome and to provide appropriate counselling measures.

From an epidemiological point of view, we agree that estimation of the frequency of the syndrome based on clinical criteria should be considered with caution, but it is the only practical way. When a population approach was used, defining the microsatellite status of all registered tumours in a period and then searching for constitutional mutations in patients with unstable tumours, as high as 2.7% of patients with colorectal tumours were positive for unstable tumours, as high as 2.7% of patients with colorectal tumours were labelled as HNPPC.8 These values are similar to those obtained with clinical criteria (Gut 2004;53:115–22) although not confirmed in other settings.9 Therefore, we believe that it is not a burden for the family if we choose to follow them with special care. Moreover, it has been demonstrated that active follow up can reduce the number of newly developed carcinomas in families with HNPPC (not all with a molecular diagnosis) and reduce cancer mortality.10
Bone density loss in Crohn’s disease: role of TNF and potential prevention by bupropion

We note with interest the demonstration by Card et al that the increased hip fracture rate in Crohn’s disease (CD), and by inference the diminished bone density commonly noted in CD, is only to a minor degree secondary to iatrogenic corticosteroid use (Cochrane Database Syst Rev 2003;34:CD003349). The subject of bone mineral density loss in CD has been recently reviewed; tumour necrosis factor α (TNF-α) is suspected of being an important mediator of this loss. Evidence has been published for localised overproduction of TNF-α being largely responsible for the bone loss seen in rheumatoid arthritis,1 psoriatic arthritis,2 multiple myeloma,3 hip prosthesis loosening,4 periodontal disease,5 and spondyloarthopathies.6 Anti-TNF-α antibody has been shown to slow the bone loss of spondyloarthopathy and rheumatoid arthritis.7,8

We have found that the commonly used antidepressant bupropion can induce remission in CD9,10 and have found that bupropion can lower serum C-reactive protein levels.11 It is possible that bupropion is effective and in lower TNF-α levels. If bupropion is found to be effective in CD and to lower TNF-α levels in large trials, it might be considered for use in bone loss and osteoporosis, in CD or otherwise.

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References

Sporadic duodenal adenoma and colorectal neoplasia

We read with great interest Murray et al’s article concerning the association between sporadic duodenal adenoma and colorectal neoplasia (Gut 2004;53:261–5).

We have also noted a lack of published literature regarding sporadic duodenal adenomas, with the exception of the two reports identified by the authors,1,2 as well as a more recent case series,3 and therefore welcome the addition of their large case series and comparison group. Although there is the potential for bias in the detection of colorectal neoplasia in their duodenal adenoma cases, as the indications for colonoscopy were somewhat different between cases and controls (with almost one third of cases of duodenal adenomas being endoscoped for investigation of anemia or melena), overall their data support a clinically relevant association between duodenal and colonic adenomas.

These results are corroborated by our own recent experience at Leeds General Infirmary where we have studied the natural history of duodenal adenoma. We also examined histopathology records and case notes for patients with sporadic duodenal adenomas between 1990 and 2002 (excluding familial adenomatous polyposis and hereditary non-polyposis colorectal cancer). We identified 35 cases; 16 males and 19 females (mean age 65 years). The majority of these were noted incidentally at upper gastrointestinal endoscopy or endoscopic retrograde cholangiopancreatography, with a similar range of indications for examination as those noted by Murray et al. Using the criteria stipulated by the authors, 25 (71%) of the adenomas were advanced. Of the 35 patients in our series, 11 underwent colorectal examination. This revealed a synchronous colonic adenoma in four patients (36%), three of which were tubulovillous adenomas and therefore advanced according to the aforementioned criteria, and in the fourth a tubular adenoma. Our findings compare with a reported rate of colonic neoplasia of 25.5% in a series of 1000 consecutive unselected patients attending the Leeds General Infirmary for colonoscopy.4

Unfortunately, Murray et al do not follow up on the follow up data relating to the duodenal adenomas in their series. We have clinical data for all our cases, with a median duration of follow up of four years. Seventeen of the 35 duodenal adenomas were removed (six surgically, four by endoscopic mucosal resection (EMR), three snared, three during biopsy, and one by argon photocoagulation), and of these, two patients had a recurrence (one with EMR, the other kept under surveillance), and all were alive at the time of review (median time from diagnosis 58 months). Among the 18 patients who had no therapy for their polyp, 10 died (median length of follow up 43 months). One patient who had a tubulovillous adenoma with high grade dysplasia developed a 3 cm adenocarcinoma of the first part of the duodenum five months following initial diagnosis and underwent a Whipple’s procedure but died 12 months later from metastatic disease. The other patients died from unrelated causes.

Despite published literature that suggests duodenal polyps have no prognostic importance,5 we believe that the optimal management of duodenal adenomas is early excision and follow up. We also concur that there is an association between sporadic duodenal adenomas and colonic neoplasia, and agree entirely that all patients found to have sporadic duodenal adenomas should undergo colonoscopy. However, owing to reasons of study size and bias in the comparison groups, the magnitude of this association cannot be accurately determined. Furthermore, the reasons for this association are as yet unclear, and...
molecular studies are required to further investigate.

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References

Dysbiosis as a prerequisite for IBD
We thank Dr Szilagyi for his very interesting comments in his letter regarding dysbiosis in inflammatory bowel disease (IBD).1 The main question remains as to why beneficial bacteria such as bifidobacteria might be lacking in IBD (Gut 2004;53:1-4). Dr Szilagyi describes an interesting hypothesis of colonic prebiotic deficiency as a possible mechanism for dysbiosis. A suggestion is made that this deficiency could be linked to increased proximal small intestinal permeability with enhanced absorption of prebiotic substrate, causing a relative deficit of prebiotics distally. Certainly, the phenomenon of increased small bowel permeability has been documented in Crohn’s disease; its importance in ulcerative colitis is less clear however. As lactulose is not a major component of the normal human diet, long term epidemiological dietary trends should also have to be consistent with a significantly decreased intake of common prebiotic substrates, if this hypothesis is correct. Unfortunately, there is currently little clinical evidence to support or refute this theory, as dietary studies in IBD have been subject to many biases inherent in their study design.

Bifidobacteria are strongly glucidolytic and show nearly no growth in the absence of fermentable sugars or polysaccharides. One group of good substrates are mucins, which are often increased in Crohn’s disease. Perhaps differences in ease of glycosylation between some substrates affect the ability of the flora to metabolise them. This has not been well studied in IBD. There are also likely to be other influences on the host’s dominant flora, including genetic factors. Observations among some of our healthy cohorts with low levels of bifidobacteria have revealed highly variable responses of bifidobacterial counts to prebiotic treatments. Whether a poor response might represent a risk factor for IBD is also an interesting question.

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The other point to note is the fact that co-infection with HCV and HBV is common in IVDAs but less prevalent in HD patients. This interesting point may highlight evidence of another difference in the main transmission route of infection in these two populations.

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References

COX 2 inhibition and bowel strictures
The letter by Mir et al (Gut 2004;53:154) caught our attention and seems to have caught the editorial staff dozing. Mir et al present a patient who had been regularly taking conventional non-steroidal anti-inflammatory drugs (NSAIDs) for 26 years for axial spondylarthropathy and ares the presence of distal ileal stricture and ulceration solely to the use of cyclooxygenase 2 (COX 2) selective inhibitor that had been taken for two years. The differential diagnosis of ileal lesions in spondylarthropathy is quite clear. Firstly, as the authors themselves stated, strictures are associated with long-term use of conventional NSAIDs. The 26 year use of NSAIDs by the patient is most significant. While such lesions are usually more proximal, slow release formulations of NSAIDs can give rise to distal disease such as in this special circumstance. The authors do not specify if this is the case. NSAID induced ulcers, when established, may take years to heal, such that the two year time lag between stopping NSAIDs and clinical symptoms is not unexpected.

Secondly, spondylarthropathy is itself associated with ileitis in 30-70% of cases, irrespective of NSAID intake. Most cases are asymptomatic but some cases present to stricturing disease. De Keyser et al, in particular, have made a case for spondylarthropathic ileitis being a form of subclinical Crohn’s disease. Finally, axial spondylarthropathy may be an extraintestinal manifestation of 5-10% of cases of inflammatory bowel disease. It is difficult to exclude this as the cause of both the recent ulceration and

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stricturing because histology does not always show typical (for example, granulomatous) changes. To date, the only small bowel pathology reported from selective COX 2 inhibition (or absence) is of ileocecal inflammation and perforation (not stricturing) in animal studies. Hence, while it is a remote possibility that COX 2 inhibition may have given rise to the symptoms in this patient, these are far more likely to be due to other factors.

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References

Intravenous pulse cyclophosphamide therapy in Crohn’s disease and ulcerative colitis

The management of refractory severe inflammatory bowel disease (IBD) is still unresolved. We read with interest the article by the authors on the safety and efficacy of intravenous pulse cyclophosphamide in acute severe IBD unresponsive to “conventional” treatment. It is also recommended as a first-line adjunct to, or replacement for, systemic corticosteroids in the treatment of IBD.

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Reference

CORRECTION

In the paper by Finotto et al (Gut 2004;53:392–400), one of the author’s names appeared incorrectly. The author name which was printed as R Khosravi-Far should have appeared as R Khosravi-Far.

NOTICES

British Society of Gastroenterology
Paul Brown Travel Fellowships

The Paul Brown Travel Fellowships are awarded by the Endoscopy Committee of the BSG. They are intended to assist trainee gastroenterologists and established consultants in visits to units outside the United Kingdom for specialist experience and training in endoscopy.

Specialist registrars who have not achieved their CCST are expected to have the approval of their Postgraduate Dean and their Regional Training Director when they apply for a Travel Fellowship. Applications are expected to provide confirmation that they have been accepted for training in the unit that they wish to visit.

Successful applicants will be expected to provide a brief written report to the Endoscopy Committee of the outcome of their visit.

Application forms are available from the British Society of Gastroenterology Office, 3 St Andrew’s Place, London NW1 4LB. Email: bsg@mailbox.ulcer.ac.uk

8th Southeast European Symposium of Paediatric Surgery

The 8th Southeast European Symposium of Paediatric Surgery will focus upon ‘Infectious Problems in Paediatric Surgery.’ The event will be held between 24–25 September 2004, at the University of Graz, Austria. For further information, please contact: Professor M E Hollwarth, Department of Paediatric Surgery, Medical University of Graz, Austria, Auenbruggerplatz 34, 8036 Graz, tel: + 43 316 385 3762; fax: tel: + 43 316 385 3775; e-mail: kinderchirurgie@uni-graz.at.

World Congress on Gastrointestinal Cancer

The World Congress on Gastrointestinal Cancer will be held in Barcelona, Spain, on 16–19 June 2004. For further information, please contact Coleson Chase (tel: +1 770 751 7332; fax: +1 770 751 7334; e-mail: c.chase@imedex.com; website: www.imedex.com/calendars/therapeutic.htm).

12th European Symposium on Neurogastroenterology and Motility

The 12th European Symposium on Neurogastroenterology and Motility will be taking place at Robinson College, Cambridge, UK. The symposium will be taking place on 15–19 September 2004.

On Wednesday 15 September, there will be a postgraduate teaching day. This will cover established and evolving assessments of esophageal, gastric and intestinal function, visceral sensitivity and brain responses. Basic science techniques including electrophysiology, imaging of gut movements and neural activation will be covered in the afternoon. Finally there will be a session on GI pharmacology covering cytokines, capsacin and tachykinins.

On Thursday 16 September through to Saturday 18 September midday, the main meeting will be held. This will include symposia, oral free papers and poster rounds. The symposia will be designed to move from basic science to clinical practice and will include sessions on stress and the gut, appetite and obesity, serotonin and inflammation, and inflammation and GI motility. There will also be state of the art lectures and prize presentations.

For registration and further information, please see the website www.neurogastro.org and follow links for ‘12th European Symposium on Neurogastroenterology and Motility.’ Please contact the conference organizers at: Conflex, PO Box 21, Rottingdean, East Sussex, BN2 4WZ (tel: +44(0)1273 302200; fax: +44(0)1273 302334; e-mail: conferex@easynet.co.uk).