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 myeloctic 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 (HNPCC)

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 (HNPCC) (Gut 2004;53:115–22). The diagnosis of HNPCC 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 MLH1 or MSH2.

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

The original Amsterdam criteria were not developed to serve as the diagnostic criteria for HNPCC 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 of the subjects happened to be aged below 50 years. Ponz de Leon and colleagues (Gut 2004;53:115–22) show in table 3 that families meeting the Amsterdam criteria but having cancers that are DNA microsatellite stable do not display the clinical features of HNPCC (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 frequently DNA microsatellite stable and that the clinical and pathological features of these families were unlike HNPCC (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 HNPCC have accumulated and been refined over time. HNPCC 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 neoplasm, 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.1 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 even when other features are met. Close mimicry of HNPCC may occur when hMLH1 has been methylated, perhaps through a familial predisposition to this chemical modification of DNA.3 In the latter instance colorectal cancers may develop in a background of multiple hyperplastic polyps.

Now that there is international agreement that the term HNPCC equates to a specific clinicopathological entity,1 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.4 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 HNPCC 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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References


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 (HNPCC), 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 proband attempt to estimate the probability of disclosing an hereditary form of colorectal cancer. In doing this, we do not label a family as HNPCC on clinical grounds alone, but we think that such families should be studied after 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 followed them with special care. Moreover, it has been demonstrated that active follow up can reduce the number of newly developed carcinomas in families with HNPCC (not all with a molecular diagnosis) and reduce cancer mortality.
Bone density loss in Crohn’s disease: role of TNF and potential for 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 (Card 2003;53:231–5). The subject of bone mineral density in CD has been recently reviewed; tumour necrosis factor (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, psoriatic arthritis, multiple myeloma, hip prosthesis loosening, peridontal disease, and spondyloarthropathies. Anti-TNF-α antibody has been shown to slow the bone loss of spondyloarthropathy and rheumatoid arthritis.

We have found that the commonly used antidepressant bupropion can induce remission in CGP1 and have found that bupropion can 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.

References

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). The main question remains as to why beneficial bacteria such as bifidobacteria might be lacking in IBD patients. McBurney describes an interesting hypothesis that dysbiosis may be a risk factor for IBD. If this hypothesis is correct, the relative deficit of prebiotics distally is quite clear. Firstly, as the authors themselves stated, strictures are associated with long term anti-inflammatory drug use.

While such lesions are usually more proximal, distal complications 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

The other point to note is the fact that coinfection 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 (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 ascribe the presence of distal ileal strictureing and ulceration solely to the use of the non-steroidal anti-inflammatory drug (NSAID) 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, distal complications may be an extraintestinal manifestation of this process in spondylarthropathy. 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 self-limited but some cases may be associated with 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 ileocaecal 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 lesions 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 Stallmach and colleagues on the safety and efficacy of intravenous pulse cyclophosphamide in acute steroid refractory IBD (Gut 2003;52:377–82). In common with other disease, the aims of therapy in IBD fall into three categories:

(a) induction of remission;
(b) maintenance of remission; and
(c) prevention of relapse, all of which should be undertaken with minimal mortality and morbidity either from the disease itself or from therapy.

Based on previous observations of improvement in autoimmune diseases (that is, vasculitides), cyclophosphamide can be a primary cytotoxic drug: pulse intravenous cyclophosphamide is probably equally effective oral cyclophosphamide in inducing remission and this remission is usually maintained by continuing cyclophosphamide for 3–6 months before changing to a combination of other oral therapies. Therapy must be continued to prevent relapse and for maintenance. 1

We would like to report on some other cases. In our cohort, we included patients with Crohn’s disease (CD) and ulcerative colitis (UC). Four patients with CD and four with UC were diagnosed according to standard criteria. They did not respond to conventional therapy and therefore we administered pulse cyclophosphamide therapy monthly (for six months, 800 mg each time). Most patients went into remission after the second/third cyclophosphamide pulse. Disease activity decreased, there were no side effects, no toxicity, and all patients achieved long lasting remission. For maintenance, patients with CD were treated with methotrexate (10 mg/week) and patients with UC were given azathioprine (100 mg/day). Remission appears to be stable.

These findings suggest that aggressive immunosuppressive therapy may be useful in some refractory patients, and further controlled studies should be considered in order to fully evaluate this type of treatment as a potential therapy in IBD.

IBD continue to pose a challenge to clinicians. Over the past few years there have been significant advances in our understanding of pathogenesis and treatment. These advances will hopefully lead to more specific and targeted treatments, with consequent improvement in clinical outcomes. Intravenous pulse cyclophosphamide may be a safe and effective treatment in patients with 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 name’s appeared incorrectly. The author name which was printed as R Khosravi-Fahr 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 CCT are expected to have the approval of their Postgraduate Dean and their Regional Training Director when they apply for a Travel Fellowship. Applicants 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

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: Professor M E Hollworth, Department of Paediatric Surgery, Medical University of Graz, Austria. For further information, please contact: Professor M E Hollworth, 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.

Advances in the Inflammatory Bowel Diseases

The conference for advances in the inflammatory bowel diseases will be held in Chicago, Illinois, USA on 8–9 October 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 15–18 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, capsaicin 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: Confrex, PO Box 21, Rottingdean, East Sussex, BN2 4WZ (tel: +44(0)1273 302200; fax: +44(0)1273 302334; e-mail: confrex@easy.net.co.uk).

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