PostScript

MATTERS ARISING

Role of HLA genes in familial spondyloarthropathy

Said-Nahal and colleagues report an intriguing finding of an association with HLA-DR4 independent of B27 in families with ankylosing spondylitis (AS),[1] a finding highlighted by an accompanying editorial.[2] The approach of studying B27 positive and B27 negative haplotypes may prove powerful in identifying further cis or trans encoded genes involved in AS. However, the reported association of DR4 with AS is quite a surprising finding given that no difference was noted in B27-DR4 haplotype frequencies in patients and ethnically matched healthy controls. Many previous studies have not reported any such association,[3–9] including a similar preliminary study by the same authors.[10] Although these studies were mainly case-control studies, population stratification is highly unlikely to cause a false negative finding if the effect size of the reported association with DR4 is as high as Said-Nahal and colleagues describe.

We are concerned that both the family and case-control results are biased by the statistical approach employed. Multicase families were used in the study, yet a form of transmission test for linkage disequilibrium (TDT) was used[11] which is only suitable for single affected families, and is a valid test only of linkage, and not of association, when applied to multicase families.[12] Therefore the TDT p values reported in tables 5, 6, and 7 of Said-Nahal's paper[1] for the patients and unaffected B27+siblings do not reflect association alone, and will be affected by the strong linkage of the major histocompatibility complex with AS, and also probably by bias due to the different numbers of parent-case trios selected from different multicase families. Forms of TDT are available for general pedigree families and are more powerful than the TDT employed in this study (for example, see Clayton[13]). These biases also apply to the case-control component of the study (results presented in tables 2, 3, and 4) where it appears that related cases were employed. If so, these results also reflect both linkage and association. We would be interested to see the results of a further analysis allowing for these considerations.

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Authors' reply

We thank Dr Brown and colleagues for their interest in our recent publication.[1] In their comment, they raise a number of questions which we have tried to address. The reported effect of HLA-DR4 appears to be independent of linkage with HLA-B27, meaning that it is not accounted for by linkage disequilibrium with HLA-B27. However, this observation does not necessarily imply that it is independent of HLA-B27, considering that HLA-B27 was almost constant among patients with familial spondyloarthropathy (SpA) (in other words, the DR4 effect may combine with the B27 effect, rather than being truly independent).

In our study the presence of DR4 increased the risk of developing SpA among HLA-B27+ siblings (odds ratio = 2.8, 95% confidence interval 1.4 to 5.7), which is far less than the effect of HLA-B27. This result is based on HLA-DRB1 typing of 185 patients and of 71 healthy siblings. Only one of the previous association studies cited by Brown and colleagues had comparable sample size.[2] Even in that study, however, no more than two thirds of the patients belonged to multiplex families and their controls were from the general population. The DR4 effect may be specific for familial disease, requiring the use of healthy siblings from multiplex families as B27+ controls, to demonstrate an association. Given these considerations, previous studies cited by Brown and colleagues were presumably underpowered to detect a DR4 effect. This was obviously the case with our preliminary report analysis[3] which concerned only 13 of the 70 multiplex families included in the present publication.

We used Spielman's transmission disequilibrium test (TDT) to examine whether the transmission of HLA alleles to patients differed from random.[4] As opposed to association studies, these statistics are not exposed to population stratification bias. Yet, it was originally designed to test the transmission of biallelic markers in single families, and we agree with Brown and colleagues that its results in multiplex families need to be interpreted with caution. Hence linkage of the disease examined with a locus in a region might interfere with the results of a TDT applied to another locus in the same region, which might wrongly be interpreted as evidence for meaningful association with particular markers. In the specific case of HLA region such risk is even present when using single-affected families because of the strong linkage disequilibrium between alleles at separate loci. Such bias is notably illustrated in our study by the influence of linkage disequilibrium with HLA-B27, which affected the transmission of several alleles at HLA-A, C, and DR loci, when studying all haplotypes together. However, when the analysis was confined to the non-B27 haplotypes, all these alleles appeared to be randomly transmitted, except for HLA-DR4. Such unique disequilibrium strongly suggested that HLA-DR4 itself contributed to SpA predisposition, albeit as already discussed in our publication, we could not entirely rule out that it was secondary to a preferential association between SpA and another major histocompatibility complex gene.

Additional studies will clearly be needed to confirm our results. However, according to our present data, we would have needed to type 50 more multiplex families to reach a power sufficient to demonstrate a DR4 effect, by using statistics developed for general pedigree families as suggested by Brown and colleagues.[5]

Finally, regarding the case-control component of the study, we disagree with Brown and colleagues that our results reflected both linkage and association, because any HLA-B27 haplotype identified in a family was counted only once, even if present in several patients.

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BOOK REVIEWS

Disease modifying therapy in vasculitides

Eds C G M Kallenberg, J W Cohen Tervaert. (Pp 216; Euros 110.) Basel: Birkhauser Verlag, 2001. ISBN 3-7643-6147-6.

The target readership for this slim book on the treatment of vasculitis is identified from the outset. Only one chapter is on standard regimens based on cyclophosphamide and steroids. There is widespread recognition of the potential toxicity of standard treatment, especially with prolonged usage. Thus two more chapters deal with alternative approaches to conventional immunosuppressive drugs, discussing methotrexate—which is in widespread use—and the newer agents, mycophenolate mofetil and desoxyspergualin. Five subsequent chapters deal with more experimental treatments, ranging from tumour necrosis factor blockade through intravenous immunoglobulin to various forms of anti-T cell treatment.

This is thus mainly an update for those specialists already familiar with the standard treatment for vasculitis and all its problems. Minor but important aspects of disease control, such as control of blood pressure, renal function, and even psychological support, are not considered as the editors are dealing only with disease modifying approaches. As such, this is a timely review of knowledge in a rapidly advancing field which will also provide good reading for those who see vasculitis less frequently. It should convince them that there are alternative approaches for relapsing or resistant cases, even if they have received full courses of standard treatment. Referral of cases to specialist centres may even be encouraged, which is probably the only way to obtain a sufficient pool of patients to conduct the necessary studies that will advance knowledge in these rare but serious disorders.

The chapters have been written by those at the forefront of their fields who have largely discussed the benefits and the risks of the treatments they describe. This will help clinicians faced with difficult treatment choices to make decisions relevant to their individual patients. The idea of a single treatment for a diverse set of diseases that can affect any organ is no longer appropriate. Different stages of disease require different approaches. In the future, treatment may be further individualised according to pathogenesis, as suggested by the chapters on the virus related systemic vasculitis and the prevention of relapse in ANCA related small vessel vasculitis. The last is particularly relevant, both because ANCA associated vasculitides form a major part of the systemic vasculitis seen in Europe/America and because relapse is one of the major problems now that initial remission can be induced in at least 90% of patients. Movement in this field in the past 10 years has occurred and the reader is given clear indications of the current excitement in this steadily progressing area.

Paul A Bacon

Vasculitis

Eds G V Ball, S L Bridges, Jr. (Pp 601; £110.) Oxford: Oxford University Press, 2002. ISBN 0-1926-3053-9.

Seventy contributors collaborated with the editors to produce this work on vasculitis and vasculopathies that may mimic inflammatory vessel diseases. The first four chapters deal with classification of vasculitic syndromes and basic scientific information on hypersensitivity, endothelial cell biology, and theories about the pathogenesis of vasculitis. The next seven chapters summarise the clinical manifestations that are common to vasculitides such as cutaneous and mucous membrane, ophthalmological, pulmonary, neurological, and renal manifestations as well as digital ischaemia. Imaging techniques used for the diagnosis of vasculitis are the subject of two chapters. All the vasculitic diseases and syndromes, as well as mimicking diseases and thrombotic syndromes, are then covered in 26 chapters. About half of the contributors are from the United States and the other half from Europe, Asia, the Middle East, and Africa. These authors cover the many specialties in internal medicine necessary to collaborate on the diagnostics of vasculitides such as rheumatology, radiology, immunology, dermatology, nephrology, pulmonology, and others.

The target readership is doctors of many different disciplines, but the book may also be used by medical students who need more information than most ordinary textbooks can offer. The main emphasis has been placed on the various clinical syndromes and thus will be of long term interest to readers. Less importance has been given to the more theoretical topic of immunopathogenesis, mainly because such theories are constantly changing as cell biology and molecular biology techniques used for the study of patients give rise to many new data and ideas every day. Nevertheless, the chapters covering the more theoretical aspects of vasculitis contain most of the current theories about the immunopathogenesis and immunopathology for vasculitides.

The general outline is logical, but the different chapters are very unevenly and differently structured, indicating that each author has been left the freedom to organise the individual chapter. Some chapters are nicely tabulated and have many good illustrations, although most of the pictures of clinical manifestations and histopathology are in black and white in the text. The editors have tried to compensate for this by adding 13 pages of full colour illustrations in the middle of the book. It would certainly have been preferable to place these full colour illustrations adjacent to the text where they belong. Most chapters have many references that will allow readers to find original information. The chapters covering strategies of diagnosing vasculitis within the spectrum of diseases in adults and children are somewhat difficult to read and contain only one algorithm to visualise a useful diagnostic approach. In addition, it is unfortunate that childhood vasculitides are classified differently from those of adult patients. There ought to be general agreement that the Churg-Strauss syndrome, Wegener's granulomatosis, and primary vasculitides of the central nervous system belong to small vessel vasculitides also in children. Tables to summarise diagnostic strategies would have made the chapters more readable. The chapters on imaging techniques are really excellent and well illustrated, and the epidemiology of the vasculitides is well covered. More illustrations would have added value to the chapter on assessment of disease activity and damage.

It is impossible to avoid rather large overlaps between the different topics of the book, but this allows the reader to concentrate on a given topic and still get most of the necessary information in one chapter. There is a good index but many of the abbreviations used throughout have not been listed in the section on abbreviations at the beginning. Generally, the content is comprehensive and there are no major omissions. It is not quite obvious why polyarteritis nodosa is covered in the same chapter as microscopic polyangiitis, as these topics are clearly separated both in current publications and in the authorship of this chapter. The fact that both the pathogenesis and the treatment strategy are usually different would also indicate that separate chapters would have been more logical. In some of the illustrations detailing events in the pathogenesis of Wegener's granulomatosis a number of abbreviations have been used which are not explained to the reader. Treatment of this disease is well covered, although several of the more recent treatment modalities in use are not mentioned. The chapter on Behçet's disease is excellent, but the illustration of the geographical distribution of the disease cannot be read owing to the use of very similar grey scale spectra. A non-specialist reader will find the chapter on the immunogenetics of Behçet's disease very complicated. The difficult topic of central nervous system vasculitis is very explicit and clear considering the complexity of this clinically challenging diagnostic field. It is not quite clear why the antiphospholipid syndrome has been included in a book on vasculitis, but the topic is well covered and illustrated.

The less well structured chapters and the slightly deficient illustrations and explanation of abbreviations may be because this is a first edition, but the book probably lives up to the expectations of the authors and the readership, and can fill a gap in the market.

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