

Henoch-Schönlein purpura: recent advances

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ABSTRACT

Recent developments in relation to Henoch-Schönlein purpura (HSP) include:

a) a proposed new classification of childhood vasculitides including new classification criteria for HSP; b) the identification of various, potentially important, genetic polymorphisms in HSP that may be relevant in terms of predisposition to or protection from complications; c) evidence that prophylactic steroid at the onset of disease does not protect against renal or gastrointestinal complications but does seem to have beneficial effects in treating them.

Introduction

Henoch-Schönlein purpura (HSP), the most common systemic vasculitis of childhood, has an incidence of 10-20 per 100000 (1, 2) and although, in general, it has a benign outcome there is a significant morbidity associated with gastrointestinal disease in the short term and nephritis in the long term. Estimates of end stage renal failure in unselected patients vary but are of the order of 2 per cent (3) although this is greater in those with significant renal involvement. In adults the incidence is far lower, reportedly of the order of 0.12 per 100000 (4), but there appears to be greater morbidity in relation to renal involvement compared to children with the need for more aggressive therapy although the prognosis is still, in general, favourable (5, 6).

A substantial literature concerning HSP exists covering epidemiology, pathogenesis, clinical manifestations, diagnostic features, treatment options and long term outcome (7, 8) and it is not the purpose of this mini-review to reiterate this material. On the contrary, a number of selected areas will be addressed that are of recent topical interest.

Classification

The classification of vasculitides has, for many years, been a contentious issue in adult medicine let alone paediatrics. The American College of Rheumatology (ACR) criteria (9), the most widely used classification criteria, had

a number shortcomings from a paediatric perspective although were used by paediatricians for classification purposes in childhood. Similarly, the Chapel Hill Consensus Conference (CHCC) proposal for a standard nomenclature of systemic vasculitis (10), although not determining criteria for classification, had problems when applied within its terms of reference to paediatric vasculitis. Various attempts by paediatricians to overcome these difficulties resulted in a number of proposed classifications although none proved to be entirely satisfactory. On this background a recent attempt was made to develop a general classification for vasculitis observed in children as well as specific criteria for individual types of vasculitis. This took the form of a Consensus Conference which was held in Vienna in 2005 under the auspices of the European League Against Rheumatism (EULAR) and the Paediatric Rheumatology European Society (PReS) with the participation of the ACR and the European Society for Paediatric Nephrology (ESPN). A consensus was reached and reports concerning the suggested criteria were published in 2006 (11, 12). To fulfil the classification criteria for HSP by the existing ACR criteria (13), two of the following four criteria were required: age less than 20 years, palpable purpura, abdominal pain and vessel wall granulocytes on biopsy. The proposed new classification deleted the age criterion, made palpable purpura mandatory, clarified the characteristic biopsy findings substituting predominant IgA deposition in any biopsy for the ACR criterion of vessel wall granulocytes and since arthritis is very common in childhood HSP it was also included as a criterion. The proposed new classification criteria were that at least one of the following four should be present: diffuse abdominal pain, any biopsy showing predominant IgA deposition, arthritis or arthralgia, renal involvement (any haematuria \pm proteinuria) in the presence of palpable purpura which was a mandatory criterion.

The next step will be to validate these criteria using patient and control groups.

Genetic polymorphisms

Recent data concerning genetic polymorphisms and HSP are of interest and may have important implications. These have recently been reviewed by Brogan (14) and a resumé of this paper follows. A study of Israeli children revealed that familial Mediterranean fever (FMF) genotypes (mutation in MEFV) were more prevalent (10%) in HSP (15), a finding also found in Turkish children (16). This is of interest in view of the well known association between FMF and HSP (17). Other genetic factors/polymorphisms possibly predispose to renal involvement in HSP including positivity for HLA-B35 (18), polymorphisms in PAX2 (19), VEGF (20), inducible NO synthase 2A promoter (21), interleukin 1 beta (22), interleukin 8 (23) and IL1Ra (24). The interleukin 1 beta and IL1Ra polymorphisms maybe of importance in the light of potential use of agents such as the IL-1 receptor antagonist, anakinra, therapeutically in recalcitrant cases of HSP. In contrast there seems to be no association of HSP nephritis with polymorphisms in ACE although numbers of children studied were small (25, 26, 27). However, it has been shown that patients not carrying the codon ICAM-1 469 K/E genotype are at decreased risk of developing severe gastrointestinal complications of HSP (28).

Treatment

Treatment for HSP has been essentially supportive. However, in relation to severe extra-renal and renal disease, a number of therapeutic approaches have been utilised including steroids, various immunosuppressives and anti-inflammatory agents, IVIG, plasma exchange and tonsillectomy but very few have been subjected to randomised controlled trials and hence results are difficult to interpret. In spite of a plethora of recent studies demonstrating the benefits of biologic agents in the treatment of various vasculitides (29, 30) there are, as yet, no data on their use in HSP or HSP nephritis.

However, anti-TNF (infliximab or etanercept), anti-CD20 (rituximab) and anti-IL1 (anakinra) may all have potential roles in HSP for severe drug resist-

ant disease but it remains to be seen if indeed they prove valuable.

In contrast some interesting new work has emerged in the recent past in relation to therapy aimed at preventing renal or other complications of HSP. The importance of renal disease in terms of acute morbidity and in influencing the long term outlook for HSP in childhood has raised the question of whether glomerulonephritis might be preventable by prophylactic intervention with steroid on presentation with the illness before renal disease was manifest. In the past only limited data were available with conflicting findings. Buchanec *et al.* (31) and Mollica *et al.* (32) concluded from retrospective and prospective non randomised studies respectively that immediate treatment with steroids reduced or prevented renal disease. Saulsbury (33), on the other hand, in a retrospective review concluded that pre-treatment with steroids did not prevent nephritis. More recently two prospective randomised, placebo controlled studies of early oral prednisone treatment in HSP have been published. Huber *et al.* (34) found that early prednisone therapy in HSP did not reduce the risk of renal involvement at one year or the risk of acute gastrointestinal complications. Ronkainen *et al.* (35) also found that prednisone did not prevent the development of renal symptoms but was effective in treating them; renal symptoms resolved in 61 percent of the prednisone patients after treatment compared with 34 percent of those receiving placebo. In this study treatment was also found to be effective in reducing the intensity of abdominal and joint pain which would fit in with earlier studies of the use of steroids in the acute phase of the condition. The conclusion from the results of these trials would seem to be that the routine use of prednisone therapy in HSP is not supported but that there might be some benefit from early treatment if marked renal or extra-renal complications were to develop.

Conclusions

The proposal of new international classification criteria for childhood HSP will need appropriate validation but

hopefully will provide paediatricians with a valuable tool in studying childhood vasculitides. The various genetic polymorphisms identified in patients with HSP may lead to a greater understanding of predisposing and protective factors in relation to complications such as renal and gastrointestinal disease. Newer biologic agents may have a role, as yet untested, in treating severe drug resistant manifestations of the condition. Prophylactic steroid therapy at commencement of the condition does not prevent renal or gastrointestinal involvement but does seem to be effective in treating these complications.

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