Henoch-Schönlein purpura (treatment and outcome)

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Henoch-Schönlein purpura (HSP) is the most common systemic vasculitis of childhood. It is a form of leukocytoclastic vasculitis that is characterized by inflammation and necrosis involving small vessels, predominantly post-capillary venules, capillaries, and arterioles. There is a neutrophil infiltration of the necrotic vessel walls with scattered nuclear debris (leukocytoclasia), hemorrhage, and fibrin deposits. Immunofluorescence microscopy reveals deposits of immunoglobin A (IgA) in capillaries and post-capillary venules as well as complement and fibrin. It is characterized by nonthrombocytopenic purpura, arthritis and arthralgia, abdominal pain, gastrointestinal hemorrhage, and glomerulonephritis. However, clinical manifestations vary, and the extent to which individual patients manifest features of the condition govern, at least in part, the approach to management. Furthermore, even though the characteristic features allow for confident diagnosis, there is overlap with other forms of leukocytoclastic vasculitis that can lead to diagnostic confusion and to therapeutic dilemmas.[1]

CLINICAL FEATURES WITH THERAPEUTIC IMPLICATIONS

Cutaneous manifestations

The palpable purpuric lesions, often on dependent or pressure-bearing areas, usually do not require special therapeutic steps.[2,3] At times, however, they might ulcerate or may present as extensive hemorrhagic bullae.[4] In children younger than 3 years, the clinical picture may be dominated by subcutaneous edema involving the scalp, periorbital area, dorsi of the hands and the feet, and the genitalia.[5] This might manifest itself as acute hemorrhagic edema that has in the past been considered to be a separate entity but is now viewed as a variant of HSP.[6-8] Although spontaneous resolution will eventually occur, the pain, discomfort, and appearances frequently justify therapeutic intervention.

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Gastrointestinal disease

Two-thirds of children with HSP develop gut symptomatology.[9-11] Abdominal pain due to submucosal and subserosal hemorrhage and edema is the commonest feature, but gastrointestinal hemorrhage is common and can be massive and life threatening.[11] Intussusception develops in 4 to 5% of patients, and bowel ischemia and infarction, intestinal perforation, fistula formation, and late ileal stricture are recorded.[11,12] The severity of the abdominal pain and the seriousness of the complications of gut involvement have influenced many clinicians to treat the gut manifestations even though eventual improvement without therapy is well recognized. Hemorrhagic pancreatitis, hydrops of the gall bladder, and pseudomembranous colitis also occur, but infrequently.[13]

Articular features

Joints are involved in 50 to 80% of patients, with the knees and ankles most affected and with wrists, elbows, and the finger joints less often.[2,9,10,14] Nonsteroidal anti-inflammatory drugs have a role, but in severe situations steroids have been used with seeming benefit even though, as emphasized subsequently, resolution occurs without therapy.

Renal manifestations

Renal involvement occurs in 20 to 34% of children with HSP with a wide spectrum of manifestations ranging from microscopic hematuria and mild proteinuria to nephritic/nephrotic syndrome or even rapidly progressive crescentic glomerulonephritis and renal failure.[15-18] It is in the context of the renal disease that the greatest therapeutic endeavors have occurred, yet sadly without definitive randomized controlled trials.

Other features

Orchitis,[19,20] central nervous system involvement with seizures and coma,[21,22] Guillain-Barré syndrome,[23] parotitis, carditis, and pulmonary disease with hemorrhage are reported[24,25] and may require treatment in their own right.

TREATMENT

Treatment of HSP is, in general, supportive. There is a need to maintain hydration, nutrition, and electrolyte balance. Pain relief with simple analgesics is indicated. If hy-

pertension is present, this might require antihypertensive therapy. The role of glucocorticoids is controversial. They can dramatically benefit joint and skin findings (and the pain of orchitis) although they are not usually needed in the management of these features. Allen et al (1960)[26] concluded that in their study painful edema and arthritis resolved with or without steroids within 24 to 48 hours after onset. However, systemic steroids are indicated in patients with severe gastrointestinal hemorrhage,[9,26] for example, as prednisolone orally in a dose of 1 to 2 mg per kg per day for a week, with then gradual reduction over the next two to three weeks. Pulsed intravenous methylprednisolone in doses of 300 to 600 mg per m^2 per dose for 3 consecutive days may also be effective in these circumstances, possibly followed by a gradually reducing oral regimen. However, a number of retrospective studies have shown that abdominal pain resolves eventually with or without steroids but that steroids expedite this process. The role of glucocorticoids in preventing nephritis remains unclear. Some studies have been undertaken with variable results. Buchanec et al (1988)[27] and Mollica et al (1992)[28] concluded from a retrospective and a prospective nonrandomized study respectively that immediate treatment with steroids prevented renal disease. Saulsbury (1993),[29] on the other hand, in a retrospective review concluded that pretreatment with steroids did not prevent nephritis. Hence, at present it is not possible to give precise recommendations but there is a mandate for a well-randomized controlled trial to be undertaken.

Children with HSP who have clinical and histopathological features of moderately severe or severe renal disease have been treated with glucocorticoids with or without cytotoxic drugs. At the present time, no prospective controlled studies have been undertaken that clearly define the approach to treatment in these patients. Counahan et al (1977)[30] reported no benefit in terms of moderately severe nephritis utilizing prednisolone and/or immunosuppressive drugs. Foster et al (2000),[31] studying similar patients, showed that prednisolone and azathioprine therapy was associated with a better outcome compared to untreated patients. Administration of intravenous "pulsed" methylprednisolone in rapidly progressive glomerulonephritis has been shown to have a role if started early in the course of the disease.[32,33] There is also some evidence, in severe cases, that a combination of prednisolone, cyclophosphamide, heparin or warfarin and dipyridamole can result in clinical and histological benefit in severe cases.[34] This approach is similar to that advocated for the management of rapidly progressive glomerulonephritis with crescents histopathologically from any cause, as opposed to being selectively beneficial for the situation as a result of HSP.[35] The use of high- or low-dose intravenous immunoglobulin has been shown in limited studies to stabilize poor renal function or slow progression of renal disease in HSP nephritis.[36,37] Plasma exchange has been advocated by some and has resulted in an encouraging outcome in one study[38] and transient benefit in another,[39] but has still to be confirmed in large trials. In the patient left with persistent proteinuria after the acute disease process has settled, angiotensin converting enzyme inhibitors may have a role.

COURSE AND OUTCOME

In two-thirds of children, HSP runs its entire course within 4 weeks of onset.[30,40] Younger children usually experience a shorter course and will have fewer recurrences than older patients. Approximately 16 to 40% have at least one recurrence, which usually consists of a rash and abdominal pain. The majority of these recurrent episodes take place early in relation to the disease onset but can occur up to two years afterwards.The episodes may recur, seemingly spontaneously, or be associated with intercurrent infections. The prevention of recurrent attacks is sometimes attempted, and anecdotally a period of alternate-day low-dose prednisolone may help; some have advocated the use of dapsone in this situation.[41]

The overall prognosis is good. Significant morbidity is associated with disease of the gastrointestinal tract in the short term and in the long term with nephritis. The clinical and pathologic features are, to an extent, predictive of the long-term outcome. In patients who present with a nephritic, nephrotic, or nephritic/nephrotic syndrome, 44% have hypertension or impaired renal function on long-term follow-up, whereas 82% who present with hematuria (with or without mild proteinuria) are normal.[42] Children with renal manifestations in the acute phase require prolonged follow-up. This is especially important if there was extensive crescentic involvement on initial renal biopsy.

Long-term studies confirm that renal failure and hypertension can develop up to ten years after the disease onset. Overall 1 to 5% of children with HSP progress to end-stage renal failure. These patients account for approximately 10% of children entering into end-stage renal failure programs.[16,17] Renal transplantation has been successfully undertaken. Histologic features recur in one-third to one-half of all patients, but clinical recurrence and graft loss are uncommon.[43,44]

CONCLUSION

As can be seen, Henoch-Schönlein purpura is a disorder that in the majority of circumstances spontaneously remits in time with no more than supportive measures required therapeutically. However, there is a significant morbidity associated with the disease of the gastrointestinal tract in the short term and with nephritis in the long term. No clear guidelines exist in terms of treatment, but steroid therapy probably has a role in the initial phases of the disease for gut and other complications and may have a protective contribution in preventing the development of nephritis or modifying its course. For established glomerulonephritic disease, steroid and immunosuppressive therapy may be indicated, but controlled trials are needed to establish this. In the context of crescentic nephritis with a rapidly progressive glomerulonephritic picture clinically, the aggressive approach utilized for this pattern of illness would seem to be indicated in view of the serious renal prognosis with which it is associated.

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