ELSEVIER

Vascular Reactions in Children

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Urticaria

It has been estimated that 10–20% of the general population experiences an episode of urticaria during their lifetime.[1] Urticaria is a common disease of childhood, and the incidence in children is reported to range between 2.4% and 8.3%.[2] Chronic urticaria, defined arbitrarily as lesions present for longer than 6 weeks, develops in a variable proportion of patients ranging, from 5% to 30%. Between 42% and 50% of children with chronic urticaria continue to have symptoms for $>$ 1 year. Within the chronic category, it is suggested that children under the age of 8 years have a higher resolution rate.[1,2]

Clinical Picture

Urticarial lesions may involve any area of the body. Wheals assume variable sizes and shapes and oftentimes have raised erythematous, serpiginous edges and blanched centers (Fig 1). In the young child, hemorrhagic patterns are not infrequent. Characteristically, the lesions are intensely pruritic and evanescent. Angioedema, a similar process occurring in deeper dermal and subcutaneous layers, appears on the face and extremities. Pruritis may or may not be present.[2]

Etiology-Pathogenesis

Urticaria is a type I hypersensitivity reaction and involves mast cell degranulation. Stimulation of mast cell mediator release may result from both immune- and nonimmune-mediated mechanisms. Perhaps the most clinically relevant of these mechanisms is the cross-linkage of high-affinity immunoglobulin E (IgE) receptors (FcϵRI) on mast cells by antigen-specific IgE.[3–8] It has been shown that a category of chronic idiopathic urticaria is associated with circulating, functional, histamine-releasing auto-antibodies that bind to IgE receptors (FcϵRI) or, less frequently, to IgE.[9] In addition to histamine, mast cell mediators include prostaglandin D_2, proteases, and various cytokines.[5,10] Urticaria can be caused by a wide variety of factors.[1] Success in identifying a cause in childhood urticaria is variable and ranges between 21% and 83%. The acute form of urticaria appears to occur more often in the atopic population, and the likelihood that the underlying cause can be identified is significant. In contrast, the cause of chronic urticaria is identified $<$ 3% of the time.[1,7,11]

In children, various acute, benign infections, including viral illnesses, frequently trigger urticaria. In such instances, drug therapy has been instituted, making it difficult to distinguish between these two triggering factors. Food allergy is yet another common cause of acute, recurrent urticaria in childhood. The frequency ranges between 11% and 62%.[1,2,12,13] Sensitivity to eggs and, less often, milk is common during the first year of life. This sensitivity is lost during early childhood. In young children, peanuts, nuts, and berries are often implicated, while shellfish and fish sensitivity usually does not occur until later.[1]

Treatment

If a cause is identified, avoidance of the causative agent or addressing the associated disease is indicated. Antihistamines of the H1 class (sedating/nonsedating) remain the treatment of choice, usually providing symptomatic control.[1,7] It is unclear whether the addition of histamine-2–blocking drugs to H-1 antihistamines is of any additional benefit.[10] Although systemic corticosteroids are rarely indicated, a brief course may be necessary to control severe, acute reactions.[1] In acute angioedema in which airways are affected, epinephrine may be life-saving. Cromolyn sodium preparations have not been useful in urticaria.[10] Ketotifen may be useful in chronic urticaria, and photochemotherapy may be considered.[10,14] With evidence incriminating circulating autoantibodies against IgE receptors in chronic forms of urticaria, new treatment modalities have been introduced. These include immunosuppressive drugs such as cyclosporine and intravenous immunoglobulins. Additionally, leukotriene inhibitors have been assessed and may be beneficial.[5,17]

Erythema Multiforme

The clinical spectrum of erythema multiforme (EM) includes two different presentations. The mild, mainly cutaneous process, originally described by Von Hebra, is known as EM minor, and a more serious mucocuta-

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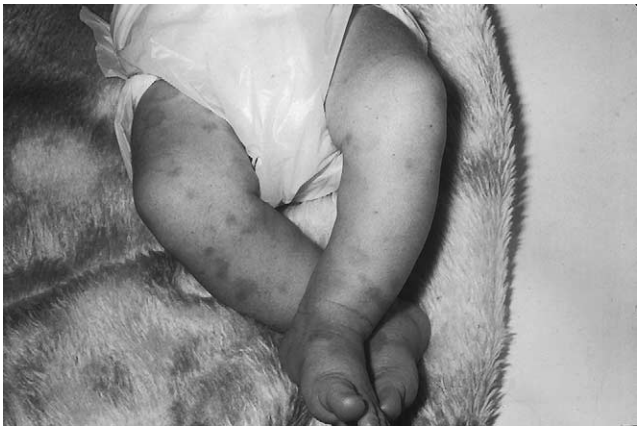

Figure 1. *Urticarial lesions; legs.*

neous disease described by Stevens and Johnson is known as EM major.[16]

Clinical Picture

EM minor is an acute, self-limited mucocutaneous eruption, generally occurring without a prodrome. The onset of skin lesions is abrupt, with virtually all lesions appearing within the first 72 hours of the illness. Young adults aged 20–40 years are most likely to suffer, although children and rarely, infants are affected.[17,18] The majority of children are preadolescents or adolescents, in whom the course and evolution of lesions are the same as those observed in young adults.[19]

Lesions include symmetrically distributed, fixed red macules, papules, and plaques, with the upper extremities being mostly affected (Fig 2). Generally, the erythematous border of the papule expands and the central zone becomes dusky in color, producing the distinctive "target" or "iris" lesion. Involvement of the oral mucosa sometimes occurs.[16,19,20] The development of lesions at sites of trauma (isomorphic phenomenon) has been described.[21] Symptoms include itching, burning, and prickling sensations. The duration of EM minor ranges between 1 and 4 weeks, with a median duration of 2–3 weeks. Patients are febrile and lymphadenopathy is usually absent, except when oral lesions are present.[16]

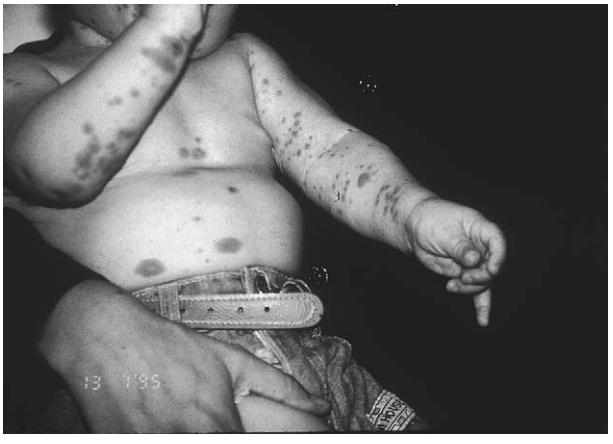

Figure 2. *Erythema multiforme (including target lesions).*

Etiology-Pathogenesis

The best-documented precipitating factor of EM minor is an antecedent infection with herpes simplex virus (HSV). The EM lesions typically develop from 3 to 21 days after herpes infection. Recurrent EM minor does not necessarily follow each episode of recurrent HSV, nor does a clinically apparent HSV infection always antedate EM minor.[22–25] Immunohistochemical studies have shown that the inflammatory infiltrate is predominantly composed of T lymphocytes, of helper and suppressor subsets. These findings, together with the histological evidence that the keratinocyte is a primary target of inflammatory injury, support a cell-mediated immune response directed against HSV antigens within the epidermis. Genetic differences in the host response to HSV might explain why only certain patients who suffer from HSV infection develop EM minor.[25,26]

Management

Systemic steroids are commonly used in the treatment of EM minor, despite the lack of objective evidence supporting their value in the treatment of this disease.[20,23,24] It is likely that by the time the patient seeks medical attention, much of the immunological tissue damage will have already occurred.[27] Suppression of the host response might permit HSV replication to go unchecked, resulting in continuous, overlapping episodes of EM minor.[23,24] Discontinuing suspected medications and dealing with possible infections are needed. Oral antihistamines to relieve itching and burning sensations as well as anti-herpesvirus medications such as acyclovir are helpful. Acyclovir is best used for prophylaxis in patients with recurrent EM minor.[16]

Stevens-Johnson Syndrome (Erythema Mutliforme Major)—Toxic Epidermal Necrolysis

There is growing evidence that Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) constitute a spectrum of disease process distinct from erythema multiforme minor.[28] SJS is a serious mucocutaneous illness in which lesions involving at least two mucosal sites, in addition to skin lesions that evolve into bullae and extensive areas of epidermal necrosis and separation, develop. SJS occurs at any age, with the main peak in the second decade and a smaller peak in the fifth decade.[16] In some series, the majority of patients were children.[29,30]

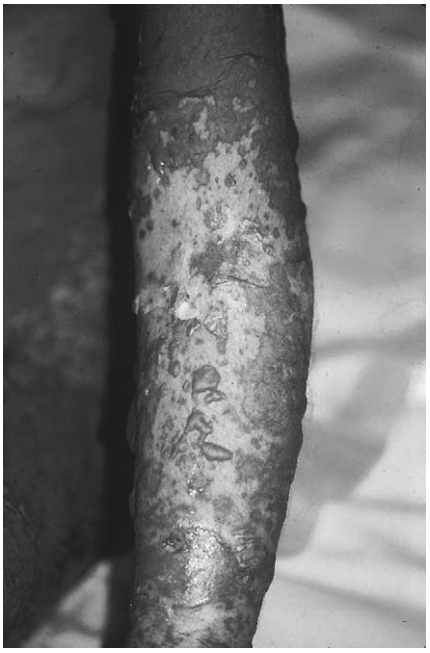

Figure 3. *Toxic epidermal necrolysis.*

Clinical Features

A prodrome lasting from one to several days with fever, headache, malaise, sore throat, vomiting, and diarrhea present in > 50% of patients. Skin lesions appear as in EM minor; however, there is rapid evolution to involve large areas with bulla formation, epidermal necrosis, and separation. Nickolsky sign is positive. On top of the oral mucosa, the conjunctiva and genitalia may be involved. In up to 39% of patients, all three mucosal surfaces are affected.[16,29,30] Characteristically patients develop hemorrhagic crusts on the lips that evolve into a pseudomembrane of necrotic epithelium and inflammatory cells. More severe involvement of the oral mucosa may interfere with eating, swallowing, and talking. When the eyes are involved, redness, erosions, and purulent exudate may be present.[16] Damage to the respiratory mucosa with persistent cough and pleural effusion may be seen. Injury to the gastrointestinal tract results in dysphasia, abdominal pain, diarrhea, and melena.[16]

Patients with this illness have been classified according to the extent of detached/detachable epidermis. If it is < 10%, SJS is used; those with cutaneous detachment of 10–30% are called transitional SJS-TEN patients; and those with more than 30%, are designated TEN patients (Fig 3). In general, patients with SJS and SJS-TEN have better prognosis than do those with TEN.[28]

Etiology-Pathogenesis

Drugs are clearly the leading causative factor in SJS-TEN, mostly sulfonamides, anticonvulsants, and nonsteroidal anti-inflammatory agents.[31] The predisposing factors that may promote the development of SJS-TEN include a genetic susceptibility as well as drug interactions.[32] It has been suggested that SJS-TEN is linked to a defect of the detoxification systems in the liver and skin. The disease process is viewed as a cytotoxic immune reaction aiming at destruction of keratinocyte-expressing foreign antigens related to drugs or their metabolites.[33,34]

Management

Prompt withdrawal of suspected drugs is very essential. It was shown that early discontinuation of causative drugs (with short elimination half-lives) was associated with a better outcome. That was independent of the main known prognostic factors, age, and the extent of epidermal detachment.[28] Most authorities recommend treatment of patients in a burn unit. Careful attention to secondary infections and replacement of lost fluids, electrolytes, and calories are essential.[16] The use of systemic corticosteroids is disfavored; however, some studies report a favorable influence of an early and short course of corticosteroids in children with SJS.[34] Recently, treatment of TEN by intravenous immunoglobulins rapidly reversed disease progression and the outcome was favorable. It was shown that the antibodies present in the pooled human immunoglobulins block the death receptor Fas that is normally expressed on keratinocytes. This inhibits the interaction between the Fas receptor and its respective ligand and thus, prevents apoptosis.[35]

Henoch-Schönlein (Anaphylactoid) Purpura

Henoch-Shönlein purpura (HSP) is a form of leukocytoclastic vasculitis characterized by palpable, purpuric skin lesions, arthritis, abdominal pain, and glomerulonephritis. It is the most common form of vasculitis occurring in childhood, mainly 3–10 years of age. It represents an immunological response triggered by a multitude of drugs and infectious agents.[36]

Clinical Picture

Palpable purpura occurs in 100% of cases (Fig 4) but is the presenting sign in only 50% of patients. Hemorrhagic vesicles are uncommon. Dependent areas such as the legs and buttocks are primarily involved. Scrotal involvement is not uncommon.[36,38] Edema of hands, feet, scalp, and ears may be early findings. Arthritis and arthralgias are common in HSP, affecting 60–84% of patients, with the ankles and knees primarily involved.[37,39] Gastrointestinal involvement occurs in up to 76% of patients. This presents as abdominal pain, nausea, vomiting, and gastrointestinal bleeding.[40] Major hemorrhage occurs in 5% and intussusception in 3–5% of patients.[37] Renal involvement occurs in 10–50% of patients, with children older than 9 years and those

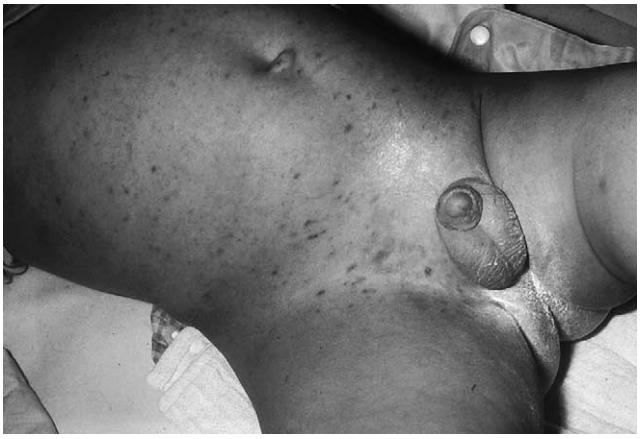

Figure 4. *Purpuric papules in Henoch-Schönlein purpura.*

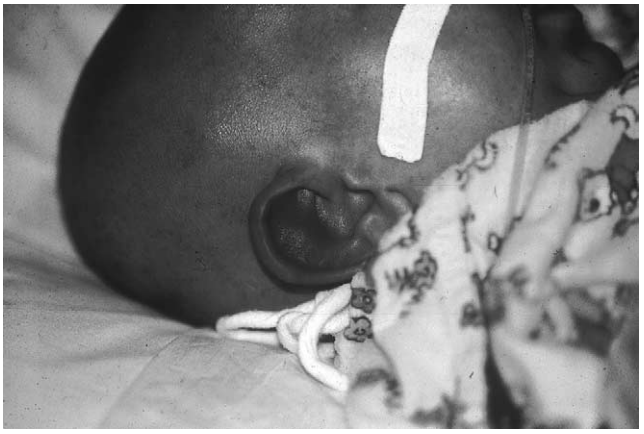

Figure 5. *Echymotic plaques in acute hemorrhagic edema of infancy.*

with bloody stools reportedly having an increased risk.[36] However, the overall prognosis is good, with 2–5% left with persistent renal disease.[41] Rare complications include pancreatitis, cholecystitis, neurological involvement, and myocardial infarction.[42,43]

Histology

Histologically, HSP cannot be distinguished from other forms of leukocytoclastic vasculitis, although the degree of vascular damage is less. Immunofluorescence studies demonstrate the deposition of IgA in capillaries.[44] IgA deposits are found in 75% of specimens from involved skin and in 67% of specimens from uninvolved skin.[45]

Treatment

Management of HSP is mainly supportive. The disease is self-limited, remitting after 1–2 weeks. It has a tendency, however, to recur a number of times over a period of weeks to months. Systemic corticosteroid has been used, especially when significant abdominal pain or renal involvement is present, although its effectiveness has been questioned. Older children who are more likely than younger children to develop progressive renal disease may benefit from early treatment.[36]

Acute Hemorrhagic Edema of Infancy

Acute hemorrhagic edema of infancy is an acute, leukocytoclastic vasculitis occurring in infants. It has some common clinical features with HSP and is considered by some authors to be a variant of that syndrome.[46] Yet others regard it as a distinct clinical entity.[47]

Clinical Picture

Acute Hemorrhagic Edema of Infancy occurs between the ages of 4 months and 2 years. It appears usually in winter, with an acute onset of echymotic plaques and inflammatory edema. The purpuric plaques often show a cockade or targetlike morphology. The ears, cheeks, and extremities are commonly affected (Fig 5).[47,48] The condition is believed to represent an immune complex-mediated disease triggered by respiratory infection, drugs, streptococci, staphylococci, adenoviruses, and possibly, mycobacteria. The clinical differential diagnosis may include EM minor, child abuse, and Sweet syndrome.[47,49]

Treatment

The prognosis of Acute Hemorrhagic Edema of Infancy is excellent, with resolution occurring in 1–3 weeks. Visceral involvement is rare in contrast to HSP.[47,49]

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