Asymmetric Periflexural Exanthem of Childhood

A Clinical, Pathologic, and Epidemiologic Prospective Study

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Objective: To assess the clinical, pathologic, and epidemiologic features of asymmetric periflexural exanthem of childhood (APEC), a clinically distinctive eruption, especially its link with pityriasis rosea and pattern of transmission.

Design: A prospective case series, including an analysis of epidemiologic triggering factors and mode of transmission. Pathologic study, including immunohistochemistry of the inflammatory infiltrate.

Setting: A mixed, community-based referral center.

Patients: A total of 37 girls and 30 boys with typical APEC referred from April 1994 to December 1996 were included in the study; 82% came from the greater Bordeaux area in France.

Intervention: None.

Main Outcome Measure: Possible interhuman transmission of APEC.

Results: No triggering factor was identified; no interhuman transmission occurred; and no demonstrable link with pityriasis rosea was apparent. Several new clinical variants were recognized or confirmed (high fever, facial and peripheral involvement, prolonged course). Distinctive perisudoral interface CD8+ infiltrate was suggestive of diagnosis.

Conclusions: Interhuman transmission was doubtful, but inoculation disorder was still possible. Histopathologic findings seem more specific than previously thought.


In 1962, under the heading “a new papular exanthem of childhood,” Brunner et al1 mentioned 75 cases of a previously undescribed eruptive disorder in children from the Chicago, Ill, area and commented about exposure to sandboxes. This exanthem had a unilateral periflexural onset and often spread bilaterally. In 1967, under the heading “Gianotti-Crosti syndrome—papular eruption of infancy,” Hjorth et al2 described many cases of a papular dermatitis with a unilateral distribution—which can retrospectively be assigned to the same disease, and mentioned earlier reports on this condition.

In 1986, Taieb et al,3 without being aware of the reports by Brunner et al and Hjorth et al, described what appeared to be the same exanthem in 5 children under the designation “localized erythema with regional lymphadenopathy” and suggested an inoculation disorder because of the mode of onset of the rash. Clinically, the eruption was characterized by a pruriginous micropapular exanthem, starting asymmetrically and unilaterally close to the axilla or other flexures, and then spreading centrifugally to jump, in a second stage, to contralateral territories in most cases (Figure 1). The eruption was usually preceded by digestive or upper respiratory tract prodromes. Enlarged regional lymph nodes and moderate general signs with low-grade fever were associated with the cutaneous lesions, but general health was not affected. All symptoms disappeared spontaneously without recurrence in 3 to 6 weeks. In a 1992 report of 18 observations, Bodemer and de Prost4 proposed the term unilateral laterothoracic exanthem, based on the most common site of onset of this rash and suggested a viral cause. Following this report, Melski5 and Laur6 commented about US cases seen in the 1950s and 1960s in the Middle West and Texas, respectively, and recalled the publication by Brunner. A link with pityriasis rosea was suggested.5,6

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Pediatricians and dermatologists of the Aquitaine, France, region were informed about the study at a meeting held in January 1994 and received written information about the disease and the planned study. They were asked to refer patients with the classical criteria of APEC (including a reprint showing the clinical features of the rash) to our center for clinical evaluation and blood and skin sampling. A local ethical committee agreed on the protocol.

**EPIDEMIOLOGIC AND CLINICAL STUDY**

The following information was obtained by a physician (D.C., C.L.-L., L.L., A.T.) for each patient: sex; age; area (rural, urban, or semiurban, ie, suburban area of the city of Bordeaux); profession of the parents; type of housing (house or apartment); date of diagnosis; personal and familial medical history; complications (especially infections during pregnancy); existence of similar cases among relatives, friends, or classmates; existence of other infectious or eruptive diseases in the family or community; contact with animals; and playing in the sand. Cases of pityriasis rosea among relatives and other contact persons were looked for by giving a description of this disease and showing photographs. The following precipitating factors were systematically reviewed: injury, insect or animal bite, immunization, drugs, and outdoor activity. Parents were also asked their opinions concerning an eventual precipitating factor.

The following clinical features were reviewed: prodromes (ear, nose, and throat; respiratory; digestive; or other), characteristics of the exanthem (date of onset, initial topography, description of elementary lesions, pruritus, pattern of spread, duration of eruption), fever, enanthem, lymphadenopathy, hepatomegaly, and splenomegaly. A research nurse obtained follow-up information when a patient could not come for a control visit. A standardized 4-page file, which was subsequently computerized with spreadsheet software, was adapted for data analysis (File Maker Inc, Santa Clara, Calif).

**HISTOPATHOLOGIC STUDIES**

When consent was obtained from the parents, skin biopsy specimens were obtained from the involved skin area during the first 3 weeks of eruption. Specimens were either snap frozen or fixed in 10% formaldehyde, processed routinely, and stained for the following markers: CD20, CD4, and CD8 (DAKO-CD20, DAKO-OPD4, and DAKO-Leu-2b, DAKO A/S, Glostrup, Denmark) by immunoperoxidase.

Since then, cases of APEC have been reported at several local meetings in Europe. Published articles include 2 cases in children from northern Italy reported in 1994 by Gelmetti et al,8 in the United Kingdom reported in 1994 by Mendelsohn and Verbor,9 in southern Hungary described in 1995 by Harangi et al,10 in Quebec described in 1996 by McCuaig et al,11 1 boy in Germany described in 1996 by Cremer,12 and 2 adults reported by Corazza and Virgili13 in 1997 and Gutzmer et al14 in 1997.

The origin of this eruption remains unknown, despite a recent active search for an infectious cause.10,11 Because of the seasonal pattern and association of nonspecific prodromes and fever in a number of cases, several authors have hypothesized an infectious cause. However, the link of the rash with viral diseases is not firmly established as with Gianotti-Crosti syndrome.2

This study, which contains an etiologic part (D.C., unpublished data, February 1995 to April 1996) was undertaken to prospectively assess the clinical and epidemiologic features of APEC, especially its link with pityriasis rosea and possible pattern of transmission.
RESULTS

EPIDEMIOLOGIC FINDINGS

From April 1994 to December 1996, 67 children were included in the study: 37 girls and 30 boys (sex ratio: 1:2). Most of the children (82%) came from the area of Gironde, France, which surrounds Bordeaux, without notable clusters in localized areas. Mean age at diagnosis was 27.5 months (range, 1-5 years). Median age group was 18 to 24 months. A total of 31 children (46.3%) lived in an urban area, 23 (34.3%) in a rural area, and 13 (19.4%) in a semiurban area. A total of 47 children (70%) lived in a house and 20 (30%) in collective housing.

Most patients (60/67; 90%) were diagnosed between February and September, with a peak in September (19.6% of cases). No concomitant or subsequent case of APEC, pityriasis rosea, or other rash or infectious disease was noted among relatives or contacts in the community. Nine percent of children had been playing in the sand, and 36% of families had pets. There was no precipitating or triggering factor identified.

CLINICAL FINDINGS

Prodromes were noted in 61% of cases, most often ear, nose, and throat (66%) (rhinitis, pharyngitis, otitis), digestive (41%) (gastroenteritis, isolated diarrhea), respiratory (17%) (cough, bronchitis), or other (10%) (conjunctivitis, general fatigue).

Fever was found in 40% of cases. Most were low-grade temperatures around 38°C, but some were as high as 40°C (2 cases). Mean occurrence of fever was on the sixth day of eruption (range, 8 days before to 20 days after onset of eruption). Duration was less than 4 days in 62% of cases with known duration. However, prolonged low-grade fever was noted up to 42 days in one case.

Usually, the eruption started unilaterally on the trunk (58%) close to the axilla (27%), without right or left predomination. Other areas of onset were the lower limb (29% of cases) and upper limb (in 14%), especially the extremities (3 cases). Eruption spread centrifugally, and although both sides of the body were eventually involved in 70% of cases, almost all had unilateral predominance.

Facial (3 cases) (Figure 2) and peripheral (3 cases) involvement, including unilateral palmar erythema, was noted. Spontaneous regression of the eruption occurred between the third and sixth week of evolution (Figure 3). Most often, the eruption consisted of erythematous micropapular lesions, with an occasional eczematiform or purpuric aspect. Pruritus was noted in 65% of patients; with mild intensity in 23% of cases, moderate in 47%, and severe in 30%. Two children had an associated enanthem.

Lymphadenopathy was noted in 44 patients (70%), usually in the areas adjacent to the primary area involved. Liver or spleen enlargement was not noted.

HISTOPATHOLOGIC FINDINGS

In 9 skin biopsy specimens taken during the first 3 weeks of the eruption, similar aspects were observed: a mild-to-moderate mononuclear interface dermatitis, with some necrotic and apoptotic keratinocytes, and a dermal mononuclear infiltrate made of T lymphocytes of mostly T8 phenotype, mixed with rare B lymphocytes. This infiltrate was essentially dermal, with a clear predominance around sweat glands going from the acrosyringium to the coiled sweat gland, with less pronounced involvement around blood vessels and hair follicles (Figure 4 and Figure 5).

COMMENT

Since 67 cases of APEC were easily collected during the 20 months, we consider it a common disorder in our area. Because our study was not population based, the exact incidence is not possible to estimate. No characteristic of the patients (such as living area, type of housing, profession of the parent) showed significant variation when compared with population-based databases available among departmental and regional authorities. Our study confirms that affected children are generally
2 to 3 years old, but 2 adult cases were recently reported in Italy and Germany. Another case in a 15-year-old individual was mentioned by Laur. The sex ratio was nearly equal (close to 1:1) in this prospective study, which contradicts our retrospective series and other reports showing a female overrepresentation of around 2:1. Despite a careful study that included sensitizing the families to this aspect of the study and telephone calls by the nurse to trace other cases that could have been noted in the neighborhood of each patient, no interhuman transmission could be documented. No familial case was found. Both Harangi et al and McCuaig et al found 2 familial cases. In addition, if APEC is similar to pityriasis rosea in terms of duration, seasonality, and benign course, then no spatial or chronologic relation with pityriasis rosea in the community seems to exist. In our previous report, one mother had an isolated lesion compatible with onset of pityriasis rosea when her child had a diagnosis of APEC. Gelmetti hypothesized (oral communication, 1996), based on the model of varicella zoster virus infection, that APEC could represent a primary infection and pityriasis rosea a secondary infection. Melski and Laur considered APEC a possible childhood variation of pityriasis rosea, which is often atypical in this age group. Bodemer and de Prost rejected this hypothesis and believed that the only resemblance was a possible infectious origin.

In regard to clinical data, this series confirms such atypical clinical features as facial and peripheral extension of the eruption. The high temperatures (up to 40°C) shown in this study in the absence of other causes have, to our knowledge, not been previously reported. An extended course (up to 60 days) of the eruption is possible, as mentioned in our previous report. In our series, recurrences were not noted. In the series by Laur, 2 patients had a recurrence: the first, 11 months and 6 years after the first episode; and the second, 4 months after. In the series of McCuaig et al, many patients reported brief, mild recurrence 1 to 4 weeks after spontaneous clearance but no long-term recurrence.

Because of these data, clinical differential diagnosis may be more challenging than previously envisaged, including other eruptive disorders of childhood—either infectious or systemic—and, on the other hand, chronic dermatitis—mainly atopic dermatitis—because of the associated pruritus and distribution of lesions at the final stage of eruption.

Our pathologic findings, together with previous reports, confirm that APEC is not nonspecific, as stated earlier. A pattern of interface perisudoral dermatitis is suggestive of the diagnosis of this disorder. These characters may evoke a cytotoxic viral reaction to the basal layer of the epidermis and eccrine sweat glands. In the only published study with immunophenotyping of the infiltrate, CD4 predominance was found. Our data suggest that CD8 lymphocytes usually associated with a cytotoxic function are predominant, which makes sense in the context of a lichenoid infiltrate and apoptotic basal keratinocytes.

In contrast, the main histologic feature of pityriasis rosea is spongiosis, associated with an absence or decrease of the granular cell layer, erythrocytes in the papillary dermis, and dyskeratotic cells in the epidermis. We did not observe these features in APEC. Furthermore, the perivascular lymphohistiocytic cell infiltrate in pityriasis rosea is situated in the superficial dermis but is not perisudoral as in APEC. Eventually, the dermal T-cell infiltrate of pityriasis rosea is dense in well-developed lesions, and CD4 lymphocytes are predominant.

APEC is a common disease of the young child. An infectious cause seems most probable. The lack of interhuman transmission is the main finding of this study, and suggests that the inoculation disease hypothesis remains valid.

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REFERENCES


News and Notes

National Registry for Ichthyosis and Related Disorders. The National Institutes of Health, through the National Institute for Arthritis, Musculoskeletal and Skin Diseases, is sponsoring a National Registry for Ichthyosis and Related Disorders. The goals of the Registry are to promote the search for basic defects, improve methods of diagnosis, and develop effective methods of treatment and/or prevention of these disorders. Diagnosis of affected individuals will be based on specific, listed clinical and histological criteria and will be confirmed by determination of steroid sulfatase activity where indicated. Investigators and practitioners caring for individuals afflicted with these disorders or desiring access to the Registry database are encouraged to contact the National Registry for Ichthyosis and Related Disorders, Department of Dermatology, University of Washington, Box 356524, Seattle, WA 98195-6524; telephone: (800) 595-1265.