Papular pruritic eruptions: A marker of progressive HIV disease in children: Experience from eastern India

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Abstract

Context: Papular pruritic eruptions (PPEs) are a commonly seen dermatological manifestation in children with Human Immunodeficiency Virus (HIV) stage 2 disease, whereas recurrent upper respiratory tract infection (URTI) (>2 episodes in 6 months) is the most common presenting illness in this category. Papular pruritic eruptions has been associated with progressive HIV disease in adults though it is categorized in early stage.

Aim: To evaluate PPE as a clinical marker for progressive pediatric HIV.

Setting and Design: In Pediatric HIV/AIDS clinic, Medical College, Kolkata, a prospective longitudinal hospital-based observational study was carried out.

Materials and Methods: A total of 108 children in WHO stage 2 HIV disease aged between 2 and 12 years were selected, of which 58 had recurrent URTI without PPE and another 50 had PPE with or without secondary bacterial infection. Clinico-immunological deterioration was compared between the groups in terms of progression to undernutrition, WHO clinical stage 4 disease, severe immunodeficiency, need for initiation of Highly Active Anti Retroviral Therapy (HAART) and mortality over a period of 2 years.

Statistical Analysis: SPSS statistical software version 10 was used. $P$ value, relative risk (RR) with 95% Confidence Interval (CI), sensitivity and specificity was estimated. $P < 0.05$ was considered significant.

Results: Significantly higher incidence ($P < 0.001$) of clinico-immunological progression of disease at a significantly shorter time period ($P < 0.05$) was found in those with PPE in comparison to those without PPE. Papular pruritic eruption has high sensitivity, specificity and positive predictive value as a clinical marker for severe immunodeficiency.

Conclusion: Papular pruritic eruption could be a useful clinical marker of progressive HIV disease in children.

Key words: Papular pruritic eruptions human immunodeficiency virus, clinical marker

INTRODUCTION

Papular pruritic eruptions (PPE), a common cutaneous manifestations of pediatric HIV has been merited in revised WHO clinical stage 2 disease\(^1\) while recurrent upper respiratory infection (URTI $\geq$2 episodes in any 6 months) is the most frequent presenting illness in this category. Studies have shown correlation between PPE and worsening immune status of HIV-infected adult patients\(^2\) but such database in children is lacking. Hence we carried out a comparative study on clinico-immunological disease progression of children with PPE and those with recurrent URTI without PPE to evaluate whether PPE is a useful marker for progressive HIV in children.

MATERIALS AND METHODS

A prospective longitudinal hospital-based observational study was conducted at Pediatric HIV/AIDS clinic, Medical College, Kolkata over a period...
of 2 years (January 2006 to December 2007). This clinic is the regional center for pediatric HIV in eastern India treating over 500 HIV-positive children.

Children were determined to be HIV-infected by third generation enzyme-linked immunosorbent assay and Western blot analysis. Ethical approval was obtained from ethics committee of Medical College and Hospital, Kolkata. Children were enrolled in the study only after written-informed consent was obtained from their parents or legal guardians to be a part of this study. All children were outpatients, being evaluated in the HIV clinic, Medical College, Kolkata. Records of HIV-positive children for the preceding 6 months were analyzed by going through the HIV clinic register. Number of children who suffered from ≥2 episodes of URTI and those who had PPEs considered due to HIV dermopathy were assessed. Papular pruritic eruption is characterized by symmetrically distributed pruritic papules 2–5 mm in diameter, typically found on the extremities and trunk, with sparing of the palms, soles and digital web spaces[3] [Figures 1 and 2].

We included those cases of PPE, already confirmed by histopathological examination (HPE) of skin biopsy specimen after exclusion of skin infections, infestations, photodermatitis, xerosis and drug reactions. Most common HPE findings were dermal lymphocytic vasculitis, eosinophilic folliculitis and prurigo simplex associated with epidermal hyperkeratosis and acanthosis.

Children from other states were excluded to decrease chance of loss to follow-up. Majority of children belonged to either low or lower middle socioeconomic status and none of them had received HAART. There were 300 children in HIV stage 2 disease, of which 210 were in age group 2–12 years. Of these 27.6% suffered from recurrent URTI without PPE. Another 50 children with PPE with / without secondary bacterial infection were selected from the same age group in such a way that, clinico-demographic variables like age distribution, sex ratio and socio-economic status were comparable among both the groups. Both the groups were followed up for two years and the following parameters were compared, namely progression to:
1. Undernutrition (assessed by body mass index for age <5th centile by CDC chart)
2. WHO pediatric HIV/AIDS clinical stage 4 conditions
3. Initiation of HAART
4. Severe immunodeficiency
5. Death

During the course of study no case was lost to follow-up. On monthly visits to the HIV clinic, all children were clinically evaluated. Clinical evaluation included detailed history and examination to detect nutritional status, clinical stage of disease, presence of opportunistic infections, advent to HAART and side effects to antiretroviral drugs. Also their caregivers were counseled regarding hygiene, nutrition (based on home available food item) and importance of adherence to regular follow-up. Nutritional assessment was done by body mass index (BMI) for age as it is the only indicator that allows us to plot a measure of weight and height with age on the same chart starting from 2 years to 20 years of age. Both BMI for age and weight for stature performed equally well in screening for underweight in age given 3 and 5 years. For school-going children (6–11 and 12–14 years age group), BMI for age performed better as an index to predict undernutrition when compared to weight for stature.

Cotrimoxazole prophylaxis was given as per WHO guidelines[5] and adherence to it was 100%. Severe immunodeficiency was defined as CD4 count ≤750
cells/µl in age group 12–35 month, ≤350 cells/µl in 36–59 month and ≤200 cells/µl in ≥5 years. During the course of study, a 6 monthly CD4 count analysis (by flowcytometry) was done to assess the progression to severe immunodeficiency. The decision to start HAART was based on age of child, CD4 count and stage of disease. HAART composed of a fixed dose combination of stavudine, lamivudine and nevirapine. Furthermore, the adherence to HAART was monitored by pill box count and targeted questionnaires regarding dosing regimen. Adherence to HAART was also 100%.

Data was recorded on a predesigned proforma and managed on an Excel spreadsheet. Data were analyzed using SPSS statistical software version 10. Numerical data were expressed as mean ± standard deviation (SD), and compared by independent t-test. Categorical data were expressed as percentages and compared by chi-square test ($\chi^2$) and Relative risk (RR) with 95% CI was calculated. A p-value of <0.05 was considered significant for all statistical comparisons. Also sensitivity, specificity and positive predictive value of PPE as a clinical marker for severe immunodeficiency was compared to that of recurrent URTI.

RESULTS

One hundred and eight HIV-positive, HAART naive children spanning 2–12 years of age in stage 2 disease were enrolled in the study. Fifty eight children had recurrent URTI without PPE in the past 6 months while 50 were suffering from PPE. The mean age (6.64 ± 2.14 versus 6.81 ± 2.58 years, respectively; $p = 0.727$) of both groups were comparable. After a follow-up for 2 years, it was found that, progression to undernutrition, WHO clinical stage 4 disease, severe immunodeficiency and initiation of HAART was significantly higher in those with PPE with/without secondary bacterial infection as compared to those with URTI without PPE ($p < 0.05$ and RR > 1 for all the above parameters). However no significant difference in death rate was found among the two groups ($p = 0.255$) [Table 1]. The mean duration (in months) for clinical and immunological deterioration of HIV disease in those with PPE in terms of undernutrition (12.73 ± 3.97 and 20.40 ± 3.30; $p = 0.0001$), stage 4 disease (12.78 ± 5.21 and 20.07 ± 6.07; $p = 0.001$), severe immunodeficiency (13.28 ± 5.22 and 18.9 ± 5.79; $p = 0.001$) and initiation of HAART (13.61 ± 4.7 and 19.34 ± 5.88; $p = 0.0002$) was significantly shorter than those without PPE ($p \leq 0.001$) [Table 2]. Predictive value

| Table 1: Analysis of outcome among the two groups |
|--------------------------------------------------|
| **Outcome**                                    | **PPE with or without secondary bacterial infections (n = 50) (%)** | **Recurrent URTI without PPE (n = 58) (%)** | **Relative risk (95% CI)** | **P value** |
|--------------------------------------------------|-------------------------------------------------|-----------------------------------|--------------------------|-------------|
| Undernutrition                                   | 40 (80)                                         | 25 (43.1)                         | 1.86 (1.34–2.57)         | 0.0001      |
| WHO clinical stage 4                             | 20 (40)                                         | 12 (20.7)                         | 1.93 (1.05–3.55)         | 0.0291      |
| Severe immunodeficiency                          | 40 (80)                                         | 16 (27.6)                         | 2.9 (1.87–4.5)           | 0.0000012   |
| Death                                            | 3 (6)                                           | 1 (1.7)                           | 3.48 (0.37–32.41)        | 0.25509     |
| Cases with initiation of HAART                   | 40 (80)                                         | 18 (31)                           | 2.58 (1.71–3.88)         | 0.0000016   |

*P value was calculated by Chi-square test

| Table 2: Comparison of time interval (in months) of clinical and immunological deterioration |
|-------------------------------------------------------------------------------------------|
| **Factors compared**                                                                      | **PPE with or without secondary bacterial infections (Mean ± SD)** | **Recurrent URTI without PPE (Mean ± SD)** | **P value** |
|-------------------------------------------------------------------------------------------|-------------------------------------------------|-----------------------------------|-------------|
| Progression to WHO stage 4                                                                 | 12.78 ± 5.21                                    | 20.07 ± 6.07                      | 0.001       |
| Severe immunodeficiency                                                                   | 13.28 ± 5.22                                    | 18.9 ± 5.79                       | 0.001       |
| Undernutrition                                                                           | 12.73 ± 3.97                                    | 20.40 ± 3.30                      | 0.0001      |
| Initiation of HAART                                                                       | 13.61 ± 4.7                                     | 19.34 ± 5.88                      | 0.0002      |
| Death                                                                                    | 10.86 ± 1.94                                    | 20.8                              | 0.047       |

*P value calculated by independent t test
of PPE as a clinical marker of progressive HIV disease as assessed by sensitivity, specificity, positive and negative predictive value (71.43, 80.77, 80 and 72.41%, respectively) was significantly higher when compared to recurrent URTI ($p < 0.001$) [Table 3].

**DISCUSSION**

Our study shows that in comparison with recurrent URTI, PPE is a better clinical tool and a prognostic indicator for rapidly progressive HIV disease in children, though both URTI and PPE belong to stage 2 HIV diseases. The significant relationship of PPE with severe immunosuppression suggests that in settings where CD4 counts are not available, PPE may be considered as a clinical surrogate for progression to severe CD4 depletion (graph 1). However, the absence of PPE does not necessarily exclude progression to severe immunosuppression.

Pediatric HIV disease has a rapid progressive nature and early detection of immunosuppression is of paramount importance. Plasma viral load and CD4 count are the key laboratory markers that are independent predictors of clinical course in HIV-infected children. However, adequate data on clinical markers for progressive HIV disease in children is lacking. Skin rash may be initial presentation of HIV or may serve as a harbinger of disease progression. Though skin manifestations in HIV are frequently seen, they are often not adequately investigated and treated symptomatically. Previous prospective studies have shown that PPE is highly responsive to HAART. Hence, identifying the association of PPE with immune dysregulation of HIV and distinguishing it from other pruritic disorders found in HIV-infected patient is important for optimal management.

Analysis of 20 HIV-positive patients with characteristic PPE by Boonchai et al. revealed that 81.25% had an advanced degree of immunosuppression with a CD4 count below 100/mm$^3$ and 75% below 50/mm$^3$, thus concluding that PPE can be regarded as a cutaneous marker of advanced HIV infection. Sanchez et al. evaluated 41 patients with HIV-associated pruritic eruptions and found that 80% had CD4 T-cell counts <100 cell/mm$^3$, 77% had elevated IgE levels and 55% had elevated eosinophil counts. In the Haitian study, PPE was seen in 46% of patients with AIDS and was the presenting manifestation in 79%, often appearing months before the diagnosis of an AIDS-defining condition. Patients consistently have CD4 counts below 200. The above findings are based on adults with HIV. Our study on pediatric population yielded a similar result wherein a strong correlation of PPE and severe immunosuppression was found (RR = 2.9). Also the mean time interval of progression to severe immunodeficiency and stage 4 HIV diseases was significantly less in those with PPE than those with recurrent URTI without PPE ($p = 0.001$). The number of deaths when compared in both groups was not statistically significant ($p = 0.255$) probably owing to early initiation of HAART in children with PPE. Though the terminal-end point was essentially same but the duration to reach this point was significantly shorter in children with PPE group ($p = 0.047$).

Immune dysregulation is of paramount importance in the pathogenesis of PPE.

**Table 3: Predictive value of PPE versus recurrent URTI as a marker of severe immunodeficiency as assessed by following outcome variables**

| Outcome variables                  | PPE with/without secondary bacterial infection | Recurrent URTI without PPE | P value |
|------------------------------------|-----------------------------------------------|-----------------------------|---------|
| Sensitivity (95% CI)               | 71.43% (58.45-81.66%)                         | 28.57% (18.34-41.55%)      | <0.001  |
| Specificity (95% CI)               | 80.77% (67.91-89.40%)                         | 19.23% (10.60-32.09%)      | <0.001  |
| Positive predictive value (95% CI)| 80% (66.77-88.95%)                            | 27.59% (17.67-40.29%)      | <0.001  |
| Negative predictive value (95% CI)| 72.41% (59.71-82.33%)                         | 20% (11.05-33.23%)         | <0.001  |

* $P$ value was derived from z test for proportions
The role of cytokines in pathogenesis of PPE as studied by Aires et al. in Brazil\cite{10} revealed higher levels of IL2, IL12, gamma IFN and IL5 in those with HIV and PPE than in HIV-negative group. Negative correlation between gamma IFN and CD4 count suggested early phase of immunosuppression in PPE. PPE has also been reported in the syndrome of idiopathic CD4+ lymphocytopenia. Immune dysfunction precipitates opportunistic infections and rapid progression of asymptomatic HIV infection to AIDS.

On the other hand, with disease progression and viral load increments, there is overproduction of cytokines such as TNF that culminates in wasting syndrome of HIV.\cite{11} In our study HIV-infected children with PPE were 1.86 times more likely to develop undernutrition at a significantly shorter time interval \((p = 0.0001)\) than those with recurrent URTI without PPE. Also PPE as a clinical marker for severe immunodeficiency yielded significantly high sensitivity, specificity and positive predictive value when compared to recurrent URTI \((p < 0.001)\).

Hence it seems that PPE is a better prognostic indicator for rapidly progressive HIV disease in children when compared to recurrent URTI. Those with PPE require stringent follow-up as they are prone to progress to undernutrition, HIV stage 4 disease and severe immunodeficiency at an earlier date. Also they require early initiation of HAART. In other words, in HIV-infected children, PPE may be a useful clinical tool to assess disease progression especially in resource-limited countries where frequent estimation of viral load or CD4 count may not be feasible.

**CONCLUSION**

Study shows that HIV-infected children with PPE have early and significantly higher rates of progression to severe immunodeficiency and undernutrition when compared to those with recurrent URTI without PPE, though both belong to HIV stage 2 disease. To conclude, PPE could be a useful clinical marker of progressive HIV disease in children.

**REFERENCES**

1. National Guidelines on Pediatric HIV – India. Prepared by Indian Academy of Pediatrics on behalf of NACO Pediatric HIV Group.
2. Boonchai W, Laohasrisakul R, Manomukul J, Kultthanon K. Pruritic papular eruption in HIV seropositive patients: A cutaneous marker for immunosuppression. Int J Dermatol 1999;38:348–50.
3. Bason MM, Berger TG, Nesbitt LT Jr. Pruritic papular eruption of HIV disease. Int J Dermatol 1993;32:784–9.
4. Mei Z, Grummer-Strawn LM, Pietrobelli A, Goulding A, Goran MI, Dietz WH. Validity of body mass index compared with other body-composition screening indexes for the assessment of body fatness in children and adolescents. Am J Clin Nutr 2002;75:978-85.
5. HIV/AIDS Prevention and Control office (HAPCO) Federal Ministry of Health. Guideline for cotrimoxazole prophylaxis in HIV/AIDS care and treatment; 2006.
6. WHO Case Definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children; 2007.
7. Castelnovo, Byakwaga H, Schaefer P. Response of Papular pruritic eruption (PPE) to Highly active antiretroviral therapy (HAART) may represent a clinical marker of virological outcome. Int Conf AIDS; 2006.
8. Sanchez M, Fotiades J, Soter NA. The characterization of HIV-associated papular eruptions. Int Conf AIDS 1993;9:447.
9. Rosatelli JB, Machado AA, Roselino AM. Dermatoses among Brazilian HIV-positive patients: correlation with the evolutionary phases of AIDS. Int J Dermatol 1997;36:729–34.
10. Aires JM, Rosatelli JB, de Castro Figueiredo JF, Roselino AM. Cytokines in the pruritic papular eruption of HIV. Int J Dermatol 2000;39:903-6
11. Gilden D. No attrition in research on wasting therapies. GMHC Treat Issues 1997;11:12-6.

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