Common Infectious Diseases and Skin Test Anergy in Children From an Urban Slum in Northeast Brazil

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Background: Acute respiratory infection (ARI), diarrheal disease (DD) and infective dermatitis (ID) are important causes of morbidity in children under five, in Northeast Brazil. Objectives: (a) to evaluate the morbidity of ARI, DD and ID; and (b) to determine their association with cellular immunity in poor urban children from Fortaleza, Brazil. Materials and Methods: A prospective cohort study. At enrollment, multipuncture skin-tests (Multitest CMI) were performed and interpreted according to standard procedures. Children were followed for infectious diseases by weekly home visits. Results: Seventy-one children aged 6 to 21 months were recruited in an ongoing cohort of newborns. A mean of 39 (6 to 63) home visits per child were made, which detected 184.5 symptomatic days per child-year of observation. ARI was present in 62% of the days of illness (6,378 out of 10,221), DD in 23% (2,296 days), ID in 6% (597) and other infections in 4% (373). Episodes per child-year were: 10 for ARI, 7 for DD and 1 for ID. Twelve (17%) out of 71 children were anergic. The incidences of ARI, DD and ID were similar in responsive versus anergic children. The mean duration of ID in anergy was 8.5 days, while it was 4.3 in the responsive group (P=0.007). Anergy was independent of age, sex and nutritional status. Conclusions: A high incidence of ARI and DD was found in these poor urban children. Skin-test responsiveness was not related to malnutrition, nor to morbidity due to ARI and DD, however anergic children had a longer duration of infective dermatitis.

Key Words: Diarrhea, acute respiratory infection, cellular immunity, skin test, child.

Infectious diseases and nutritional deficiency, the principal causes of mortality in children under five years of age in developing countries, are amongst the priorities of Public Health Systems in the developing world and take a large part of the Health Care budget [1,2].

Few prospective protocols in the Americas have analysed the role of cellular immunity in the recurrence of common infections, or in the degradation of the nutritional condition of children. Studies in developing countries have shown that anergy to skin tests is associated with an increase in the frequency and duration of episodes of diarrhea and acute upper respiratory infections. In Kenya, anergic children had a 20% greater incidence of diarrhea compared to responsive children, and in Bangladesh these children had 50% more new episodes of diarrhea [3-5].

We studied the cellular immunity of children from a poor urban community in Northeast Brazil and examined the association of this type of immunity with common diseases, such as acute respiratory infection, diarrhea and infective dermatitis.

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Materials and Methods

Study location and population. The study was conducted at Gonçalves Dias, a slum in Fortaleza, the capital of Ceara state. In this 1,629-inhabitant borough,

17% (277) of the inhabitants are children under five; houses are made of wood and mud or bricks, and have no indoor running water or sanitation. Water for cooking and drinking is taken from scattered hand-operated pumps around, or from a nearby small polluted lake.

Cohort children and surveillance system. Children older than five months of age were enrolled from an ongoing cohort study of patients with persistent diarrhea [6], and were visited weekly. Informed parental consent was requested before enrollment, and a trained Community Health Worker performed the home visits. Visits consisted of interviews of the parents about the children's health and nutrition, using a structured questionnaire.

Disease definition and classification. A pediatrician examined every child with clinical complaints. Diarrhea was defined [7] as three or more liquid stools in 24 hours, the last episode being followed by 48 hours without diarrhea. Acute respiratory infections (ARI) were classified [8] as rhinopharyngitis (cough, running nose, sore throat); otitis media (local pain, running ear, a bulging or red tympanic membrane), and bronchitis (cough, rhonchi, wheezing). Pneumonia was defined according to reports of coughing and fast breathing [respiratory rate (RR) $\geq$50 breaths/min (bpm) in children younger than12 months and RR $\geq$40 bpm in children older than 12 months] [9]. Infective dermatitis (ID) included impetigo, folliculitis, furunculosis, erysipels and cellulitis.

Nutritional assessment. Anthropometric data, recorded at recruitment, were compared with the NCHS standards [10], and analyzed according to z-score deviations of $\leq$ -2 and $\leq$ -3 for weight/height/age, using the software Epi Info 6.04 [11]. Wasting was defined as weight/height z-score < -2, while stanting was defined as height/age z-score below <-2.

Cell-mediated immunity test. Intradermal skin tests were performed with Multitest CMI (Mérieux Institute U.S.A., Miami, FL), standardized for delayed-type hypersensitivity testing in children [12,13]. A multiple-puncture device simultaneously applied 7 antigens: tetanus toxoid (TT), diphtheria toxoid (DT), tuberculin, *Streptococcus* antigen, *Candida, Trichophyton, Proteus,* and a negative control.

The Multitest CMI was applied to the volar surface of the forearm. A pediatrician performed all 48-hour test applications and measurements. Indurations were measured with a caliper in two directions, and the mean value was recorded. Only induration diameters $\geq$2 mm were considered positive [14]. Children without reaction to any antigen were considered non-responsive and those with at least one positive test were considered responsive. The other variables that were analyzed were: number of positive tests in a child, and the sum of the diameters of positive tests.

Statistical analysis. The cell-mediated immune status was correlated with the episodes of infectious diseases during the follow-up. Analysis of variance for parametric variables and non-parametric tests comparing independent series (Mann-Whitney) were used. A P-value $\leq$ 0.05 was considered significant.

Results

Population description, childhood immunization and nutritional status. Seventy-one children were enrolled from a newborn cohort and followed in a 12-month period. The age mean was 9.6 ± 3.5 months (6 to 21 months); 52% (37/71) were boys; 6 children (8%) were not followed during the entire study, but were included for the available period (Table 1).

Thirty children (42%) were up-to-date according to the official vaccine schedule for DTP and BCG; 36 (51%) had less shots than required; and 5 (7.0%) had not received any BCG or DPT vaccine.

The study of nutritional status revealed 1/71 (1.4%) wasted, and 12/71 (17%) stunted, according to weight-for-height and height-for-age standards, respectively.

Morbidity description. Among 19,551 child-days of observation, no information was available for 329 visits (1.7%). In 19,222 child-days of observation, the average duration of monitoring per child was 38.7 ± 15.5 weeks (range = 6 to 63 weeks).

During the 12-month period (Table 2), 71 children presented 1,026 infectious events, a mean of 18.2 episodes/child-year. ARI were the most common, with 52.2% (536/1,026), and 10.3 episodes per child-year; diarrhea represented 35.1% (360/1,026), with 7.0 episodes per child-year; and infective dermatitis represented 12.7% (130/1,026) episodes, an incidence of 1.18 per child-year.

The duration of disease was longest for ARI (excluding pneumonia) with 31% (bronchitis 3,510/19,222 study-days, rhinopharyngitis 2,276 study-days, respectively and 1% otitis media: 208 study-days), followed by 12% for diarrhea (2,296 study-days), 3.5% scabies (675), 2% impetigo (404), and 1.6% for pneumonia (301 study-days). The remaining diseases were found in less than 1% of the study-days.

Of the 360 cases of diarrhea detected, 41 (11.4%) evolved to persistent diarrhea, with an average duration of 25 days.

Children whose mothers attended school less than three years had 19.8 ± 6.4 episodes/child-year, similar to those whose mothers attended school during a longer period (18.8 ± 5.5 episodes/child-year). No differences were seen in disease rates according to the family income (<US$ 75.00 or ≥ US$ 75.00/month: 20.2 ± 7.1 and 18.9 ± 5.2 episodes/child-year, respectively).

Immunization status. Twenty-five children (35%) received two doses of DPT, but, according to the official immunization schedule, only 42% (30/71) were up-to-date, with three DPT doses. BCG was given to 65 (91.5%) of the 71 children. Five children (7%) had not received any vaccine.

Cell-mediated immune response. No local or systemic reactions were reported after the skin tests in 71 children; 59 children were responsive (83%); 41 participants (58%) responded to one or two antigens; 17 (23%) to 3 and 4 antigens; only 1 (1.4%) responded to 5 antigens and no child was responsive to 6 or 7 antigens. There were 12 non-responders (17%); 6 out of 14 (43%) of the children older than one year were non-responsive (Table 1).

No significant differences of responsiveness occurred according to the socio-economic status, level of maternal education, age or sex. Most of the children (72%) were responsive to tuberculin, 35% to TT and DT, 25% to *Candida* and less than 10% were responsive to *Proteus*, *Trichophyton* or *Streptococcus* antigens.

All children responsive to the tetanus toxoid component had received one or more doses of Diphtheria-Tetanus-Pertussis (DTP) vaccine, representing 39% (26/66) of the vaccinated participants. The highest percentage (47%) was found in children with three doses of DPT. The DT component produced a positive response in 33% (22/66) of the vaccinated children, regardless of the number of DPT shots.

A tuberculin-positive test was present in 50/65 (77%) of BCG-vaccinated children, and in 1/6 (17%) of the BCG-non-vaccinated children ($P < 0.05$). Of the 5 non-vaccinated tuberculin-negative children, 4 were non-responsive to all skin tests and one was responsive only to *Candida* antigen.

Among all 7 antigens, only the tuberculin gave a significant decrease in responsiveness with age: 85% (45/53) of the children younger-than-one year, but only 42% (5/12) of the participants >one year were positive.

The average follow-up period was 37.2 ± 14.7 weeks in the responsive and 45.8 ± 18.1 weeks in the non-responsive group. The number of infectious episodes was similar in both groups, with 18 episodes per child-year. No differences were seen in the number of bouts of ARI, diarrhea or other infections. The total number of days per child-year of each infectious disease is shown in Table 3. Non-responsive children had a higher number of days per child-year of illness (228.0) than the responsive children (182.2), especially total days of infective dermatitis (19.5 ± 35 days per child-year in the responsive and 9.6 ± 20.1 in the non-responsive group); however, these differences were not significant.

The mean duration of episodes of acute diarrhea (≤14 days) (Table 4) was similar in the two groups. Persistent diarrhea had a higher mean duration in the non-responsive (40.0 days per bout) than in the

Table 1. Distribution of responsiveness to skin tests according to age and sex of children from the community of Gonçalves Dias, Fortaleza, CE, Brazil

Age group (months)	N	Sex				Skin tests			
		Female		Male		Responsive		Non-responsive	
		n	%	n	%	n	%	n	%
6-11	57	30	52.6	27	37.4	51	89.5	6	10.5
12-24	14	7	50.0	7	50.0	8	57.1	6	42.9
Total	**71**	**37**	**52.1**	**34**	**47.9**	**59**	**83.1**	**12**	**16.9**

Table 2. Distribution of infectious diseases in children from the community of Gonçalves Dias, Fortaleza, CE, Brazil

Type of infection	No. of episodes	(%)	Episodes/Child-year
Respiratory	536	(52.2)	10.25 ± 2.7
Diarrheal disease	360	(35.1)	6.97 ± 4.4
Dermatitis	61	(5.9)	1.18 ± 2.3
Miscellanelous*	37	(3.6)	0.62 ± 1.0
Fever without localizing signs	32	(3.1)	0.56 ± 1.1
Total	**1026**	**(100.0)**	**18.2**

* Whooping cough, conjunctivitis, herpetic stomatitis, varicella, rubella, infectious hepatitis, measles, septicemia, nonspecific exanthema and urinary infection.

Table 3. Infectious disease morbidity in 59 responsive and 12 non-responsive children from the community of Gonçalves Dias, Fortaleza CE, Brazil

Type of infection	Days per child-year (Mean ± SD)				Mann-Whitney P value
	Responsive	(%)	Non-responsive	(%)	
Respiratory	119.3 ± 71.87	(65.4)	146.1 ± 73.71	(64.1)	NS
Diarrhea disease	48.4 ± 56.74	(26.4)	52.8 ± 80.95	(23.2)	NS
Dermatitis	9.6 ± 20.09	(5.3)	19.5 ± 34.96	(8.6)	NS
Miscellanelous*	4.8 ± 9.07	(2.9)	8.3 ± 14.35	(3.6)	NS

* By order: whooping cough, conjunctivitis, stomatitis, varicella, rubella, infectious hepatitis, measles, septicemia, nonspecific exanthema and urinary infection. NS: Non-significant.

Table 4. Episode duration by type of infection in 59 responsive and 12 non-responsive children from the community of Gonçalves Dias, Fortaleza CE, Brazil

Type of infection	Days per episode				Mann-Whitney P value
	Responsive		Non-responsive		
	N. ep.	Mean ± SD	N. ep.	Mean ± SD	
Respiratory	427	11.7 ± 9.4	109	12.5 ± 10.2	0.44
Acute diarrhea	247	4.0 ± 3.1	72	4.3 ± 3.1	0.33
Persist. diarrhea	35	21.7 ± 11	6	40.0 ± 31	0.09
Dermatitis	45	8.3 ± 4.3	16	13.9 ± 8.5	0.007

N. ep. : number of episodes; SD: standard deviation; Persist.: Persistent.

responsive children (21.7 days), but this difference was not significant. ARI episodes had a similar duration in the non-responsive (12.5) and the responsive (11.7 days per episode) groups, though infective dermatitis lasted 8.3 days in responsive children and 13.9 days in the non-responsive group (P= 0.007).

Discussion

The children involved in this prospective study represent about 30 per cent of the under-five-year old group in the Gonçalves Dias community. As a community-based protocol, the clinical and epidemiological information reported here probably represent the general pattern for poor urban communities in Northeast Brazil. Most of the diagnoses were made clinically, due to the difficulties in obtaining laboratory tests.

Weight-for-height was adequate for 99% of the participants and malnourished children were predominantly stunted, with only a few wasted children. This pattern is similar to that found in other developing countries [15] and is due to the low age of the participants (< 24 months), in a population affected by intra-uterine malnutrition. Breast feeding can prevent wasting, despite economic and social deprivation; Social Care Programs, such as the distribution of milk and food, are important means to avoid a poor nutritional status for these impoverished mothers and children.

The 53% incidence of infectious diseases in child-days of observation (18 episodes per child-year) is similar to that found in previous cohort observations in developing countries, with rates varying from 46.6% to 75% [15-17]. Acute respiratory infections (ARI) and diarrhea (DD) were the most frequent types of episodes observed, as reported elsewhere [15,17-19]. The high incidence of respiratory infections in this community, 52% (10.3 episodes per child-year), has been reported previously in Ceara, where 64% of children under five showed at least one respiratory symptom during a nine-month surveillance [20]. The incidence of 0.48 episodes of pneumonia per child-year was close to the 0.26 episodes found in Papua New Guinea [21], 0.29 in Navajo children in the US [22], 0.33 in Peru [15], and 0.57 in children in Bangladesh [17]. The incidence of lower respiratory infections was probably underestimated due to difficulties in assessing the duration of the episodes.

The incidence of 7 episodes per child-year of diarrheal diseases is among the highest ever reported [15,17,19,23]. The 11% rate of acute diarrhea evolving into persistent diarrhea was similar to other reports [24-26], although higher than previously found in Ceará [27].

The 3% incidence of ID was similar to that found in Guatemala [19]. In Bangladesh [17] the 13.1% incidence of ID was attributed to the difficulty to provide water for bathing during the dry season, a finding not observed in our study.

The socio-economic level and the low level of schooling of the mothers were not associated with morbidity in Gonçalves-Dias, different from other studies in which infection episodes were significantly reduced in the group with higher maternal education. Our observations may have been influenced by the few mothers (only 12%) with three or more years of schooling and the low number of families with an income higher than US$ 150.00 per month.

The tuberculin, TT and DT antigens were those that contributed most to the positive skin test response. The 72% (51/71) positive tuberculin response rate was greater than reported in Peru among BCG recipients (56%). In India, positive tuberculin tests ranged from 65% to 82% in children under three [28]. The percent children responsive to TT and DT (39% and 33% respectively) was lower than in Peru (53%) [29], and the United States (54.5%) [30]. Above optimal temperatures for the transport and storage of DPT vaccine in our environment could explain such low responsiveness. The response rates to *Candida* (25%), *Proteus* (8.5%) and *Streptococcus* (5.6%) were lower than found in Peru (39%, 23% and 13% respectively) [29]. This could be explained by the young age of our participants, with less exposure to these agents.

The 17% rate of anergic children in Fortaleza was higher than found in the USA [14] (6.8%), and Peru [29] (8%), at the same ages, but similar to the 10-20% observed in children between 6 and 60 months old in India [13]. Even if we exclude unvaccinated children, the non-responsive rate was as high as 16%.

The probable causes of the observed anergy were not investigated, and should be the aim of further studies. Although the nutritional condition was similar in the two groups, micronutrient deficiencies (vitamin A and D, pyridoxine, folic acid, zinc, iron) could have influenced the responsiveness [30-33]. Asymptomatic infections, particularly viral (herpesvirus group), might cause an unspecific immunodeficiency. HTLV-I infection has been associated with prolonged infective dermatitis in Jamaica. Chronic infective dermatitis is associated with human T lymphotropic virus type I (HTLV-I) as well as with delayed-type hypersensitivity impairment [34]. However, HTLV-I infection in the city of Fortaleza is as low as 0.34% of the population, with prevalence increasing with age [35], and thus could not be implicated in our study group. It has not been reported that HTLV-I infection in Northeast Brazil is associated with skin-test anergy.

No association was detected between the incidence of infections and negative skin tests. Similar results in under-35-month-old children were found in India with other methods [3]. Studies using Multitest CMI, in children under three and under five, showed an increase in diarrhea episodes among anergic children in Peru [29] and India [13], respectively. Particularly in the Indian study, the disparity could be due to fewer episodes of diarrhea when compared to our community (4.6 vs. 7.0 episodes per child-year, respectively). Also, the nutritional condition of the Brazilians (1% wasting) was better than in rural India (15 to 30% wasting). The greater nutritional deficiency may also involve micronutrient deficiencies, thus influencing the immune response. The duration of the episodes of infection, which play a role in the severity of the disease, was significantly longer only for episodes of infective dermatitis among the non-responsive children. In a previous study, Koster et al.[3] also found longer episodes in non-responsive children.

Very few (7%) of the children did not receive any vaccine, though only 42% had up-to-date immunization cards according to the official schedule. There is an imperative need to improve immunization coverage rates, since non-responsive children would be at greater risk of severe infections. A surveillance of vaccine coverage must be set up in high poverty slums, where Health Education and easy access to Immunization Programs are not assured.

Although there was a correlation between the duration of dermatitis and anergy, the sample size was probably not large enough to demonstrate a correlation between episodes of infection and anergy. Also, children older than two years should be included. Larger studies are necessary, in order to determine the reasons why children living in poor socioeconomic conditions behave differently in terms of infectious morbidity.

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