Global Pediatric Health
January-December 2015: 1–6

DOI: 10.1177/2333794X15594183
gph.sagepub.com
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Sociodemographic, Epidemiological, and Clinical Risk Factors for Childhood Pulmonary Tuberculosis in Severely Malnourished Children Presenting With Pneumonia: Observation in an Urban Hospital in Bangladesh

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Abstract

We aimed to evaluate sociodemographic, epidemiological, and clinical risk factors for pulmonary tuberculosis (PTB) in children presenting with severe acute malnutrition (SAM) and pneumonia. Children aged 0 to 59 months with SAM and radiologic pneumonia from April 2011 to July 2012 were studied in Bangladesh. Children with confirmed PTB (by culture and/or X-pert MTB/RIF) (cases = 27) and without PTB (controls = 81; randomly selected from 378 children) were compared. The cases more often had the history of contact with active PTB patient ($P < .01$) and exposure to cigarette smoke ($P = .04$) compared with the controls. In logistic regression analysis, after adjusting for potential confounders, the cases were independently associated with working mother ($P = .05$) and positive tuberculin skin test (TST; $P = .02$). Thus, pneumonia in SAM children is a common presentation of PTB and further highlights the importance of the use of simple TST and/or history of contact with active TB patients in diagnosing PTB in such children, especially in resource-limited settings.

Keywords

children, history of contact, pulmonary tuberculosis, pneumonia, severe acute malnutrition, tuberculin skin test

Introduction

The World Health Organization (WHO) in their report in 2012, based on vital registration data, estimated that globally there were 530000 cases of tuberculosis (TB) among children under 15 years of age and 74000 deaths in HIV-uninfected children.[1] However, the real picture might be different than the estimates, as with accurate diagnosis and good reporting system, children are likely to contribute as high as 20% of the total TB disease burden in endemic areas.[2] On the other hand, case detection and reporting of TB cases are alarmingly low, especially in resource-poor settings of developing countries including Bangladesh.[3] Moreover, diagnosis of TB in children who present with acute pneumonia and severe malnutrition is also very difficult due to difficulties in differentiating the clinical signs of pulmonary TB (PTB) from pneumonia in such children.[4] Furthermore, mortality is high among these children with PTB.[5] The comorbidity of acute pneumonia with severe malnutrition is a serious problem among children under 5 in developing countries.[6-8] The duration of symptoms in PTB presenting as

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acute pneumonia, especially in children with severe malnutrition, such as cough, fever, anorexia, and failure to thrive, is often less than 2 weeks.[9] A number of recently published data suggest that, in addition to the usual respiratory bacterial etiology in community-acquired acute pneumonia in severely malnourished children, TB is more common than generally considered.[4,9-11] Thus, it is imperative to understand the risk factors for severely malnourished children who have PTB presenting with acute pneumonia in order to initiate early treatment to have better outcome. Nevertheless, clinical predicting factors of PTB in severely malnourished children presenting with acute pneumonia has never been evaluated, although this is important for clinicians in the management of pneumonia in children living in communities where TB is highly endemic.[10] Dhaka Hospital of the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) often treats TB cases who present with severe malnutrition and pneumonia and is often associated with fatal outcome.[9] Thus, we aimed to evaluate the sociodemographic, epidemiological, and clinical predicting factors associated with PTB in severely malnourished children who present with community-acquired acute pneumonia.

Methods

Ethical Standards Disclosure

This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving patients were approved by the Research Review Committee and Ethical Review Committee of icddr,b. Written informed consent was obtained from all legal guardians of the patients.

Study Design

The study was conducted at the Dhaka Hospital of icddr,b. We used an unmatched case–control design and studied severely malnourished children of both sexes, aged 0 to 59 months, admitted to the intensive care unit, high dependency unit, or acute respiratory infection ward of the Dhaka Hospital of the icddr,b with cough/respiratory difficulty and radiological pneumonia between April 2011 and July 2012. Children with severe acute malnutrition (SAM) and pneumonia who had confirmed PTB (diagnosed by mycobacterial culture and/or by real-time polymerase chain reaction by Xpert MTB/RIF from a single sample of induced sputum and gastric lavage in a reference laboratory of icddr,b) constituted the cases, and SAM children with pneumonia having "no TB" (no "confirmed PTB" and no "probable TB") constituted the controls. Controls were randomly selected by computer randomization using SPSS (version 17.0; SPSS Inc, Chicago, IL) from all eligible children in a computerized data source of this study. A 1:3 unmatched case–control ratio was used to increase the statistical power of our analyses. Pneumonia was defined radiologically as the presence of end-point consolidation or other (non-end-point) infiltrate in lungs according to the WHO radiological classification of pneumonia,[12] and the finding was confirmed independently by a radiologist and a pediatrician (MJC). Children with severe wasting (z score for weight for height less than −3 of the median of the WHO anthropometry), severe undernutrition (z score for weight for age less than −4 of the median of the WHO anthropometry), or nutritional edema were considered as severe malnutrition. "Confirmed TB," "probable TB," and "no TB" have been defined in a recently published article.[9]

The collection and laboratory procedure of induced sputum and gastric lavage has been described elsewhere.[9,13]

Setting

Study setting has been described in a recent publication.[9]

Patient Management

Patient management of the study has already been described previously.[9] Pneumonia in severe malnutrition was managed according to the WHO algorithm,[14] other components of severe malnutrition were followed according to the hospital's guidelines,[15] and childhood TB was managed following the national TB guideline.[16]

Measurements

Case report forms were developed, pretested, and finalized for data acquisition. The data were collected by a trained study physician on enrolment. Characteristics analyzed include demographics (age, gender, working mother [daily laborer or garments worker], slum dweller, socioeconomic status, lack of intake of BCG vaccination [no scar in upper arm], lack of window/exhaust fan at home, exposure to cigarette smoke at home), clinical characteristics (presence of cough, duration of cough prior to admission, history of poor feeding, history of contact with TB patient, breathing difficulty on admission, severe wasting, severe underweight, fever with duration on admission, oral thrush on admission, no adventitious sound in lungs on admission, crackles in lungs on admission and nutritional edema, z score against weight for height/length and weight for age, abnormal mental status, hypoxemia [SPO_2 < 90% in air]), and positive tuberculin skin test (TST).

Analysis

All data were entered into SPSS for Windows (version 15.0; SPSS Inc, Chicago, IL) and Epi-Info (version 6.0, USD, Stone Mountain, GA). Differences in proportions were compared by the χ^2 test. In normally distributed data, differences of means were compared by Student's *t* test, and Mann–Whitney test was used for comparison of data that were not normally distributed. A probability of less than .05 was considered statistically significant. Strength of association was determined by calculating odds ratio (OR) and their 95% confidence intervals (CIs). In identifying risk factors of PTB in children with SAM and pneumonia, variables were initially analyzed in a univariate model, and then independent risk factors were identified using logistic regression after being adjusted with potential confounders.

Results

Among a total of 1482 children who were screened with severe malnutrition during the study period, 405 fulfilled the eligibility criteria. There were 27 cases. Among the remaining 378 children, 60 had probable TB and 318 did not have any evidence of TB (either probable or microbiological). A total of 81 controls were randomly selected from 318 children. Among the cases, PTB was confirmed by culture in 10 children, by X-pert MTB/RIF in 21 children, and 4 children were common in both tests. Diagnostic procedure of PTB among these children has been described elsewhere.[9] The cases more often had the history of contact with an active PTB patient, exposure to cigarette smoke, and more often had higher duration of fever compared with the controls (Table 1). In logistic regression analysis, after adjusting for potential confounders such as exposure to cigarette smoke and poor socioeconomic status, severely malnourished under-5 children with pneumonia who had PTB more often had working mother and positive TST (Table 2). As one cell in a 2/2 table analysis for the patient having a history of contact with TB patient was "0," we could not fit it in the logistic regression model, although it has been revealed as a strong predictor of PTB by 2/2 table analysis. The distribution of other variables on admission is shown in Table 1, and the variables were comparable among the cases and the controls.

Discussion

Our study has a number of important observations: first, PTB in severely malnourished children having pneumonia had strong association with the history of contact with active PTB patients; second, PTB in such children was also strongly associated with TST; third, it had strong association with working mother; fourth, they had more exposure to cigarette smoke at home and more often had the higher duration of fever compared with those who did not have PTB.

The observation of strong association of childhood PTB with a history of contact with TB source case is very important. Children under 5, especially under 1 year of age, who come in contact with TB source cases usually have 50% chances to develop TB and 95% of the cases develop TB within 1 year of the exposure.[17] The median age of our study children with confirmed TB was 14 months and most of them had the contact within 1 year of their age. Moreover, all of them had respiratory symptoms (cough or difficult breathing), signs (severe malnutrition and fever and/or crackles on auscultation in lungs), and abnormal radiological findings. Although the duration of fever and cough of our study children was less than 2 weeks, childhood TB in children with severe malnutrition having pneumonia could be as high as 23%.[9] Thus, observation of history of contact with TB source case as one of the predicting factors in diagnosing childhood PTB is understandable. The finding indicates that any severely malnourished child hospitalized for presumed pneumonia and has a history of contact with TB source case may be treated as TB disease after performing relevant investigations in diagnosing PTB.

Our observation of TST as one of the independent predictors of PTB in severely malnourished children having pneumonia is understandable. Severely malnourished children are often immune-compromised, resulting in poor inflammatory response,[18] and thus, TST often results false-negative in such children.[19,20] However, positive TST increase the chance of having TB in children with severe malnutrition.[21] Moreover, positive TST in children with severe malnutrition presenting with pneumonia defined by abnormal chest radiography[12] is highly associated with PTB.[9] Thus, clinicians in resource-limited settings may rely on positive TST in diagnosing and treating TB in severely malnourished children having cough or respiratory difficulty and radiological pneumonia, although further evaluation for TB may be required in such children with negative TST.

The observation of working mother as one of the independent predictors of childhood PTB having severe malnutrition and pneumonia was interesting. We screened all the working mothers of the confirmed TB cases and almost none of them had evidence of active TB. As almost all the working mothers were slum dwellers, these abandoned children at home might have lacked in care and probably had exposure to fire-wood smoke and indoor air pollution, common in slums, and these are strongly associated with childhood TB.[22]

Table 1. Sociodemographic, Epidemiological, and Clinical Features in Children Under 5 Presenting With Severe Acute Malnutrition and Pneumonia With Pulmonary Tuberculosis (Cases) and Without Pulmonary Tuberculosis (Controls)[a].

Characteristic	Cases (n = 27)	Controls (n = 81)	OR	95% CI	*P* Value
Male sex	18 (67)	45 (56)	1.60	0.59 to 4.41	.43
Age in months (median, IQR)	14.0 (6.0, 24.0)	8.5 (5.0, 18.0)	—	—	.19
Working mother	9 (33)	10 (16)	3.50	1.10 to 11.19	.02
Slum dweller	13 (48)	38 (47)	1.05	0.40 to 2.74	.91
Poor socioeconomic condition	24 (89)	67 (83)	1.67	0.40 to 8.06	.55
Lack of intake of BCG vaccine	4 (15)	9 (11)	1.39	0.32 to 5.63	.73
History of contact with TB patient	5 (19)	0 (0)	4.68[b]	3.23 to 6.78	<.01
Exposure to cigarette smoke at home	22 (82)	46 (57)	3.35	1.06 to 11.27	.04
Lack of window/exhaust fan at home	13 (48)	20 (67)	0.60	0.19 to 1.8	.48
Presence of cough	25 (93)	70 (86)	1.96	0.37 to 13.82	.51
Duration of cough prior to admission (days)	7.0 (3.5, 8.5)	5.0 (3.0, 7.0)	—	—	.13
History of poor feeding	1 (4)	5 (6)	0.62	0.03 to 5.89	1.0
Breathing difficulty on admission	8 (30)	31 (38)	0.68	0.24 to 1.90	.56
WHZ (mean ± SD)	−3.73 ± 1.62	−3.82 ± 1.47	−0.09[c]	−0.57 to 0.76	.79
WAZ (mean ± SD)	−5.04 ± 0.97	−4.80 ± 1.37	−0.24[c]	−0.80 to 0.33	.41
Fever on admission (≥38°C)	14 (52)	45 (57)	0.86	0.33 to 2.25	.91
Duration of fever prior to admission (days)	6.5 (5.0, 22.5)	4.0 (3.0, 5.5)	—	—	<.01
Crackles in lungs on admission	14 (52)	55 (68)	0.51	0.19 to 1.35	.20
Hypoxemia on admission (SpO_2 <90% on air)	1 (4)	8 (10)	0.35	0.02 to 3.02	.45
Positive tuberculin skin test	6 (22)	1 (1)	22.86	2.47 to 532.40	<.01

Abbreviations: OR, odds ratio; CI, confidence interval; IQR, interquartile range; SD, standard deviation; WHZ, weight for height z score (wasting); WAZ, weight for age z score (underweight); SpO_2, transcutaneously measured blood oxygen concentration.
[a]Data represent n (%), unless specified.
[b]Relative risk (as odds ratio was unidentified there).
[c]Mean difference.

Table 2. Results of Logistic Regression Analysis to Explore the Independent Sociodemographic, Epidemiological, and Clinical Risk Factors of Pulmonary Tuberculosis in Children Presenting With Severe Acute Malnutrition and Pneumonia.

Characteristics	OR	95% CI	*P* Value
Poor socioeconomic condition	1.97	0.41 to 9.53	.40
Slum dweller	0.37	0.11 to 1.23	.10
Exposure to cigarette smoke at home	2.82	0.80 to 9.489	.10
Working mother	3.67	1.01 to 13.90	.05
Lack of intake of BCG vaccine	1.12	0.23 to 5.53	.89
Lack of window/exhaust fan at home	2.12	0.58 to 8.10	.25
Positive tuberculin skin test	16.44	1.51 to 179.17	.02

Abbreviations: OR, odds ratio; CI, confidence interval.

Exposure to passive cigarette smoke had been observed to have the association with confirmed TB among severely malnourished children having pneumonia in 2/2 table analysis; however, it become insignificant after adjusting for confounders in logistic regression analysis. It might be due to the strong confounding role of other parameters such as TST and working mother. However, association of passive smoking with childhood TB has also been previously reported.[22] Although the duration of fever among our study children with severe malnutrition and pneumonia was less than 2 weeks, the comparative higher duration of fever among confirmed PTB cases compared with those without TB is understandable.

There were 2 limitations of this study. First, the collection of only one sample of induced sputum and gastric lavage might limit our confirmed cases. Second, the small sample size might limit risk factors of childhood TB in such children.

In conclusion, the results of our data suggest that severely malnourished children with cough and/or respiratory difficulty and radiological pneumonia having

history of contact with active TB patients, or positive TST, or working mother are prone to have PTB. The results are very simple but further underscore the value of the use of history of TB contact or TST in diagnosing TB among severely malnourished children with respiratory symptoms/signs and radiological pneumonia. Use of these simple parameters may help avoid delay in managing such children in order to prevent long-term morbidity and deaths especially in resource-limited settings.

Acknowledgments

We gratefully acknowledge the donors for their support and commitment to the research efforts of the International Centre for Diarrhoeal Disease Research, Bangladesh. We would like to express our sincere thanks to all physicians, clinical fellows, nurses, members of feeding team, and cleaners of the hospital for their invaluable support and contribution during patient enrollment and data collection. We would also like to express our gratitude to caregivers/mothers of the study participants for their consent to enroll their children in the study.

Author Contributions

All the authors contributed in designing the study, carrying it out, analyzing the data, and writing the article. Additionally, MJC led the write-up and finally approved the article.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was funded by International Centre for Diarrhoeal Disease Research, Bangladesh (Grant No. Gr-00233) and its donors who provide unrestricted support to the institution for its operations and research. Current donors providing unrestricted support are the following: Australian Agency for International Development; Government of the People's Republic of Bangladesh; Canadian International Development Agency; Swedish International Development Cooperation Agency; and the Department for International Development, United Kingdom.

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