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Pediatric Tuberculosis: The Litmus Test for Tuberculosis Control

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Abstract

Background—The epidemiology of pediatric tuberculosis (TB) from 1995–2000 in Harris County, TX has been previously reported. This study was conducted to evaluate the continued trends of *Mycobacterium tuberculosis* (MTB) clustering and the role of genotyping in pediatric TB.

Methods—Data came from the Houston Tuberculosis Initiative, a prospective population-based active surveillance and molecular epidemiology project. The study population consisted of TB patients ≤ 18 years of age diagnosed in Harris County, TX from 2000 to 2004. Available MTB isolates were characterized by IS6110 restriction fragment length polymorphism and spoligotyping.

Results—103 pediatric TB cases were enrolled in the Houston Tuberculosis Initiative study from 2000–2004. Sixty-one (59%) patients had potential source cases. MTB isolates were available and genotyped for 36 pediatric cases; 27 (75%) were clustered into 22 different genotypes. Of the 20 genotyped patients with a potential source case, 16 (80%) were clustered. Genotypes matched the potential source case in 12 cases. Eleven of the 16 (69%) genotyped patients without a potential source case were clustered.

Conclusions—Compared with pediatric cases in 1995–2000, there was a significant increase in the number of patients with unknown potential source cases that were clustered within the Houston Tuberculosis Initiative database. Since genotypic clustering is associated with recent transmission, there appears to be a failure in the identification of potential source cases through contact tracing. Reduced funding of public health departments forces more limited TB control activities and therefore could pose a threat to TB control.

Keywords

tuberculosis; pediatric; genotype; cluster

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Conflicts of interest For the remaining authors, none were declared.

Introduction

Harris County, TX contributes significantly to not only the overall national burden of tuberculosis (TB), but also to pediatric TB cases. In terms of annual TB case counts by city, Houston ranks second behind New York. In the Houston Metropolitan Statistical Area, 402 cases of adult and pediatric TB were confirmed in 2010 accounting for a case rate of 6.7 per 100,000. [1] This was nearly twice the national average of 3.6 cases per 100,000 in the same year. As far as pediatric cases, between 1993 and 2006, 12 % of all US pediatric cases came from Texas [2] and in 2010 the Houston Metropolitan Statistical Area had the second highest number of TB cases among children younger than 5 years of age.[1]

The Centers for Disease Control and Prevention (CDC) recommends that control of TB in children and adolescents receive high priority. Because a case of tuberculosis in an infant and young child is inherently due to recent transmission, pediatric cases often direct TB control programs to an adult in the community that is actively transmitting disease. In as much, children are an important component of TB eradication programs and have proven to be markers for TB transmission within communities.[3]

Wootton et al. [4] reported the epidemiology of pediatric TB in Harris County, TX from 10/1/1995–9/30/2000. This study questioned the accuracy of traditional contact investigations and highlighted that molecular characterization of TB isolates may help identify source cases. We conducted this study to evaluate the continued trends in clustering of pediatric TB in Harris County, TX. Our study goal was to determine the role of genotyping in the identification of source cases for pediatric TB.

Materials and Methods

Available data was reviewed from the Houston Tuberculosis Initiative (HTI), a prospective population-based active surveillance and molecular epidemiology project. The HTI enrolled Harris County TB patients reported to the City of Houston Department of Health and Human Services and Harris County Public Health and Environmental Services from October 1, 1995 through September 30, 2004 (hereafter referred to as 1995 to 2004) and captured 85% of patients reported to these agencies.[5] The current study population consisted of TB patients who were 18 years of age and younger, counted in Harris County, TX from October 1, 2000 to September 30, 2004 (hereafter referred to as 2000 to 2004). Cases or parental proxies were interviewed using a standardized questionnaire. Available *Mycobacterium tuberculosis* (MTB) isolates were characterized by insertion sequence (IS) *6110* restriction fragment length polymorphism (RFLP) using an internationally standardized method and results were analyzed with the BioImage Whole Band Analyzer software version 3.2 (BioImage, Ann Arbor, MI). Genotype information was supplemented with spoligotyping to discriminate among isolates with 5 or fewer IS*6110* copies.[6] Spoligotype families were identified by matching the octal code to the SPOLDB4 database.[7]

Geographic Information Systems tools were used to assess for any geographic clustering, within previously identified genotypic MTB clusters and spatial autocorrelation with risk factors associated with TB transmission. These risk factors included bus-ridership, a covariate shown previously to be associated with HTI Homeless TB cases and census tracts with endemic TB in Harris County.[8]

Definitions

Cases were considered clustered if their TB isolate matched another isolate in the HTI database with an identical number of bands and molecular weight pattern by RFLP, and among isolates with 5 or fewer IS*6110* copies, matching spoligotypes.

A potential source case (PSC) was defined by public health and/or HTI interviews as a close contact to a case patient who carried a diagnosis of tuberculosis disease. Cases were considered to have geographic proximity if they shared the same zip code.

Case definitions included: laboratory-confirmed, clinical case, or provider diagnosis. Laboratory confirmation signified that the organism was isolated by culture, PCR, or acid-fast bacilli were observed in pathologic specimens. Clinical criteria included a positive tuberculin skin test, clinical findings consistent with TB, and treatment with at least 3 anti-TB drugs. Provider diagnosis was at the discretion of the clinician but in general followed criteria set forth by the American Academy of Pediatrics.[9]

Data were analyzed using Stata 10 (Stata Corp. 2007, College Station, TX). Categorical variables were compared using the χ^2 test, logistic regression or Fischer's exact test when appropriate. All p-values were 2-sided with $\alpha = 0.05$ as the significance level.

Results

Between 2000 and 2004, 121 pediatric TB patients were reported to the Harris County public health departments. Eighteen patients were excluded because they were prevalent cases ($n = 4$), unable to be located ($n = 11$), and refused interview ($n = 3$). Thus, 103 pediatric TB cases were enrolled in the HTI study. The characteristics of the pediatric cases are listed in Table, Supplemental Digital Content 1, http://links.lww.com/INF/B280. Forty-seven percent of cases were younger than 5 years-old. Females represented 52% of cases. Sixty-three percent of cases were Hispanic and the majority (81%) of cases were US-born. One-half of patients had extra-pulmonary sites of disease. Two case isolates were drug resistant, isoniazid-monoresistant and isoniazid/streptomycin, respectively. Contact investigations or HTI interviews were able to identify that sixty-one patients had a potential source case. Table 1 summarizes the characteristics of pediatric TB cases with and without an identified source case. Having a PSC was associated with younger age and US birth.

MTB isolates were available from only 41 (40%) cases and 36 (35%) were genotyped. Twenty-seven (75 %) genotyped cases were clustered into 22 different molecularly characterized IS*6110* groups within the 1995–2004 HTI database (Table 2). At least eight of 27 (30%) clustered isolates belonged to the Beijing family; other lineages are shown in Table 2. Three of the 22 genotypes had more than 1 pediatric case, with the largest pediatric representation in one cluster being 3 patients. The median size of the 22 HTI clusters was 7.5 with matched genotypes, with a range of 2 to 122 cases per cluster. Of the 22 MTB clusters, 7 were not identified by HTI between 1995 and 2000. Thus, 7 clusters that involved pediatric patients were 'new' to HTI between 2000 and 2004. Of the 7 pediatric cases in 'new' clusters, 5 had a potential source case.

Of the pediatric patients with a PSC between 2000 and 2004, 16 patients were clustered (Figure, Supplemental Digital Content 2, http://links.lww.com/INF/B281). Matching between the genotype of the pediatric patient and the PSC occurred in all 12 cases for which genotypes were available for both the patient and source.

Of the 27 clustered pediatric cases, the age distribution was as follows: 11 were 0–4 year-olds, two were 5–9 year-olds, four were 10–14 year-olds, and 10 were 15–18 year-olds. The age distribution of clustered patients was bi-modal, with nearly 80% of cases being in the age groups 0–4 years-old or 15–18 years-old.

Eleven patients without a PSC were clustered. We further evaluated if epidemiologic links existed within clusters that included a pediatric case that did not have a public health reported source case (Table 3). The 11 cases fell into 9 clusters, of which 4 had direct

epidemiologic links which could be discerned. In another 4, possible epidemiologic links existed, including geographic proximity, shared bus routes, and the risk factor of homelessness. We could not find any epidemiologic links in 1 cluster (H040).

In cluster H218, there were a total of 7 patients across all HTI years. All cases in this cluster were either born in Vietnam or had Vietnamese parents. Direct epidemiologic links were found between 4 cases in this cluster. Three pediatric cases between 2000 and 2004 belonged to this cluster, 2 of whom did not identify a contact. One of these cases was an 18 year-old male born in Vietnam. Both pediatric cases in cluster H218 without a source case lived in the same zip code. Additionally, they shared a zip code with another US-born clinically-diagnosed pediatric case presumed to have been infected by his/her Vietnamese mother who belonged to this cluster.

Cases in cluster H147 were primarily Hispanic. Of 15 cases, 13 (87%) were Hispanic and 6 (40%) reported being born in Mexico. Cluster H147 contained 2 US-born pediatric cases without a named/known source. Six other cases in this cluster had a direct epidemiologic link to at least another case in this cluster; these had morbidity dates within an 18 month period of each other. One of the pediatric cases belonging to this cluster was a 4 month-old infant, whose mother reported the child rode a public transport bus one or more times a week. This infant shared a bus route with at least one other adult member of this cluster. The individual with whom the child shared the bus route was deemed to have been infectious for a period of 127 days. This potential source case had TB risk factors including homelessness and incarceration.

One pediatric case without a source belonged to cluster H007, which principally comprised US-born individuals. The child in this cluster was Hispanic, but 58% of the cases were African-American. At least 17 of the 85 cases in this cluster had a direct epidemiologic link to at least another case in this cluster. In cluster H014, 6 cases had a direct epidemiologic link to at least another case in this cluster.

The pediatric case in cluster L024 shared a zip code with an adult in the cluster. The 2 adults in cluster H231 had the shared risk factor of homelessness. In cluster L028, the pediatric case shared a bus route with 2 adult cases that were infectious for 100+ days. The 15 year-old patient in cluster L007 was geographically clustered with 2 other cases that were diagnosed 2 years prior.

In the n-1 method described by Small et al.[9], the index case is subtracted from the cluster size to obtain the number of cases presumed to be due to recent transmission. Between 1995 and 2004, 577 cases belonged to the 22 clusters that involved pediatric patients. Using the n-1 method, 555 were due to recent transmission.

Discussion

In the first 5 years of the HTI, 220 of 2242 (10%) cases were ≤ 18 years-old. In the subsequent 4 years, 103 of 1306 (8%) were ≤ 18 years-old, a significant decrease in the proportion of pediatric TB cases ($p = 0.048$). Hispanics were overrepresented when considering both the demographics of Houston and the demographics of pediatric cases throughout the United States. Sixty-three percent of the pediatric cases during our current study were Hispanic. In comparison, 46% of children in Harris County, TX (http://txsdc.utsa.edu/tpepp/2004ASREstimates/alldata.pdf) and 39% of national pediatric TB cases were Hispanic.[11]

Between 1995 and 2000, 7 of 78 (9%) of isolates were resistant to at least one drug vs. 2 of 41 (4.9%) in the current portion of the study ($p= 0.42$).

The CDC defines recent transmission as a transmission event occurring within the previous 2 years.[12] Genotyping offers an additional means of distinguishing cases of tuberculosis due to recent transmission from cases that are due to reactivation. The CDC National Tuberculosis Genotyping Service now uses spoligotyping and 24 loci mycobacterial interspersed repetitive units variable number tandem repeat typing to characterize isolates followed by RFLP in certain circumstances.[12] Data from the National Tuberculosis Genotyping and Surveillance Network indicate that spoligotyping alone is not able to distinguish isolates that are common in the United States, including the Beijing and T1 families. Thus, it is of benefit to use RFLP to characterize isolates and imperative that a second PCR-based method such as mycobacterial interspersed repetitive units be used in molecular characterization.[12]

Matching of genotypes does not automatically imply that cases are involved in the same chain of transmission, especially in areas with moderately high prevalence of Beijing family strains such as Houston.[6] There must be “epidemiologic links that can explain where and how they might have transmitted TB among themselves.”[12] Epidemiologic links could include living, working or spending time in the same location, social networks, sharing of risk factors, and the infectious period.[12]

In young children who tend to have rapid progression from infection to disease, pediatric tuberculosis is suggestive of recent transmission. Most TB experts also believe clustering signifies recent transmission.[10] If a significant portion of pediatric cases are clustered, this lends more credence to the fact that cases of pediatric tuberculosis result from recent transmission. We found that 27 of 36 (75%) of pediatric cases from 2000–2004 who had isolates subjected to molecular characterization were clustered. In comparison, when TB transmission dynamics were evaluated in adults in Houston for the years 1996–1998, 666 of 1131 (59%) of cases were clustered and 52% were thought to occur due to recent transmission.[13] The trend suggests a higher proportion of clustering in pediatric patients ($p=0.054$). The evolution of ‘new’ clusters in the HTI database further supports ongoing transmission of tuberculosis in Harris County, TX.

Much like in our study, the proportion of clustered cases in the pediatric population in Harris County between 1995 and 2000 was 72%. This is not an encouraging figure given that improved control of tuberculosis should lead to declines in clustered cases. However, in the current study, 11 of 16 (69%) genotyped cases without a source case were clustered with as many as 85 other cases in Harris County. In contrast, between 1995 and 2000, only 4 of 25 (16%) children without a source case matched via genotyping 1 other adult case in the HTI database.[4] The differences between the 1995–2000 and 2000–2004 data are statistically significant ($p < 0.01$).

We additionally found that there were no mismatches of genotype between pediatric cases and potential source cases identified through traditional contact investigations- 12 cases matched and the genotype of the source case was not available in four cases. This is in contrast to the data previously reported by Wootton for tuberculosis cases in Harris County, TX.[4] It is also in contrast to other published molecular investigations such as that by the Massachusetts Department of Public Health that found that 27% of epidemiologic links were not verified by genotyping. [14]

The lineages in clustered pediatric cases are representative of lineages known to circulate in North America.[15] Both Beijing and T1 families are common in the Unites States.[12] Over 10% and 20% of North American isolates are of the Beijing family or T1 families, respectively.[15]

Patients without a potential source case who are clustered and have possible epidemiologic links deserve further investigation to confirm the epidemiologic links. In Maryland, cluster investigations that occurred after genotyping results were available helped establish 30% more epidemiologic links than traditional contact investigations.[16] Identification of these cases aided in halting continued transmission by identifying cases early. The CDC has ranked by priority the scenarios that warrant cluster investigations. After ruling out false-positive cultures, investigations of clusters that include high-risk patients warrant the highest priority.[12] High-risk populations include those with increased risk of progression from latent to active disease, such as pediatric patients. In circumstances where resources are scarce, 'enhanced' cluster investigations should be conducted when there are more than 2 or 3 cases in the cluster. Using the strict criteria of more than or equal to 4 cases per cluster, between 1995 and 2004, 15 enhanced cluster investigations should have been conducted. In fact, the CDC explicitly states that if it is deemed that interviews need to be conducted for cluster investigations and local resources are insufficient, then it is the state's responsibility to provide those resources.[12]

Limitations to this study exist. Data for parent's country of origin was not routinely collected, limiting our ability to assess foreign-born household contacts as a risk factor for US-born cases. Because isolates were available for only on a few pediatric cases (35%), the extent of clustering is likely conservatively underestimated. There may be endemic strains in Houston that are not due to recent transmission but have been circulating within the pool population for a number of years. The n-1 method assumes clustered cases are due to recent transmission. However, this may not be the case in a population where characterization has occurred over ten years and endemic TB cases are known to occur. Thus, the n-1 method could overestimate associations between cases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Characteristics of pediatric cases according to potential source case (PSC) status

		PSC (*n*= 61)	No PSC (*n* = 42)	P-value (Wald)
Age (mean, median)				
		6.2, 4	9.1, 8.5	0.026
Time living in Harris County				
	< 6 months	1	1	referent
	6–12 months	7	3	0.590
	1–2 years	9	4	0.598
	> 2 years	44	33	0.841
Country of Origin, n (%)				
	Foreign-born	5	15	0.001
	US- born	56	27	
Time living in the US (mean, median)				
		5, 2.4	5.3, 4.6	0.367
Foreign travel				
	Yes	8	5	0.856
	No	53	37	

Table 2

Genotypes of clustered pediatric cases

Cluster	No. of patients	Cluster size‡	IS*6110* copy number	Spoligotype Family	Spoligotype
H003	1	99	20	Beijing	000000000003771
H007	1	85	10	Beijing	000000000003771
H015	1	42	9	Beijing	000000000003771
H033	2	94	21	Beijing	000000000003771*
H218	3	7	18	Beijing	000000000003771*
H040	1	2	12	Beijing†	000000000003771†
H014	1	8	13	U	777777777760031
H147	3	15	9	T1	777777777760771*
H200	1	4	7	T1	777777777760771
L028	1	12	4	T1	777777777760771
H231	1	3	8	S	776377777760751
H236	1	3	7	S	776377700160771
H258	1	2	7	Haarlem 1	777777034020771
H267	1	3	8	Haarlem 2	000000004020771
H222	1	5	9	Haarlem 3	777777777720771
L007	1	22	2	X1	777776777760771
L024	1	29	4	X1	777776777760771
L008	1	122	2	X2	777776777760601
L009	1	10	2	X2	777742777760601
H191	1	4	13	LAM2†	647737607760771†
H288	1	2	10	N/D	N/D
H075	1	4	11	N/D	N/D

N/D = not done

‡Number of Harris County TB Cases with the given cluster designation 1995–2004

*Spoligotype of at least one isolate in this cluster

†Spoligotyping not done on this patient' MTB isolate, designation based on consensus for RFLP- genotype

Table 3

Patients without a source case who were clustered

Cluster	Age	Race/ Ethnicity	Country of Origin	Number in cluster 1995–2004 (pediatric)	Cluster composition	Epi Links within cluster
H218	7 y	Asian	U.S.	7 (4)	100% Vietnamese assoc.	HH & relatives
	18 y	Asian	Vietnam	7 (4)	100% Vietnamese assoc.	HH & relatives
H147	4 m	Hispanic	U.S.	15(3)	40% Mexico- born	HH & friends
	15 y	Hispanic	U.S.	15(3)	40% Mexico- born	HH & friends
H007	2 y	Hispanic	U.S.	85 (3)	96% US-born	Relatives & friends
H014	18 y	Hispanic	U.S.	8 (2)	75% US-born	HH & friends
L024	18 y	Hispanic	Honduras	29 (4)	78% Mexico-born	Possible, geographic
H231	5 y	Hispanic	U.S.	3 (1)	67% Mexican assoc.	Possible, homeless
L028	6 m	Hispanic	U.S.	12 (1)	45% Mexico- born	Possible, bus routes
L007	15 y	Hispanic	El Salvador	22 (1)	53% Mexico-born	Possible, geographic
H040	10 y	Hispanic	Mexico	2 (1)	100% Mexico-born	None