

# Tuberculous Meningitis in Child Born in the US to Immigrants from a Tuberculosis-Endemic Country

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## ABSTRACT

This is a case of a child born in the US to immigrant parents from a tuberculosis (TB)-endemic area of Liberia who was diagnosed with TB meningitis after a greater than 1-month history of unremitting fever. This report aims to highlight the importance of early identification of TB in the pediatric population with risk factors for TB and considering TB as a diagnosis among US born children to immigrants from TB-endemic countries.

**KEYWORDS:** Tuberculous meningitis, refugee, pediatric, immigrant

## INTRODUCTION

Tuberculosis (TB) continues to be the second most common infectious killer in the world among patients of all ages with approximately 1.3 million deaths worldwide attributable to the disease in 2012.<sup>1</sup> While many developing countries continue to struggle with TB control, widespread surveillance and appropriate treatment has allowed the US to maintain a low incidence of the disease. The Centers for Disease Control's (CDC) 2012 annual report noted a total of 9,945 new cases of TB, the lowest number ever of new TB cases in the US in a single year.<sup>2</sup> While the majority of these cases of TB occurred in foreign-born individuals, a significant percentage (37%) occurred in US-born persons.<sup>3</sup> Reaching the appropriate populations to test for TB continues to be key to controlling the transmission of TB.

Among refugee immigrant communities in the US, the risk of TB exposure is higher than the general population. Greater than 85% of refugees worldwide come from countries with a high prevalence of TB and many live in resource poor, crowded conditions prior to immigrating to their final destination.<sup>4</sup> In 2012, more than 58,000 refugees arrived in the US through the US Refugee Admissions Program (USRAP).<sup>5</sup> The state of Rhode Island (RI) has been an important site for refugee resettlement. From 1990–2008, a total of almost 4,800 refugees emigrated to the state of RI with 96% from Africa or Iraq.<sup>6</sup> Prior to relocation, refugees undergo screening by the US Department of State in countries of emigration. CDC screening standards since 2009 require immigrants older than 15 years of age in countries with

WHO-estimated TB incidence rate  $\geq 20$  cases per 100,000 population to be screened by medical history, physical examination and chest radiograph. Only when individuals have symptoms or evidence suggestive of TB or HIV infection are sputum smears and cultures sent for TB.<sup>7</sup> Individuals with possible TB disease with negative smear and culture findings are not generally treated unless findings are highly suggestive of TB disease.<sup>7</sup> These screening exams are often completed months before departure, affording time for new exposure or reactivation. Although refugees are expected to be screened and receive treatment for active TB prior to arrival in the US, studies of refugee populations have found that when rescreened on arrival in the US, a significant percentage of refugees have active TB. A retrospective review of CDC data on refugees and immigrants arriving in the US from 1999-2005 found that 7.0% of those diagnosed with smear-negative tuberculosis and 1.6% of those with an overseas diagnosis of inactive TB (Liu et al described inactive TB as a chest radiograph with evidence of TB that was not clinically active including fibrosis, scarring, pleural thickening, diaphragmatic tenting or blunting of the costophrenic angles) were rediagnosed with active pulmonary TB.<sup>8</sup> This diagnosis was made on the results of chest radiography and sputum smears for those presenting for their follow-up evaluation upon arrival in the US. In the northeast, one study in Connecticut found that 4% of refugees with prior history of disease and presented for TB evaluation on arrival had active disease when reexamined in the US.<sup>9</sup> While the country of origin or emigration for refugees differ in each state, these data suggest that despite screening requirements, a significant number of individuals arrive in the US with active TB disease. Consequently, people who have regular close contact with the refugee community are at higher risk for TB exposure, including US-born children of refugees.

Here we describe a case of TB meningitis in a US-born child of refugee parents after a delay in diagnosis. We will highlight the importance of having a higher index of suspicion for TB in US-born children with TB symptoms and with immigrant parents from TB-endemic areas, especially in families with ongoing exposure to individuals from the immigrant community. Furthermore, we will demonstrate how a delay in diagnosis can increase the morbidity (and potentially mortality) of the disease in the pediatric population.

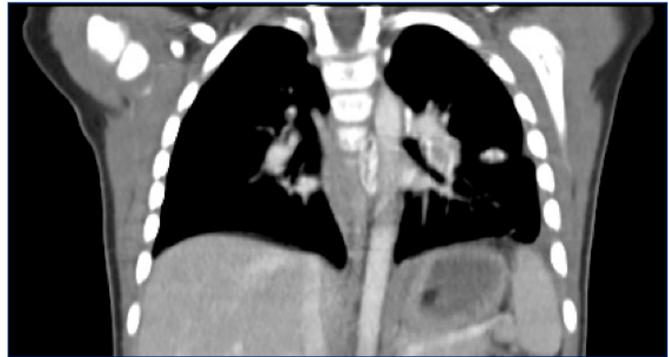
## CASE REPORT

A 2-year-old girl initially presented to her outpatient primary care physician (PCP) after developing a fever to 102.3°F, ear pain and intermittent nonproductive cough. She was the US-born child of Liberian immigrant parents who had arrived in the US 20 years prior to her birth. Both parents were known to have positive PPDs (purified protein derivative) but negative chest x-rays (CXR), and the child had no history of travel outside of the US. Caregivers initially made a diagnosis of pneumonia and sent her home with a 5-day course of azithromycin. When symptoms did not improve, she was brought to the local emergency department (ED) where a further work-up for pneumonia was started. On CXR, she was noted to have a left pleural effusion. She was hospitalized for 7 days during which she underwent a video-assisted thorascopic surgery (VATS) with a left-sided chest tube and a course of ceftriaxone. Bacterial cultures, including acid-fast bacilli (AFB) used to detect TB, were performed and results returned as negative. Adenosine deaminase (ADA) levels and pleural biopsies that can be helpful in detecting TB pulmonary infections were not performed. After completing her course of antibiotics, the patient's fever persisted, and she was brought back to the PCP and ED for further evaluation. A subsequent CXR showed a resolution of the previous pleural effusion, and additional testing including a complete blood count, viral titers for infectious mononucleosis, lead levels and urinalysis were normal. Erythema was noted around the former chest tube site, and the patient was given cefdinir to treat cellulitis.

After an additional 3 weeks of fever, the patient's mother noted signs consistent with new left-sided neurological deficits, including left upper and lower extremity weakness. When the patient returned to the ED for work-up, she was afebrile and all vital signs were stable. On physical exam, she had an abnormal gait with repeated falling to her left side. She had no meningismus, and her lung, cardiovascular and abdominal exams were normal. Other than her gait, the neurological exam was documented to be normal, including no evidence of diminished strength in the upper or lower extremities. Labs showed that the patient had an elevated white blood count with no bandemia. The respiratory viral panel which included testing for respiratory syncytial virus, influenza A and B, metapneumovirus, rhinovirus, enterovirus, adenovirus, parainfluenza and coronavirus was negative. She had a computed tomography (CT) scan of the chest, abdomen and pelvis. Scans of the chest revealed multiple calcified lymph nodes consistent with a prior TB infection (**Figure 1**). The images were otherwise normal, and there was no evidence of active lung infection.

She was admitted for further work-up and evaluation. Overnight, she became increasingly lethargic and less responsive and was transferred to the pediatric intensive care unit (PICU). A CT scan of the head showed ventriculomegaly involving the lateral, third and fourth ventricles (**Figure 2**). A magnetic resonance image (MRI) of the brain revealed

**Figure 1.** Calcified Lymph Nodes with Left Lung Focus on CT Chest



Computed tomography of the chest with IV contrast showing multiple calcified lymph nodes and left lung focus that is consistent with prior tuberculosis infection

**Figure 2.** Ventriculomegaly Seen on CT Head

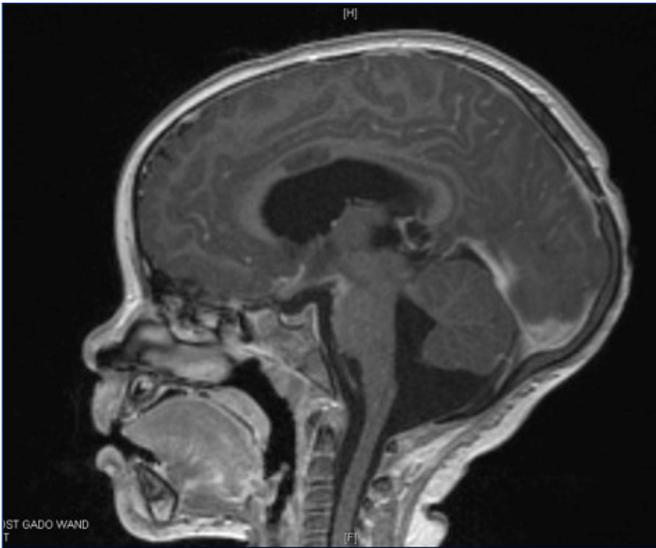


CT head demonstrating moderate dilation of the ventricles

basilar meningeal enhancement as well as acute infarcts involving the corpus callosum and bilateral basal ganglia (**Figure 3**). Later that same day, her PPD was read as positive with a 15 mm induration. In the context of these findings, her imaging was highly suggestive of TB meningitis.

Lumbar puncture and cerebrospinal fluid (CSF) analysis showed an increased white cell count of 233 with a lymphocytic predominance, elevated protein to 103 mg/100mL (normal between 15-60 mg/100mL) and a decrease of glucose to 20 mg /100mL (normal between 50-80 mg/100mL). CSF polymerase chain reaction (PCR) was additionally performed for enterovirus and herpes simplex 1 and 2 that were all subsequently negative. Quantiferon gold blood test was

**Figure 3.** Meningeal Enhancement in the Sylvian Cisterns on MRI Brain



MRI showing patchy basilar meningeal enhancement extending to the Sylvian cisterns, enhancement of the cranial nerves and acute infarcts along the genu of the corpus callosum and basal ganglia

sent as an additional test to support the diagnosis of TB and ultimately yielded a positive result. AFB cultures for blood, urine and CSF did not grow any bacteria.

Initially, the patient's diagnosis remained elusive because tuberculosis was not high on the care team's differential. Her fevers persisted through several trials of antibiotics prior to initiating her TB treatment. She had an extensive work-up for a broad range of viral and bacterial causes of her infection; all were negative except for mildly elevated *Mycoplasma* titers, thought to be an incidental finding. Given her pleural effusions, brain imaging findings, CSF analysis, PPD positivity and QuantiFERON-TB Gold test results, the patient's symptoms were attributed to TB meningitis. Her excellent response to treatment further supported the presumed diagnosis of TB meningitis.

She was started on a four-drug regimen of isoniazid, rifampin, ethambutol and pyrazinamide for a 12-month course of directly observed therapy (DOT). One year after discharge from the hospital, her symptoms have resolved and she has no neurological deficits. She has completed her treatment and has returned to her usual state of health. She was assessed to be a clinical case of tuberculosis based on evidence of exposure, a consistent clinical syndrome, and response to antituberculous therapy. To this day, the source case has not been identified.

## DISCUSSION

This case of TB meningitis demonstrates the importance of increased suspicion for TB in patients living in immigrant and refugee communities in RI, regardless of whether the patient is US- or foreign-born. Delayed diagnosis can result in significant morbidity (and potentially mortality), including further spread of TB. A recent study of US children younger than 5 with symptomatic TB infection found that it took a median of 52 days to initiate TB therapy.<sup>10</sup> Clearly, a higher degree of suspicion is needed. RI continues to welcome refugees who often live with multiple family members and have contact with close-knit communities from their countries of origin, allowing for the possibility of transmission despite efforts to screen and treat new immigrants.

The large majority of cases of active TB among pediatric patients in the US occur in children who are either foreign-born or in close contact with individuals from a TB-endemic country. In a study by Winston et al. evaluating the demographics of pediatric TB cases in the US between 2008–2010, the authors found that 69% of cases occurred in US-born children, but that 66% of these US-born children with active TB had at least one foreign-born parent.<sup>11</sup> Children younger than 5 represent a particularly vulnerable population because they are more likely to progress to active disease and are more likely to develop severe manifestations of TB disease, such as TB meningitis. In an observational study by the Tuberculosis Epidemiologic Studies Consortium from 2005–2007, the majority (53%) of cases of active TB in young children younger than 5 in the US were reported among US-born children with at least one foreign-born parent. In contrast, foreign-born children represented only 17% of cases.<sup>10</sup> This study also examined the reasons for seeking healthcare that led to the diagnosis of active TB. Among US-born children younger than 5 with active TB, only 40% were evaluated and diagnosed due to contact investigations or known TB exposures. The remainder of the children were diagnosed either by routine screening (14%) or because they were symptomatic (46%). While young children should be prioritized during contact investigations of active TB cases, these data suggest that tracing of contacts alone is likely not sufficient to catch all active TB disease in young children in the US.

A child's parents' status as refugees or immigrants from TB-endemic countries should be added as additional risk factors when considering testing for TB in pediatric patients with TB-related symptoms. Despite TB screening policies in place before and upon entering the US, not all individuals with TB are appropriately identified or completely treated. A constant influx of new immigrants as well as contact with family members visiting from TB-endemic countries may also increase a patient's TB risk. Clinicians should have a higher index of suspicion for TB in US-born children living in refugee and immigrant communities from TB endemic countries.

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## Conflicts of Interest

None of the authors have any conflicts of interest or financial disclosures to report.

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