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Original Research

Head and Neck Tuberculosis in Southeastern Region in Turkey, Near the Syrian Border

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ABSTRACT

Objective: The study was conducted to evaluate profiles, demographical data, diagnostic, clinical and treatment approaches in relation to the cases of diagnosed head and neck tuberculosis after the start of the Syrian civil war in 2011. The aim of the study is to share current knowledge on head and neck tuberculosis and to investigate whether there is an epidemiological change with the admission of immigrants after the start of the Syrian civil war.

Methods: Demographic data, contact history, relapse, localization, tuberculin test, BCG vaccination and treatment duration are evaluated variables. Two groups were created. The first group was diagnosed with head and neck tuberculosis between 2006 and 2011 before the outbreak of the Syrian civil war, and the second group was diagnosed between 2012 and 2017 after the war in Syria caused hundreds of thousands of Syrian citizens to flee their homes and cross the border into Turkey.

Results: Head and neck tuberculosis cases tend to increase after the year of 2012. The number of diagnosed non-Turkish citizens expand after the year of 2012 and reach the highest number in 2017. BCG vaccination status and contact history were found to be the only variables that display statistical significance between the groups.

Conclusions: The number of head and neck tuberculosis cases increased after the Syrian war began due to insufficient rates of vaccination among the Syrian population and this population's overcrowded living environment in Turkey. The burden of these crises affects a region rather than the whole country.

Keywords: head and neck, tuberculosis, lymphadenitis, immigrant

INTRODUCTION

Tuberculosis (TB) is among the oldest infections that remains a major health problem in developing countries. One in every three people in the world is infected with or is at risk of developing TB [1]. According to data released by the World Health Organization (WHO), TB is a major public health problem with 10 million new cases worldwide in 2018 and approximately 1.4 million deaths [2]. TB commonly affects the lungs in 80% of all cases, and extrapulmonary organs are involved in 20% of cases. Extrapulmonary tuberculosis (EPTB), the involvement is direct, through a lymphogenous or hematogenous route from the surrounding tissues [3]. Tuberculosis lymphadenitis (TBLA) is the most common type of EPTB infection, with rates varying between 1.5% and 35% depending on the country [4-6]. However, for head and neck lymph node involvement, infectious, inflammatory and neoplastic diseases such as Squamous cell

carcinoma, lymphoma, other granulomatous and inflammatory processes should not be forgotten in the differential diagnosis. [4,6]. One-sided, multiple lymph nodes between 1.5 cm and 5 cm in diameter in the supraclavicular region characterize the classic presentation of TBLA [7]. Besides, there might be different clinical presentations for different mycobacteria: for instance, structural symptoms like fever, weight loss, fatigue, anorexia, and night sweating occur only in 15–20% of TB cases [8]. Apart from cervical TBLA in the head-neck region, laryngeal (<1%), otic (0.05–0.9%), nasal, pharyngeal, retropharyngeal, and salivary organs may also be infected by TB [9-11]. As TBLA can mimic other pathological conditions, this needs to be considered in the diagnosis and treatment of lymphadenitis [12,13]. The frequency of TB is increasing in geographical areas where social crises occur [14]. Before 2015, the percentage of non-Turkish citizen with TB was 1.3% of total cases in Turkey. The rate of non-Turkish citizen with TB multiplied five times between 2015 and 2018 [15]. There are limited studies on how the distribution of EPTB changed during social crises.

We sought to identify the clinical characteristics of patients diagnosed with head-neck tuberculosis (HNTB), to investigate the number of cases, and to determine whether there were significant changes in our data after immigration from Syria to Turkey between 2011–2017 in the city of Gaziantep, which is next to the war zone on the border with Syria, in the southeastern region of Turkey, and to compare our results with international literature.

MATERIALS AND METHODS

The present study was a single-center descriptive and retrospective study conducted with HNTB cases applying to the Tuberculosis Dispensary between January 2006 and December 2017. Tuberculosis Dispensary is a specific center that keeps records and follow-up and treatment data for all the tuberculosis patients diagnosed in the city. We included 378 adult and pediatric patients diagnosed with HNTB. The diagnosis of TB was made pathologically or microbiologically with biopsy, and we evaluated the ages, genders, nationalities, first admission dates, symptoms, lymphadenopathy characteristics (location, side), accompanying systemic diseases, ear-nose-throat examination notes, presence of TB in history, contact history, Tuberculin Skin Test (TST), Acid Resistance Bacteria smear results, durations, and results of the treatments of the cases. Lung involvement was investigated using lung graphics in all cases. The patient data were obtained from the dispensary archive files.

Main Points;

- Head and neck tuberculosis numbers increases in our region after the beginning of the Syrian war
- Tuberculous lymphadenitis was the most common form of HNTB with a right side superiority.
- Patient family contact is found to be statistically significant refugees or socioeconomically low-level local people live in crowded areas
- Low rates of BCG vaccination is risk factor for the occurence of head and neck tuberculosis.
- Isolation of Tuberculosis patients and vaccination of all newborns may contribute to protection against the occurrence of head and neck tuberculosis.

Randomisation

After identifying the numbers of TBLA cases after the Syrian crisis, we divided them into two groups delineated by the onset of the Syrian civil war and the resulting arrival in Turkey of refugees from Syria.

The first group (group 1) included patients diagnosed with HNTB between 2006 and 2011 who were citizens of the Republic of Turkey (RT). The second group (group 2) of HNTB patients included those diagnosed between 2012 and 2017 including non-Turkish and Turkish citizens.

Ethical Considerations

Before the study began, we obtained approval from the Ethics Committee of Clinical Research at Gaziantep University (2018/95), and the necessary institutional permissions were obtained from the Gaziantep Provincial Health Directorate.

Data Assessment

The data were recorded and analysed by using the SPSS 21 Software Program (SPSS Ltd, Chicago, Illinois, the USA). The normality of the data was determined using the Kolmogorov-Smirnov Test. The numeric data were defined as median, frequency, percentages, and standard deviation. The comparison of numeric values between the groups was determined using the Student-t Test in independent samples and the difference among the categorical data was determined with the Chi-Square Test. The significance level was determined as $p< 0.05$.

RESULTS

A total of 378 patients diagnosed with HNTB presented to the Tuberculosis Dispensary during the 12-year study period. The

patients were divided into two groups based on two periods, the beginning of the Syrian conflict (2006–2011) and after the start of the Syrian conflict (2012–2017). Group 1 had 169 patients and Group 2 had 209 patients. Figure 1 shows the total number of HNTB patients diagnosed annually. In group 1, the highest number of diagnoses was in 2007 (40 patients). However, in group 2, 50 patients were diagnosed with HNTB in 2012. In addition, the largest number of non-Turkish citizens (six Syrian national patients) was diagnosed in 2017.

Group 1 consisted of 52 males (30.8%) and 117 females (69.2%). There were 66 males (31.6%) and 143 females (68.4%) in group 2. When evaluated according to age, the mean age was 40.01±18.12 years (min 1; max 86) in group 1 and 38.21±20.22 years (min 1; max 91) in group 2. Diabetes mellitus, hypertension, and hepatitis B were the commonest additional diseases in both groups. All the patients in group 1 were Turkish citizens and in group 2, 25 patients were non-Turkish citizens (23 were Syrian citizens, one was a citizen of the United Kingdom, and one was a citizen of Azerbaijan). The commonest complaints were neck swelling, headache, and neck pain.

Treatment of 152 (89.9%) patients in this study resulted in cure, and 7 patients (4.1%) died during treatment (Table 1).

Table 1. Evaluation of the treatment results of the patients included in the study

Treatment Results	n (%)
Misdiagnosis	1 (0.6)
Transfer to another city	3 (1.8)
Cure	152 (89.9)
Abandoning the Treatment	6 (3.6)
Death	7 (4.1)
Total	169 (100)

When the treatment results were examined, it was determined that four (%57.1) of the 7 patients who died had lymph node involvement, and the other three (%42.9) were TB patients with central system involvement. It was determined that three (25%) of 12 patients with central system involvement died, and the highest death rate among TB localizations was found to be TB with central involvement (Table 2).

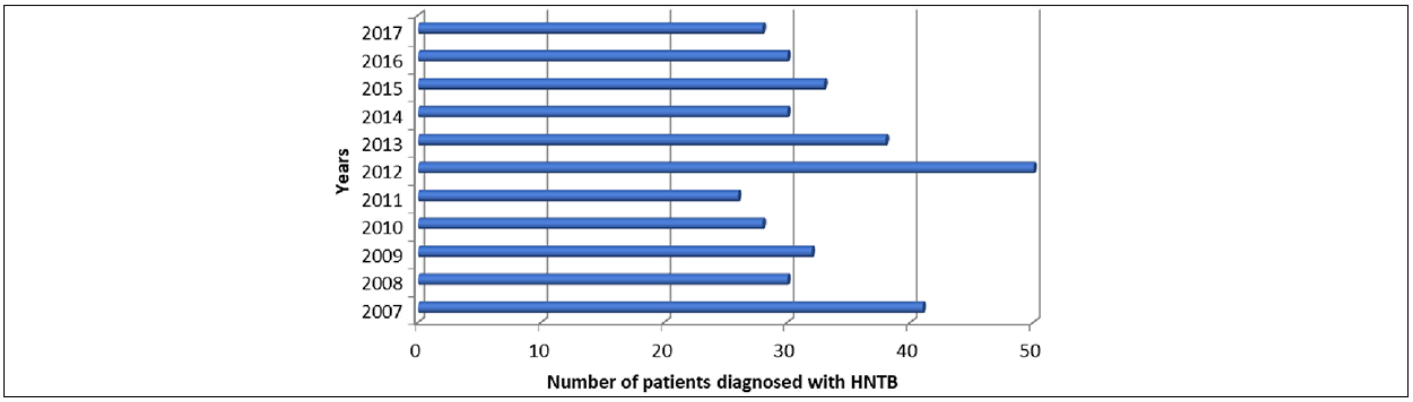

Figure 1. Number of patients diagnosed with Head and Neck Tuberculosis (HNTB) by years

Table 2. Treatment results according to location of disease

Location of Disease	Treatment results					
	Misdiagnosis	Transfer to another city	Cure	Abandoning the Treatment	Death	Total
Skin TB	-	-	1	-	-	**1**
Larynx TB	-	-	3	-	-	**3**
Lymph node TB	1	2	134	6	4	**147**
Orbita TB	0	-	2	-	-	**2**
Parotis TB	0	-	2	-	-	**2**
Parotis and lymph node combined TB	0	-	1	-	-	**1**
Meningitis TB	0	1	8	-	3	**12**
Thyroid TB	0	-	1	-	-	**1**
Total	**1**	**3**	**152**	**6**	**7**	**169**

Presence of Contact

The contact history is history of contact with a patient diagnosed with TB. Twenty-one of 148 patients had a contact history in group 1, meanwhile 47 of 148 patients had a contact history in group 2. This difference was significant between the two groups. Within the family, 16 patients had a contact history in group 1 and 31 patients in group 2, and this was statistically significant (p = 0.012).

Relapse Status

When the recurrence status was evaluated, group 1 had 163 patients admitted for the first time and six patients admitted with a recurrence of TB, and 201 patients were new in group 2 and eight patients had relapses (p = 0.486).

Superiority of Direction and Localization

Concerning the location of lesions, 52% of patients in group 1 and 60.5% of patients in group 2 had it in the right.

When classified according to anatomical localization, the most common is cervical lymphadenitis with a total of 325 patients (86%) of the 378 patients diagnosed with HNTB. There was central nervous system involvement in 27 patients (7.1%), orbital involvement in seven patients (1.9%), larynx involvement in five patients (1.3%), parotid involvement in five patients (1.3%), and other involvements (thyroid, skin, tongue, nasopharynx, oral cavity and maxillary sinus) in nine patients (2.4%) (Figure 2).
When evaluating the localization of lymph nodes, we found that although lymph nodes were more common in the supraclavicular and submandibular regions, there were no significant differences in lymph node localizations (p = 0.162).

Tuberculin Skin Test (Tst) and Bacillus Calmette Guèrin (BCG) Vaccination Scar

We could obtain the TST results of 153 patients. The mean TST was 15.82±6.53 (min 0; max 35) mm in group 1 and 17.21±6.67 (min 0; max 32) mm in group 2, with no statistically significant difference (Student-*t* test p = 0.201).

When the records on scar tissue showing the BCG vaccination were examined, we found that 55 patients in group 1 lacked information, while 90 patients had scars and 24 had no BCG scars. In group 2, 46 patients lacked the scar tissue records, 104 patients had scar tissue, and 59 patients did not have a BCG scar. Evaluating the presence of scars in accordance with nationalities, that of 99 RT citizen patients was not known, 189 patients had scar tissues, and 65 patients did not have them. In non-RT citizen patients, that of two patients was unknown, five patients had scar tissues, and 18 patients did not have BCG scars. We found a significant difference in the vaccination rates when independently evaluating the groups and nationalities (p = 0.018).

Treatment Duration and Result

Concerning the treatment durations, the mean treatment duration in group 1 was 9.32±3.45 months (min 1; max 18) and 8.64 ± 3.47 months (min 1; max24) in group 2, with no significant difference. We found no significant differences when comparing the treatment success rates between the two groups (p = 0.361). Based on the duration of the treatments (nine months or more), 109 (64%) patients in group 1 and 122 (58%) patients in group 2 received adequate treatment, with no statistically significant differences (p = 0.225).

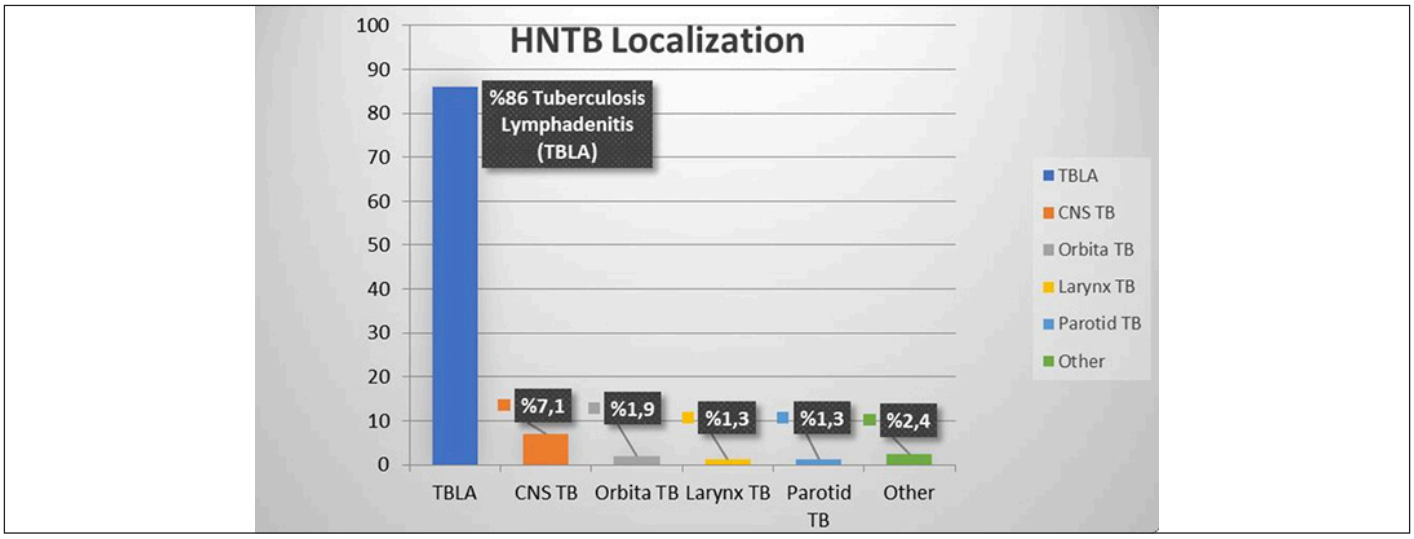

Figure 2. Head and Neck Tuberculosis (HNTB) localization percentages

We found differences between the recommended treatment times because the patients referred from the different healthcare centers. The treatments were given in different ways; the standard four-course treatment with Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), and Ethambutol (E) for the first two months and then binary treatment (HR) for four months, seven months, and 10 months.

DISCUSSION

Tuberculosis is a leading cause of mortality and morbidity worldwide. The spread of this fatal disease increases in crisis-affected populations. The ongoing Syrian civil war has led to significant damage to the national healthcare system and forced millions of Syrians to take refuge in neighboring countries, where the majority face miserable conditions. These circumstances increase the risk of TB development and spreading among Syrian refugees and their host communities. After the beginning of the Syrian crisis in 2011, a remarkable increase in TB cases was reported in countries bordering Syria and is essentially attributed to the massive displacement of the SR population [16]. There is an increased risk for TB disease due to the widespread unhealthy conditions in which the majority of refugees live. Three out of four refugees who live outside the refugee camps stay in very crowded places with more than six people [17]. Vaccination rates are found to be lower among refugees who live outside the camps [18].

Furthermore, these groups are more vulnerable to the extrapulmonary dissemination of TB [19]. In our study, we found that Syrian refugees in Gaziantep have the same situation and living conditions.

Tuberculosis is a preventable infectious disease that is caused by the respiratory transmission of "Mycobacterium tuberculosis" and can spread to all organs by lymphohematogenous route [20]. Having a history of tuberculosis lymphadenitis or sharing the same environment with people who have had TB is a risk factor [21]. Nalini and Vinayak found a history of contact in 9% of patients [10]. The contact rates in HNBT patients in this study is in line with that in the literature. Moreover, in terms of TB transmission, we found that rather than the nationality of the patient, the family contact is statistically significant. Refugees or socioeconomically low-level local people live in crowded areas in which TB is easily spread; this may be the reason why the family contact history was statistically significant in our study groups. We evaluated various variables between two groups and the presence of contact and vaccination were found to be statistically significant in the assessment of HNTB.

Although the efficacy of the BCG vaccine continues to be controversial, live attenuated BCG is still the only vaccine in use for the prevention of TB in humans. It is effective against the severe forms of TB and its use prevents a large number of deaths that would otherwise be caused by TB every year [22]. The rate of BCG vaccine protection in adults aged over 18 years in Turkey was 72.7% and 85% in children aged 0–6 years [23]. The administration of the BCG vaccine in newborns is associated with a lower mortality and morbidity in children under five years of age [24]. EPTB is very common in patients who have not had the BCG vaccine [25]. BCG vaccination rates between 2011 but 2018 did not change in Turkey and decreased year-by-year in the Syrian Arab Republic [26].

In our study, when evaluating patients after 2011, we found that the vaccination rates had decreased; this could be because the migrant patients had not been vaccinated before. Based on these data, it is possible to argue that HNTB may be seen more frequent in unvaccinated TB patients.

HNTB frequently presented as cervical lymphadenopathy in previous studies [9,11,27]. Sayın et al. reported that TBLA (85.4%) was the most frequent HNTB presentation form and right-side involvement was more frequent [11]. In our study, TBLA (86%) was the most common form of HNTB with a right-side prevalence. TBLA involves mostly posterior and supraclavicular lymph nodes [9,27]. Ammari et al. indicated that the deep cervical region had highest number of TBLA (54%) [28]. Nalini and Vinayak [10], on the other hand, found a higher posterior cervical involvement (76%), and found that most patients had a lymphadenopathy of less than 3 cm. Baskota et al. [29] found 51% of TBLA in the posterior triangle, 48% in the upper jugular region, and 36% in the submandibular region. In their study, Sayın et al. [11] found the most frequent involvement (53.6%) in the rear angle. In our study, TBLA was seen in the posterior cervical region, especially in the supraclavicular area and in the submandibular region.

Since the introduction of the tuberculin skin test (TST) also known as the Mantoux test in 1890, it has been widely used for the initial diagnosis of patients suspected of TB and to detect latent infections [30]. TST positivity was reported at a rate of 50% in TBLA patients [31]. When evaluating the 153 patients

with TST results, we found that the average TST in group 1 was 15.8 mm and in group 2 was 17.2 mm. Since atypical TB bacillus is more frequent in children, there is a high risk of false positivity in the tuberculin test. Although it is highly positive in patients with neck masses, a remarkable number of researchers state that the tuberculin test is the first examination method to be used due to its simplicity and low cost [32]. It is considered with an induration of 15 mm or more in those with the BCG vaccine and 10 mm or more in those who do not have the BCG vaccine [23]. We detected 57 patients (61%) in group 1 and 44 patients (72.1%) in group 2 as positive in our study. Although it was not statistically significant, there was an increase in terms of both TST positivity and induration width in group 2.

CONCLUSION

The number of HNTB increased in the Gaziantep province after the beginning of the Syrian war. The risk factors for the occurrence of HNBT include living in a crowded place and lower rates of BCG vaccination may have a greater significance in terms of risk factors than the lymph node location, side, tuberculin skin test result, and nationality. Isolation of TB patients and vaccination of all newborns may contribute to protect against HNTB.

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Conflict of Interest: The authors declare that they have no competing interests.

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Informed Consent: Informed voluntary consent form was prepared due to the nature of the study, ethics committee approval and permission were obtained from the provincial health directorate.

Authors' Contributions: Conception: KT, İA, SA; Design: KT, İA, SA; Supervision: SA; Fundings: SA; Materials: KT; Data Collection and/or Processing: İA, SA; Analysis and/or lnterpretation: AY; Literature Review: AY; Writing: AY; Critical Review: KT, İA, AY, SA.

Ethics Committee Approval: The study was approved by the Ethics Comittee of the Faculty of Medicine of Gaziantep University (2018/95). The study followed the Declaration of Helsinki.

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