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MAJOR ARTICLE

Delayed Diagnosis, Leprosy Reactions, and Nerve Injury Among Individuals With Hansen's Disease Seen at a United States Clinic

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Background. Hansen's disease (HD), or leprosy, is uncommon in the United States. We sought to describe the characteristics of patients with HD in a US clinic, including an assessment of delays in diagnosis and HD reactions, which have both been associated with nerve damage.

Methods. A retrospective chart review was conducted on patients seen at an HD clinic in the southern United States between January 1, 2002 and January 31, 2014. Demographic and clinical characteristics were summarized, including delays in diagnosis, frequency of reactions, and other complications including peripheral neuropathy.

Results. Thirty patients were seen during the study time period. The majority of patients were male (73%) and had multibacillary disease (70%). Brazil, Mexico, and the United States were the most frequent of the 14 countries of origin. Hansen's disease "reactions", severe inflammatory complications, were identified among 75% of patients, and nerve damage was present at diagnosis in 36% of patients. The median length of time between symptom onset and diagnosis was long at 12 months (range, 1–96), but no single factor was associated with a delay in diagnosis.

Discussion. The diagnosis of HD was frequently delayed among patients referred to our US clinic. The high frequency of reactions and neuropathy at diagnosis suggests that further efforts at timely diagnosis and management of this often unrecognized disease is needed to prevent the long-term sequelae associated with irreversible nerve damage.

Keywords. delay in diagnosis; Hansen's disease; leprosy; leprosy reactions.

Hansen's disease ([HD] leprosy) remains a public health problem in many regions of the world and still causes significant fear and stigma, which can hamper control strategies of this curable disease [1]. Most patients with HD in the United States are immigrants from highly endemic countries including India, Brazil, the Oceania region, as well as other countries in Asia, Africa, and Latin America. The highest risk immigrants in the United States are those from the Federated States of Micronesia or the Marshall Islands, with half of these patients being diagnosed in Hawaii [2]. However, local transmission of *Mycobacterium leprae* infection appears to occur in the southeastern United States with endemic cases from Louisiana, Texas, Mississippi, Georgia, and possibly Florida. These are areas where *M leprae* has been found to also infect nine-banded armadillos [3–6].

Because HD is uncommon in the United States, with an average of approximately 200 cases per year, many providers are unfamiliar with its clinical manifestations, which can range from a myriad of skin lesions to nerve damage [7, 8]. Nerve damage is defined by the World Health Organization as sensory loss, paresthesia, and/or muscle weakness [9]. As sequelae, deformities of the extremities are also considered evidence of nerve damage. It is unfortunate that the symptoms and signs of HD and the associated immunologic reactions can resemble other, more common conditions. The disease may not be familiar to many, and therefore it is often not considered in the differential diagnosis of skin lesions or nerve problems. This can lead to misdiagnoses, delays in treatment, and irreversible nerve damage. Patients with HD have been misdiagnosed with diabetic neuropathy, Lyme disease, lupus vulgaris, numerous rheumatologic diseases, and others affecting the skin or peripheral nerves [10]. Furthermore, stigma, misinformation, and limited access to resources can prevent patients from seeking care [11, 12]. Delays in diagnosis have been reported in Asia, Africa, Europe, and North America, and delays are associated with higher rates of permanent nerve damage and disability [13–17]. One study shows that patients with a delay of diagnosis greater than 1 year have a 10%–15% increase in impairment, and delays of 2 years can result in a 15%–25% increase in

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impairment [17, 18]. However, few studies in North America have investigated the role of delay in diagnosis on outcomes in HD [2, 16].

Permanent nerve damage can arise from the natural progression of untreated *M leprae* infection or inflammatory reactions. These reactions occur in 30%–50% of patients and account for the majority of permanent nerve damage [19]. Common symptoms of Type 1 (reversal) reactions include enlargement and erythema of skin lesions (Figure 1A) and nerve impairment that can be reversed with appropriate and timely care [19]. Type 2 reactions, also known as erythema nodosum leprosum, occur in multibacillary disease and may cause a severe systemic illness accompanied with painful, erythematous nodules with potential neuritis [20].

In this retrospective analysis, we seek to describe the demographic and clinical characteristics of patients with HD seen at our clinic over the past 12 years, focusing on 2 factors known to be associated with neurologic damage: the duration of time between symptom onset and diagnosis (delay) and the presence of HD reactions. The analysis performed in this article builds upon a previous case series describing reactions among 14 patients seen in our clinic from 2002 to 2008 [21]. In this previous report [21], we focused our attention on addressing the prevalence of HD reactions among those seen at our institution. Herein, we were interested in assessing the impact of delays in diagnosis and the degree of nerve damage identified among those patients in our cohort. Because our cohort of patients has increased significantly, and because reactions are still a major cause of nerve damage, we were also interested in assessing their contribution to nerve damage in this larger study population.

METHODS

A retrospective chart review of patients evaluated at the Emory TravelWell center, a designated satellite clinic of the US Department of Health and Human Services National Hansen's Disease Program (NHDP) since 2011, (Atlanta, GA) was performed. The study included all patients with a diagnosis of HD seen between January 1, 2002 and January 31, 2014. Patients are typically referred to our clinic by local dermatologists, primary care doctors, or other infectious disease physicians. Since our designation as an NHDP satellite clinic, referrals may also come from their website or directed inquiries to the NHDP. Demographic and clinical characteristics collected included age, sex, country of origin, travel history, date of diagnosis, date of first clinic visit, insurance status, duration between first symptoms and diagnosis, number of physicians seen, presence of nerve damage at diagnosis, reaction occurrence at any point during their clinic visits, and type of reaction. Nerve damage at diagnosis was defined as the presence of paresthesias, sensory loss, lagophthalmos, or other motor weakness. Abnormal monofilaments examinations performed and reported in the medical chart as well as subjective complaints of paresthesias were included as nerve damage at diagnosis. All characteristics were tabulated using standard descriptive statistics of median, range, and frequency, where appropriate. Due to the many countries of origin represented, these were grouped into 4 geographic regions for further analyses: United States, Latin America (including the Caribbean and Mexico), Asia, and Africa. Likewise, the pathologic diagnoses were grouped into 2, representing the multibacillary (mid-borderline, borderline lepromatous, and lepromatous) and paucibacillary (tuberculoid, borderline tuberculoid) ends of the spectrum.

Univariate analyses were performed with t tests, χ^2 tests (or Fisher's exact test as appropriate), correlation coefficient, and analysis of variance where appropriate using SAS version 9.4 (SAS Institute, Cary, NC). For this study, we obtained ethical approval from the Emory University Institutional Review Board.

RESULTS

Thirty patients met inclusion criteria during the study period. Most were male (70%) with a median age of 42 years (range, 16–72; Table 1). Patients originated from all 4 geographic regions, with Brazil (27%), Mexico (17%), and the United States (13%) being the most frequent countries of origin (Table 1). Those

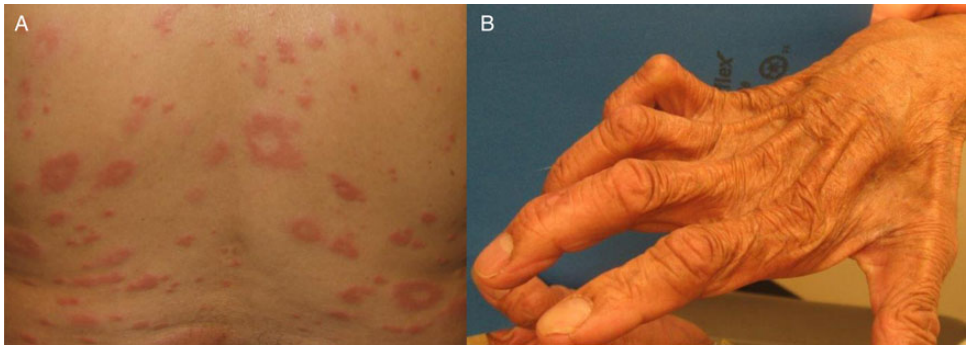

Figure 1. (A) Type 1 reaction in a patient with lepromatous disease. (B) Sequelae of nerve damage precipitated by a type 2 reaction in the setting of lepromatous disease and manifesting as atrophy of the lumbrical muscles of the hand and joint deformities secondary to loss of proprioception.

Table 1. Demographic and Clinical Characteristics of Patients Diagnosed With Hansen's Disease Between January 1, 2002 and January 31, 2014

Variable	Total n = 30	Missing
Age, years: median (range)	42 (16–72)	n = 6
Sex, %Female	26.7% (n = 8)	n = 0
Country of Origin		n = 0
Brazil	26.7% (n = 8)	
Mexico	16.7% (n = 5)	
United States	13.3% (n = 4)	
India	6.7% (n = 2)	
Vietnam	6.7% (n = 2)	
The Gambia	6.7% (n = 2)	
Nigeria	3.3% (n = 1)	
Liberia	3.3% (n = 1)	
Somalia	3.3% (n = 1)	
Haiti	3.3% (n = 1)	
Bangladesh	3.3% (n = 1)	
Nepal	3.3% (n = 1)	
Trinidad and Tobago	3.3% (n = 1)	
Leprosy classification		n = 0
Tuberculoid,	16.7% (n = 5)	
Borderline tuberculoid	13.3% (n = 4)	
Borderline borderline	3.3% (n = 1)	
Borderline lepromatous	13.3% (n = 4)	
Lepromatous	53.3% (n = 16)	
Reaction frequency, total	75% (n = 21)	n = 2
Type 1	47.6% (n = 10)	
Type 2	52.4% (n = 11)	
Months of symptoms before diagnosis, median (range), self reported	12 (1–96)	n = 9
Nerve damage present at diagnosis	36.4% (n = 8)	n = 8
Covered with health insurance at first visit	65% (n = 13)	n = 10
Number of doctors visited before diagnosis, median (range)	1 (0–4)	n = 15

from the United States were all from the southern United States and had no international residence or long-term travel within the last 20 years. In fact, 3 of 4 patients from the United States had no reported travel in the medical record in this time frame, and the fourth patient reported only a 1-week trip to Brazil a few months before symptom onset. The median length of time between symptom onset and diagnosis was 12 months (range, 1–96 months; Table 1). Over one third of patients had nerve damage at diagnosis, and 75% of the patients had a reaction at some point, either at diagnosis, during treatment, or after the end of treatment. Among the 15 patients who had the number of providers documented in the medical record, the median number of providers seen before HD diagnosis was 1 (range, 0–4 providers). Information about comorbidities was available for 24 patients, and 18 of these patients were without comorbidities. Two patients had diabetes mellitus type 2. Other reported medical problems included Parkinson's disease, membranous glomerulopathy, hypertension, hypothyroidism, and mycetoma of the foot.

Geographic region of origin, age, and sex were not associated with the number of months between symptom onset and diagnosis (as a continuous variable) or with nerve symptoms at diagnosis on univariate analysis. Length of time between symptom onset and diagnosis was also not associated with nerve damage at diagnosis. Half of the patients who had a reaction at any point of their care during the study period also had nerve damage at diagnosis. Of those without reported reactions, none of them had nerve damage at presentation. This finding was significant with a P value of .03. There was no association between the number of providers seen before diagnosis and nerve damage at diagnosis. Finally, whether a patient had health insurance was not associated with either symptom duration before diagnosis nor nerve damage at diagnosis.

DISCUSSION

Our findings demonstrate that more than half of patients with HD seen at a US clinic had been symptomatic for at least 1 year, and one third had nerve involvement at the time of their diagnosis. Although this analysis did not reveal a significant association between nerve damage and the length of symptoms before diagnosis, these numbers show the large burden of neurologic complications, some of which may be irreversible in this patient population (Figure 1B). Consistent with a previous case series performed at our center, patients with HD continued to have a high likelihood of reactions, with 75% of our patients suffering from one at some point in their disease course, higher than the 30%–50% rate of reactions reported in the literature [2, 21]. Although a causal relationship between the presence of reactions and nerve damage at diagnosis cannot be determined from our data (because the reactions occurred at various points in the illness, not only at diagnosis), it is notable that half of the patients with reactions had nerve symptoms at diagnosis, whereas none of the patients without reactions had them at diagnosis. Type 1 reactions are the leading cause of nerve damage in patients with HD, highlighting the need for further studies on risk factors and development of prevention strategies targeting those with HD at highest risk for developing reactions [22]. Comorbidities were few in this small series and thus limited our ability to study them as confounders or contributors to morbidity.

Patients seen in our center were typically diagnosed with HD after an extended duration of symptomatic illness (median, 1 year), consistent with a previous review of HD patients in North America [2]. In this large United States-based analysis, between 1994 and 2011, they found a long duration of symptoms, and the mean delay in diagnosis was 2.4 years. It is interesting to note that this mean delay was higher in patients born outside the United States (5.7 years) [2]. In Toronto, the mean delay in diagnosis in an HD clinic was 4.8 years [16]. Although some delays may be related to patients not seeking care or having limited access to care, misdiagnosis can also significantly delay appropriate treatment [23, 24]. Although we did not observe an association between nerve damage and length of symptoms before diagnosis, this has been established in prior studies conducted in a variety of settings [14, 16, 25]. Unmeasured

factors that could have affected delay in diagnosis include socioeconomic status, cultural and language barriers, and transportation issues. Therefore, larger scale epidemiologic studies on factors associated with delay in HD diagnosis in the United States may elucidate ways to predict and prevent adverse outcomes in HD.

Due to our modest sample size and missing data for some variables of interest, we were limited in our ability to identify significant risk factors for complications of HD. Our findings may not be generalizable to other clinics that see HD patients of different backgrounds. However, we believe that our findings are instructive to providers who might encounter HD patients in other areas with relatively low endemicity. Greater awareness of HD and its manifestations is needed in the United States to decrease delays in diagnosis and potentially reduce the morbidity caused by this infection.

CONCLUSIONS

Although it is declining in part because of aggressive control measures targeting eradication, HD remains a global problem and could face a resurgence in certain areas as borders open and worldwide travel expands [26]. A substantial decrease in the incidence of disease had been noted in many parts of the world during the 1990s, but since 2005 both worldwide prevalence and incidence rates have remained steady [27]. Furthermore, grade II nerve dysfunction continues to be prevalent in leprosy endemic areas [28]. With increasing global migration, increased efforts to promote awareness of HD among practicing clinicians, especially those caring for immigrants from highly endemic areas of Oceania, Latin America and South Asia, are urgently needed. Educating US physicians, particularly primary care clinicians, dermatologists, and rheumatologists, of the symptoms associated with HD would allow for a more timely diagnosis and initiation of appropriate medical care.

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