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The Epidemiology and Clinical Presentation of Leprosy in the Pediatric Population of Paraguay

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THE EPIDEMIOLOGY AND CLINICAL PRESENTATION OF LEPROSY IN THE PEDIATRIC POPULATION OF PARAGUAY

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Background: Several aspects concerning the biology and epidemiology of leprosy remain unknown. It has been recognized that the study of children with leprosy could provide important insight into unanswered questions, particularly if disease manifestations are carefully observed.

Methods: A retrospective chart review of 308 cases of children aged 0-14 y/o was conducted at the Ministry of Health Leprosy Department in Asuncion, Paraguay. Data regarding age, gender, leprosy classification, transmission, detection, clinical presentation, presence and class of reaction, and disability were abstracted.

Results: The study group ranged from 2 to 14 years of age. The incidence rate and the risk of having leprosy were shown to increase with age. The gender ratio of males to females was 1:1. A positive contact history was documented in 86.4% of cases, with intrafamilial contact type accounting for 98.9% of known cases. The average time to diagnosis was 1.1 years. Paucibacillary leprosy was more common than multibacillary leprosy in this study population. 16.9% of children experienced some type of nerve involvement. 1.9% of all children presented with hypersensitivity reactions, with Type 2 erythema nodosum leprosum reaction being the most common.

Conclusions: The minimum incubation period could be two years. Children may be less likely to develop severe forms of leprosy. Males and females may be equally susceptible to contracting the disease from a biological perspective. Close and prolonged contact appears to be necessary for transmission. Nerve involvement and hypersensitivity reactions are relatively uncommon in children.

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BACKGROUND

Preface

Leprosy, also known as Hansen's Disease, is an ancient disease retaining a strong historic association with stigma. (1) Almost everyone knows the word "leprosy," yet fact and fiction related to the disease are commonly confused. An extensive general background covering the biology, medical management, and epidemiology of leprosy is included as the disease is a lesser known entity in this part of the world.

Microbiology & Pathogenesis

Leprosy is caused by the bacterium *Mycobacterium leprae*. It is an acid fast bacillus that replicates slowly (generation time 13 days). (1) *M. leprae* secretes no toxins, and its virulence is based on properties of its cell wall. (2) It grows optimally at <37° C, explaining the bacterium's tendency to infect the cool areas of the body, such as the skin and the nerves close to the skin. (1) The invading bacteria have three specific targets: peripheral neural tissue (Schwann cells), small vessels (endothelial cells and pericytes), and the monocyte-macrophage system. The formation of granulomas is a common histopathologic landmark of disease. (3)

M. leprae has never been successfully cultured in artificial media, severely limiting the progress of laboratory-based research on the disease. However, the bacterium has been cultured in the foot pads of mice. (1) Leprosy is also well-known to infect wild

armadillos of the southeastern US as well as in chimpanzees and monkeys in West Africa. (1)

Transmission

The route of transmission has never been definitively proven. Transmission via the nasorepiratory route is believed to be the most plausible mechanism. There is less evidence to support transmission via skin abrasions or via fomites. Because one study showed the leprosy bacilli to remain viable for up to five months after drying in the shade and up to six months in wet soil, the possibility of transmission via aerosolized bacilli has been entertained. Transmission through breast milk and through the placenta is also a theoretical possibility. (1) The possibility of a subclinical carrier state in which a subset of individuals can carry the disease and infect others, but not develop disease themselves is also an area of debate. (4)

Contrary to popular believe, leprosy does not appear to be a highly contagious disease. In fact, most people exposed to *M. leprae* never develop the disease. Evidence suggests that prolonged and intimate contact with a leprosy patient is likely necessary in order to transmit the disease. (5,6)

Incubation Period

The incubation period of *M. leprae* is uncertain, but is believed to be generally between two and five years. (7,8) However, some assert that the incubation period could be as short as 9 months and as long as 20 years. (9)

Classification

Two main classification systems exist in order to categorize leprosy, namely the World Health Organization (WHO) and Ridley-Jopling systems.

The WHO system is based on the quantity of skin lesions and the number of bacilli on skin smear. Skin smears are made by squeezing a fold of skin and making a shallow slit in the skin with a razor blade or scalpel. The instrument is then turned at a right angle to the slit and the sides of the slit are scraped. The fluid obtained is spread on a slide, heat-fixed, stained, and evaluated. (1) The two main categories of the WHO classification system are listed below:

1) Paucibacillary leprosy (PB leprosy): ≤5 skin lesions with no bacilli on skin smears.

2) Multibacillary leprosy (MB leprosy): ≥6 skin lesions and may have bacilli on skin smears.

The Ridley-Jopling classification system is based on the histopathology of skin lesions and essentially represents a spectrum of disease. The categories of the Ridley-Jopling system are listed below:

1) Indeterminate (I)

2) Tuberculoid (TT)

3) Borderline tuberculoid (BT)

4) Mid-borderline (BB)

5) Borderline lepromatous (BL)

6) Lepromatous (LL)

Indeterminate leprosy is the most benign form of the disease with the least amount of bacilli and strong host immune response evident, while lepromatous leprosy represents the most severe form of disease with many bacilli present in tissue, and evidence of a weak host immune response.

The spectrum of disease classification is not static. For example, in some cases untreated tuberculoid leprosy can progress to lepromatous leprosy, given a long enough time and the proper immunologic environment. Nor are the two classification systems mutually exclusive. Indeterminate and tuberculoid leprosy are commonly referred to as PB leprosy, while borderline and lepromatous leprosy are commonly referred to as MB leprosy. (1,10)

Clinical Features

In short, the key clinical features of leprosy are skin lesions with sensory loss and enlarged peripheral nerves . A more detailed description of clinical manifestations is below:

The skin lesions characteristic of indeterminate leprosy are vaguely defined, hypopigmented macules with minimal neural involvement as assessed by sensory deficit testing. Tuberculoid leprosy often presents with a few well-defined anesthetic macules or plaques with neural involvement being more common. Lepromatous leprosy lies at the opposite end of the spectrum from I and TT leprosy, commonly presenting with multiple macules, nodules or diffuse infiltrates as well as neural lesions later in the natural history of the disease. Lepromatous leprosy produces the classic lesions and deformities presented in the popular media. Borderline leprosy types presents with numerous lesions having distinct borders and often with neural involvement. (1)

Nerve involvement can involve both sensory and motor loss. Sensory deficits are more common, likely because they usually occur first in the evolution of the nerve damage caused by leprosy (11). Nerve involvement of any type usually occurs in advanced disease in the lepromatous end of spectrum. However, leprosy can rarely manifest itself solely with nerve damage and without any skin lesions. This is referred to as pure neuritic leprosy. Frequently involved nerves include the ulnar nerve at the elbow, the median nerve above the carpal tunnel, the radial nerve at the spiral groove, the radial cutaneous nerve in the lower forearm, the peroneal nerve above the fibular head, the tibial nerve above the ankle, and the facial nerve at the region of the zygomatic bone. (12)

In severely advanced disease loss of eyebrows and nasal depression can be seen, leading to the characteristic leonine facies. (1,7)

It should be emphasized that leprosy is not a "flesh-eating" disease, as is still portrayed in the popular media (13,14). Much of the deformity associated with leprosy originates in the loss of sensory nerve function. For example, a patient who loses sensation of his fingers and smokes cigarettes may inadvertently burn his fingers with a lighter or with the end of the cigarettes because of his inability to perceive pain. Or, alternatively, an impoverished patient with leprosy who earns a living through manual labor may damage his extremities with dangerous machinery or through repetitive tasks because of his inability to feel. In essence, a significant portion of the deformity associated with leprosy does not originate from the infecting organism per se, but rather is an indirect sequelae of the disease. (15)

Immunology

Leprosy can be thought of as a paradigm for understanding the range of pathologic interactions between variable host immune responses and a relatively stable parasite. It is the immune response of the host that determines the position of the patient in the Ridley-Jopling spectrum of disease described above. (1) Patients who develop tuberculoid leprosy mount a cell-mediated immune response that is TH1 predominant, with production of IL-2 and IFN-γ. On the opposite end of the spectrum, lepromatous leprosy patients exhibit an impaired cell-mediated TH1 immune response, with a predominant TH2 response, resulting in the production of IL-4 and IL-5 that activate humoral immunity, and result in production of antibodies. (2,3)

Reactions

Leprosy causes several unique immune reactions in the host that occur either during the natural course of the disease or are precipitated by administration of chemotherapeutic treatment. The two most common acute reactional episodes are described below:

Type I: This reaction is also known as Reversal Reaction. This state is thought to represent an episodic upgrading of cell-mediated immunity. It is characterized by onset of erythema and edema of skin lesions and is also associated with neuritis, ulceration, and additional motor and sensory loss. Type I Reaction is most commonly seen in borderline cases. (1)

Type 2: This type of reaction is also referred to as erythema nodosum leprosum (ENL). ENL is thought to be an immune complex disorder. Common symptoms include rapid onset of tender subcutaneous nodules and fever. It is most commonly associated with lepromatous leprosy. (1)

Disease Susceptibility

In those who do develop clinical manifestations, many only acquire a single lesion that is often self-healing. (16) In other cases, however, the disease may progress to a more advanced stage. The role of genetic factors in determining disease susceptibility remains uncertain. In some ethnic groups, certain HLA-DR antigens are associated with types of leprosy, but not necessarily with disease susceptibility. (1)

Diagnosis

The diagnosis of leprosy is ideally made based on a physical examination and a skin smear or biopsy. Physical exam should, at minimum, consist of a thorough inspection of the entire skin surface, palpation of peripheral nerves for enlargement and tenderness, sensory testing in lesions using a few fibers of cotton or calibrated nylon bristles to assess any deficits in light touch perception. In resource-limited settings lacking access to laboratory facilities, such as rural areas in the developing world, a proper physical examination and history-taking is frequently considered sufficient to establish the diagnosis. (1) As of yet, there does not yet exist a widely-accepted, rapid, definitively diagnostic tool for use in the field. Recently, several immunological and molecular assays for the purpose of leprosy diagnosis have been developed. However, none, as of yet, have the potential for practical use in the field because they do not clearly differentiate between subclinical infection and disease. (17)

Treatment

Most patients today are treated with a combination of antibiotics including dapsone, rifampicin, and clofazimine, a standardized WHO regimen, commonly known as multi-drug therapy (MDT). (6)

With proper treatment, patients rapidly become non-contagious. In fact, clinical and laboratory evidence suggest that infectiousness is lost generally within a day of starting treatment with multidrug therapy. (9) Most skin lesions usually resolve with treatment. However, some nerve damage and physical deformities may be permanent. The result is

that people who are biologically free of infection can still carry the physical manifestations of leprosy, and continue to face stigma based on their physical appearance. In fact, it is estimated that there are between one and two million people in the world who are visibly and irreversibly disabled due to past and present leprosy disease. (6)

Epidemiology

The global prevalence of leprosy has declined drastically over the past two decades since the advent of multi-drug therapy. Since 1985, more than 14 million patients globally have been cured through MDT. At the beginning of 2005, the global prevalence of leprosy was 286,063 cases, down from 460,000 in 2004. (18,19) Leprosy remains a major public health problem in nine highly endemic countries around the world, namely Angola, Brazil, Central African Republic, Democratic Republic of the Congo, India, Madagascar, Mozambique, Nepal, and the United Republic of Tanzania. Within the Americas, the three countries with the highest rates of endemic leprosy are Brazil (prevalence 1.7 per 10,000 population), and Guyana (prevalence 1.3 per 10,000), followed by Paraguay (prevalence 1.1 per 10,000 population). (18)

In terms of global prevalence, it appears obvious that great strides have been made toward the goal of leprosy control. The global annual incidence, however, proves more complicated to decipher. Incidence can theoretically be estimated by new case detection rates. However, this holds true only if a stable proportion of all existing cases are notified. This assumption is clearly not met with respect to leprosy. Geographical

coverage, intensity of case-finding, re-registration of defaulted patients, and quality of leprosy information systems vary from country to country and have changed over time. Thus, it is problematic to use new case detection rates as a proxy for incidence. (20)

Momentarily casting doubt aside and assuming that new case detection rates do reflect disease incidence, trends of global leprosy incidence over time still prove perplexing in other respects. (20) The 2004 global incidence measured by the number of new cases diagnosed in the year was 407,791. This represents a 21% decrease since 2003, mainly due to a reduced number of new cases detected in India. However, when looking at new detection rates in the other highly endemic countries of the world, the numbers seem to be stable over time, or have decreased only slightly. (18) These trends certainly do not reflect the accelerated decline in incidence predicted by the advent of MDT and the resultant massive decrease in disease prevalence once expected. One would presume that with such a reduction in prevalence and therefore a decrease in the reservoir of infection that a sizable impact on incidence would be made, but this phenomenon was never seen. (20)

In sum, we do know that less people around the world today suffer from overt leprosy than ever before. However, the ambiguity revolving around the issue of disease incidence makes it difficult to say anything concrete regarding progress toward leprosy elimination goals. (20)

Of note, the annual incidence of leprosy in the US is approximately 100, as reported by the Centers for Disease Control and Prevention. (21) Most of the cases in this country are diagnosed principally in California, Florida, Hawaii, Louisiana, Texas, and in New York City and Puerto Rico. The majority of these cases occur in immigrants and refugees who acquired the disease in their native countries. However, leprosy remains endemic in California, Hawaii, Louisiana, Texas, and Puerto Rico. (9)

Disease Control Measures

The mainstay of leprosy control efforts involves early detection and treatment of cases, patient education, and evaluation of close patient contacts. (9)

It should be noted that isolation of leprosy patients is not recommended. The availability of effective and time-limited ambulatory treatment, with rapid elimination of infectiousness has limited the need for hospitalization and transformed leprosy care to an outpatient-based entity. Isolating leprosy patients is of questionable value, can lead to stigmatization, and is not suggested. (9)

Adequate public health and clinical infrastructure is also clearly an essential element of leprosy control measures. WHO advocates for integration of leprosy care into primary care healthcare systems, rather than keeping leprosy as the domain of highly specialized, vertical programs. (17)

History and Stigma

Leprosy is an ancient disease that has left behind a terrifying image of mutilation and stigma on the pages of history. The disease was present in some of the oldest civilizations, including those of China, Egypt, and India. Leprosy has carried with it the false stereotypes of being a highly contagious, flesh-eating, incurable disease. It is often thought to be a curse from God and is associated with filth and sin. Such myths and stereotypes still run rampant in present-day society, making social stigma an almost inevitable aspect of the contracting the disease. (6)

M. leprae was originally discovered by G.A. Hansen in 1873. It was, in fact, the first etiologic agent of a chronic disease identified in humans. (1) Leprosy treatment in the form of the antibiotic dapsone was introduced in the 1940s. (6) However, the effective combination therapy that is used today did not appear until the early 1980s. (20)

Isolation of patients in leper colonies was the mainstay of disease management until the 1900s. Even in the US, leprosy patients were forcefully taken from their families and placed in colonies on Molokai, Hawaii and in Carville, Louisiana. (22,23) The days of the leprosaria have since been phased out. With the advent of an effective drug therapy, leprosy is now largely treated on an outpatient basis. Some colonies do still exist, but are not leper colonies in the old sense of the term. Patients now come to these colonies on a voluntary basis. Most stay only for a brief time for physical rehabilitation while others may stay on in a more permanent fashion because their families have rejected them or because they are disabled and have no where else to turn to for support. (6)

The dark history shrouding leprosy unfortunately seems to be intractable element of the disease. The language of leprosy has even persisted as a part our English lexicon, though the disease is rarely seen in this country. "He was treated like a leper" We say it all the time without thinking. Leprosy seems to be virtual synonym for stigma.

Unanswered Questions

Many questions remain unanswered regarding the biology and epidemiology of leprosy: What is the exact route of transmission? Can infection occur through casual contact? Do subclinical carriers significantly contribute to disease transmission? Do unknown non-human reservoirs of the disease exist? Does the bacterium exist outside a host in the environment? What is the range of the incubation period? Why do some people develop severe disease while other experience self-healing lesions? Will the bacilli ever be cultured in vitro? Why is the gender ratio skewed towards males? What is actually occurring in terms of the global incidence rate? Can leprosy ever be eradicated?

JUSTIFICATION OF RESEARCH

Great successes have been achieved during the last decade in the global control of leprosy. (18) Despite these achievements, many aspects concerning the biology and epidemiology of leprosy remain unknown. (17,24,25) It has been well recognized that studies of the epidemiology and clinical presentation of leprosy in children could provide important insight into the biology of the disease, helping to unravel some of the scientific unknowns mentioned above (8,24-27) Children represent a favorable population to study because their environmental exposures are usually stable and known. In ideal situations, parents can provide essential information including the onset and evolution of the disease, possible sources of exposures, etc. In contrast, the adult population is often more mobile, experiencing a less predictable environment, making a clear history more difficult to elicit. The majority of studies on childhood leprosy have been conducted in India, while far fewer have been conducted in Latin America. Paraguay was chosen as a study site for this research because it is an understudied part of the world and it represents the third highest rate of endemic leprosy in the Americas.

SPECIFIC AIMS OF THE THESIS

- Describe the epidemiological characteristics and clinical features of childhood leprosy in Paraguay
- Use the descriptive data to generate hypotheses regarding the biological characteristics of *M. leprae*

METHODS

A retrospective chart review was conducted at the Ministry of Health Leprosy Department in Asuncion, Paraguay. The archived data at the Department includes information on all patients diagnosed with and treated for leprosy in the country. Clinical and epidemiological archived data are recorded on standardized forms. Diagnoses are based on clinical examination, along with skin slit smear and histopathological examination when available and necessary. The disease is classified according to a simplified Ridley-Jopling criteria. (all three variants of borderline cases are classified simply borderline leprosy; otherwise all other Ridley-Jopling criteria remain identical to the standard classification scheme) This study included children aged 0-14 y/o diagnosed with leprosy between 1987-2001. Data regarding age, gender, leprosy classification, transmission, detection, clinical presentation, presence and class of reaction, and disability were abstracted by the primary author of this study. A minority of the charts was abstracted from the standardized charts held at the Kilometer 81 Mennonite Hospital, as they had not yet been transferred to the permanent archive at the Ministry of Health. A unique study number was assigned to the data collected for each patient. No personal identifiers were recorded. Data were first recorded on a paper abstraction form, and then was transferred to an electronic data base. Paper records were destroyed after the electronic transfer was complete. Statistical analysis consisted of chi-squared (χ^2) tests and odds ratios. A statistically significant *p* value was considered to be a value of less than 0.05.

RESULTS

A total of 6028 cases of leprosy were diagnosed in Paraguay between the years 1987-2001. During this 15 year time period, children aged 0-14 yrs composed 5.1% (308) of the total.

Age Distribution

The study group ranged from 2 to 14 years of age. The mean age was 10 years and the median age was 11years. (n=308) Using population data for Paraguay, both the incidence rate and the risk of having leprosy were shown to increase with age.

Table 1. *Age Distribution of Children with Leprosy*

Age (years)	No. of new cases (%)	Person-year population #	Incidence per person-year	Odds Ratio (CI)
0-4	15 (4.9%)	10,596,670	1.41×10^{-6}	1.00
5-9	93 (30.2%)	9,774,037	9.52×10^{-6}	6.72 (3.90-11.60)
10-14	200 (64.9%)	8,846,766	2.26×10^{-5}	15.97 (9.45-26.99)
Total	308 (100.0%)	29217473	1.05×10^{-5}	

Gender Distribution

The gender ratio of males to females was 1:1. There were exactly 154 males and 154 females in the study population. (n=308)

History of Contact

A positive history of contact meant that it was known from whom the subject contracted leprosy. A positive history in this study population was documented in 86.4% of cases. (n=308) Of these cases, intrafamilial contact accounted for 98.9% of cases. (n=265) Extrafamilial sources of contact included 2 neighbors and 1 teacher. 79.3% of children had one contact, 14.3% had two, 5.3% had three, and 1.1% had four contacts. (n=265) 63.3% of the contacts were male. (n=265) 91.7% of contacts were known to have multibacillary (MB) leprosy. (n=239)

Time to Diagnosis

The time to diagnosis is defined as the length of time from self-reported onset of leprosy to proper diagnosis of leprosy by medical personnel. The average time to diagnosis was 1.1 years. (n=293) The time period ranged from 7 days to 11 years.

Type of Leprosy

29.5% of subjects had tuberculoid leprosy, 37.0% had indeterminate, 15.6% had borderline, and 17.9% had lepromatous leprosy. (n=308) The probability of presenting with MB leprosy significantly increased with age. ($p<0.001$)

Table 3. *Classification of Leprosy by Age Group*

	Paucibacillary (PB)		Multibacillary (MB)		
Age	**Tuberculoid**	**Indeterminate**	**Borderline**	**Lepromatous**	**Total**
0-4	11	3	1	0	15
5-9	38	37	7	11	93
10-14	42	74	40	44	200
Total	91	114	48	55	308

Characteristics of Skin Lesions

70.5% of subjects presented with multiple lesions at the time of first diagnosis. 25.6% presented with a single lesion, and 3.9% presented with primary neurologic deficits. (n=305) 84.0% of first lesions appeared in exposed areas of the body. (n=60)

Skin Slit Smear

28.9% of skin slit smears were positive. (n=114) In cases that tested positive, 90.9% had MB leprosy. (n=33)

Nerve Involvement/Disability

Nerve involvement in leprosy is routinely classified using a WHO leprosy disability grading system. It is a simple classification scheme intended for use in the field. According to the WHO system, grade 0 disability indicates the absence of anesthesia, visible deformity and damage, grade I indicates the presence of anesthesia and the absence of visible deformity and damage, and grade II indicates the presence of visible deformity and damage. (28) In this study population, 16.9% of children experienced some type of nerve involvement. (n=308) Of these, 88.5% were grade I and 11.5% were grade II. The occurrence of nerve involvement increased with age. ($p>0.05$)

Table 4. *Nerve Involvement with Age(Percent of Total by Each Age Group)*

Presence of Nerve Involvement	0-4yrs	5-9yrs	10-14yrs	Total (0-14)
YES	0 (0%)	14 (15.1%)	38 (19.0%)	52 (16.9%)
Grade I		14	32	46
Grade II		0	6	6
NO	15 (100%)	79 (84.9%)	162 (81.0%)	256 (83.1%)
Total	15 (100%)	93 (100%)	200 (100%)	308 (100%)

Hypersensitivity Reactions

1.9% of all children presented with hypersensitivity reactions. (n=308) Type I (reversal) reaction was seen in only one case, in a 6 y/o male in indeterminate type leprosy. The remaining 5 children presented with Type 2 (ENL) reaction.

Table 5. *Reactions*

Reaction	0-4yrs	5-9yrs	10-14yrs	Total (0-14yrs)
YES	**0**	**0**	**6**	**6**
Type I			1	1
Type II			5	5
NO	15	93	194	302
Total	15	93	200	308

DISCUSSION

Children represented 5.1% of all diagnosed cases of leprosy in the country during the time period of this study. This is far lower than most other populations living in endemic areas, in which children generally constitute 20-30% of all cases detected. (1) This observation is relevant because the frequency of leprosy in children is thought to be a type of epidemiologic index for determining the level of transmission in the population. (29) Following from this, because children in Paraguay develop leprosy relatively infrequently, perhaps there is a low background of disease transmission in the population as a whole.

The youngest child in this study was 2 years old, potentially representing the minimum incubation period for the disease. This is in accordance with the general consensus that the incubation period of *M. leprae* ranges from 2-5 years. (7,8)

This study found that the incidence rate of leprosy increased with age, a finding reported by other studies. (24,27) This trend might exist because the long incubation period may delay onset until later in life, younger children may have less exposure, or perhaps the disease is less severe in younger children and therefore goes unreported. Evidence in support of the latter possibility includes reports of self-healing leprosy lesions that have been documented in children. (8)

The male to female ratio in this study was 1:1, a trend in that has been widely observed in other studies of pediatric leprosy. (7,27) However, some studies of children have shown a male predominant gender ratio. (25,26,29). In sum, the gender ratios reported in children have been somewhat variable. In contrast, in the adult population, a male to female predominant ratio has been well-established. (6,7,8) This skewed ratio in adults could exist because adult women may face more barriers to healthcare and men may have a greater risk of exposure as they are more mobile than women in traditional societies. The 1:1 gender ratio in children could exist because boys and girls in the same home would theoretically be exposed to similar environments, have similar risk factors for contracting the disease, and share equal access to health care. The 1:1 pediatric gender ratio found in this study likely implies that males and females are biologically equally as likely to contract the disease, and that the ratio skewed toward males in adults in due to socio-cultural constructs. An alternative explanation to the existing gender distribution could be that testosterone may have some role in triggering the development of leprosy; this could explain why post-pubertal males have a higher prevalence of disease compared with their female counterparts, though there is no evidence in the literature to support this theory.

This study found that 86.4% of patients had a positive history of contact with a leprosy patient, a much higher proportion than seen in other studies (24-26,29). Of these subjects, 98.9% cited their contact as being intrafamilial. These figures imply that close and prolonged contact with an infected individual is necessary for transmission because most people knew from whom they caught the disease and this person was usually a

family member. If transmission occurred through more casual means, say through the sneeze of a stranger sitting next to an individual on a bus, the cases would be much less likely to be able to recall an ill contact and thus the proportion of cases with a positive history of contact would be much smaller. The high proportion of patients in this study reporting a positive history of contact could also imply that a high level of disease awareness exists among Paraguayans diagnosed with leprosy in Paraguay; if the cases did not know the typical signs and symptoms of the disease, they would probably be less likely to be aware of close contacts with leprosy. 91.7% of contacts had MB leprosy. This conforms with the logic that MB patients have a much higher bacillary load and are much more likely to be a source of contagion compared to a person with PB leprosy.

The average time to diagnosis was 1.1 years. This is comparable to several other studies of children in endemic areas. (24,25,29) It could be argued, however, that the ideal time to diagnosis should be much shorter than one year, considering that in the time period of a year, a child could conceivably already have suffered irreversible nerve damage. A further reduction in time to diagnosis should be a priority since early detection is a cornerstone of a successful leprosy control program.

In this study, the probability of presenting with MB leprosy significantly increased with age. This phenomenon could potentially be explained by the fact that MB leprosy generally takes more time develop; in other words, as a case of MB leprosy first evolves through more benign stages of the disease with a lighter bacillary load and fewer lesions,

perhaps the disease goes unnoticed and undiagnosed. Then, by the time a florid case of MB leprosy presents, the child has reached an older age.

The majority of subjects presented with multiple lesions at the time of diagnosis. Most, likely, one could assume that a subject first developed one lesion, then went on to develop additional lesions at a later date. Ideally, the subject would have been diagnosed after the appearance of single lesion and this data may imply that a more rapid approach to disease detection should be emphasized.

The vast majority (84.0%) of patients reported the first lesion occurring in an exposed area of the body, a finding well-supported by other reports (24-26,29). This could be explained by *M. leprae*'s predilection for the cooler areas of the body. Unexposed areas of the body that are normally covered with clothes potentially represent a warmer, more hostile environment for the organism to grow.

The majority of subjects presented with negative skin slit smears. This observation is consistent with the fact that the majority of subjects in the study had PB leprosy, a class of disease with a light load of bacilli that is not expected to be positive on skin slit smear examination.

16.9% of children in this study experienced some type of nerve involvement at time of presentation. This observation is similar to the findings of the WHO leprosy BCG trial in Burma in which 20.4% of new cases were shown to present with neural involvement.

(30) In this study, those children who did suffer nerve involvement, tended to experience the mildest type of disability. Again, this finding is consistent with other observations that have found severe disability and deformity to be rare in children. (7)

The frequency of nerve involvement tended to increase with age in this study population, a finding similar to other investigations. (27,31) This finding is logically explained by the fact that nerve involvement generally occurs as a function of time; therefore, children who present with leprosy at an older age probably have had the disease for a greater length of time and would logically be at a greater risk of developing nerve involvement.

1.9% of children presented with hypersensitivity reactions. Most other studies of childhood leprosy have similarly found hypersensitivity reactions at time of presentation to be relatively rare. (25,27,29)

When children did present with a reactional episode in this study, it was of the Type 2 (ENL) Reaction the majority of the time. This is in contrast to other studies that have found Type I Reversal Reaction to be more common (24,29). In general, Reversal Reaction is more commonly seen in borderline leprosy, while ENL Reaction is more commonly experienced by patients with lepromatous leprosy. In this study population, the proportion of subjects with borderline and lepromatous leprosy were approximately equal and would not account for the difference seen in types of reactional episodes. It remains unclear why the most common class of reaction in this study was of the ENL type.

It should also be noted that the annual incidence of leprosy in this population was relatively steady during the time period of the study. The great decline expected in leprosy incidence in the decades following the introduction of MDT was not seen in this population, mimicking macro-level incidence trends.

AFTERTHOUGHTS

I. Suggested Points of Improvement

Though data was not specifically collected for the purposes of evaluation and improvement of leprosy healthcare delivery in Paraguay, the time I spent in country immersed in clinical care, training, and research related to leprosy provided ample time for observation, resulting in several points for discussion and suggested points of improvement of the leprosy program in Paraguay.

1. The vertical versus integrated care model

As mentioned earlier, the WHO advocates for an integrated system of leprosy management in endemic countries. (6) In other words, leprosy care should be fully integrated into the general healthcare system in the country. This is in contrast to older vertical programs consisting of leprosy specialists. The logic behind this approach is that the general health services are widely distributed and have close and frequent contact with the local community. Following from this, involving general practitioners in leprosy control will improve case-finding and increase awareness of the disease in the local community. Over time, this approach should prove to be cost-effective considering that the long-term operational costs of an integrated program should be much less than that of a specialized leprosy program. (32)

At the time this study was conducted, Paraguay was in a state of changing from the older vertical system to the newer integrated treatment of leprosy. The vast majority of new

diagnoses of leprosy were still being made by either the Ministry of Health leprosy department or by several leprosy specialists in the country. Very few diagnoses were made by generalist physicians. The common anecdote told by leprosy patients in Paraguay is that after first recognizing unusual symptoms, they would go to their family doctor who would misdiagnose the disease as a skin fungus, prescribe a cream that had no effect, and that the correct diagnosis would generally not occur until after about one year after initiation of disease manifestations. This common story is precisely why a more integrated approach to leprosy care is imperative. If generalist physicians have the expertise to diagnose and manage leprosy autonomously, the one year time to diagnosis would be reduced as would the risk of developing irreversible sequelae from the disease.

Some progress toward a more integrated system was being made in Paraguay at the time of the study. For example, several physicians advocated for improved leprosy training in a prominent medical school in the country's capital in order to produce generalists who could diagnose and manage leprosy on their own. Proper training in leprosy management in medical schools is essential in order to produce generalist physicians competent in leprosy care. However, the lag time between training and practicing in the community is potentially great, and the impact on the population might not be seen for several years. It appeared as though additional strategies needed to be employed in order to fully transform leprosy care into an integrated model of care. Several suggestions for improvement in this area follow:

- Rigorous leprosy training in all medical school (both private and public) throughout the country, perhaps including day trips or week-long rotations at the Ministry of Health leprosy clinic and lab
- Rigorous leprosy training in medical residencies throughout the country
- Regular training courses for practicing generalists and dermatologists

2. Health Education

Health education, as mentioned previously, is a crucial component to a leprosy control program. The patient must be knowledgeable about his disease in order to complete treatment properly, deal with the potential stigma of the disease, minimize sequelae of the disease, and recognize potential disease in contacts. Likewise, education of patient contacts and of the general public is important in order to decrease the stigma of the disease in society and to quickly recognize symptoms in new patients. At every site visited during the research and training period, excellent health education was being delivered to patients, family members of patients, and community members. Key aspects including the etiology of the disease, the side-effects of medications, proper recognition and care for skin ulcers related to leprosy, and the stigma and common myths associated with the disease were regularly addressed in a language appropriate for the audience. The level of dedication seen among the health educators was impressive, specifically at the Ministry of Health Leprosy Department, the Kilometer 81 Mennonite Hospital, and several smaller district hospitals near the country's capital. Despite the heroic efforts of leprosy health educators in the country, a significant level of stigma and misconceptions associated with the disease still exist in the country in the general public. Though

financial constraints are surely a challenge, increasing leprosy health messages to the general public would be ideal. Several methods by which to accomplish this include:

- Public service announcements on TV and radio
- Using a local celebrity or well-respected individual in the public eye to deliver such messages
- Health education talks on leprosy in schools and workplaces

II. A Day without Leprosy?

Though incredible achievements have been made in the realm of leprosy control with a dramatically decreased prevalence in recent decades, the possibility of complete disease eradication seems unlikely. A lack of vaccine, a vague knowledge of transmission, the long incubation period, a lack of a rapid, simple diagnostic test, and the long duration of treatment make leprosy an unlikely candidate for disease eradication. (33) In order to strive for the day of possible eradication in the future, more research is essential in the areas of leprosy epidemiology and biology to better understand and tackle this ancient disease we ironically know so relatively little about. Though leprosy may seem here to stay at least in the immediate future, maximally effective control of the disease on the population level is possible and the continued political and community-level commitment to achieve this short-term goal is imperative.

APPENDIX

Interview with Dr. Carlos Wein, Leprosy Clinician and Researcher

Conducted by Jessica Kattan
Hospital Mennonita, Kilometro 81
Translated from Spanish to English by Jessica Kattan
23 July 2002

Dr. Carlos Wein was raised in Paraguay as a member of a close-knit Mennonite community outside the country's capital. As a young man he was inspired by the work of Father Damien, a Belgian priest who selflessly provided spiritual guidance and medical care for hundreds of leprosy victims forcefully confined to the island of Molokai, Hawaii in the late 1900s. (17) Driven by this inspiration, Dr. Wein studied medicine at the National University of Asuncion, Paraguay. After graduating at the top of his medical school class and completing training in general surgery at the same institution, he went on to become medical and religious director of the Kilometer 81 Mennonite Hospital, a prominent leprosy care center and general hospital run by the Mennonite community in Paraguay. Since taking this post, he has served countless leprosy patients free of charge, conducted research and published voluminously on leprosy, invented new surgical techniques for leprosy-related procedures, taught medical students, and has worked as an advocate in the public health community to improve leprosy control and decrease stigma of the disease.

Upon hearing the word "leprosy," most people, unfamiliar with the disease, immediately think of severe deformity and suffering. In your experience, how do new cases usually present?

Eighty to ninety percent of new cases present with skin problems, lacking any noticeable markings of the face, in the hands, or on the feet. This means that when you are looking for new cases, you should not exclusively expect ulcers, mutilations, and deformities. Instead, attention should be focused on skin lesions that could be very mild or insignificant.

In the present day, do you still see cases of people who are very deformed or is this a thing of the past?

About five to ten percent [of patients] present with irreversible lesions.

Currently, what is the stigma related to leprosy?

People still think that leprosy is a punishment from God, or from the devil, or a curse that you receive for a sin that you need to pay or that you need to pay for ancestors. People believe a lot in superstition—the belief that there is something supernatural that causes leprosy. That means that curing leprosy with a simple pill is very novel for the people because they expect an act of exorcism or some way to take the evil spirit or curse out of the person. There is a lot left to do so that people understand that leprosy is exclusively an infectious disease. It is a bacillus that causes problems, and working with the bacillus we can resolve the problem. It is very difficult to modify [these superstitious beliefs] because [they are] stuck in the subconscious of the people.

Can you give me an extreme example of how stigma manifests itself in the lives of the patients?

The case that surprised me is the case of a man who was in leprosy treatment and was visited by the priest of the community. This priest said to the wife and three daughters of the patient that he should go into seclusion because he was a leper. When this man came to see me, I told him that what the priest said was not true. However, the family told me that, in the end, they would do what the priest told them to do. I felt surprised that they

would listen more to the priest than to me. They told me that leprosy is a biblical disease—that priests know more about the disease and its treatment than the doctors, and that the doctors should not involve themselves in a matter that is not medical. Leprosy is a spiritual thing, they said. He had to leave his family and he was living for months far from home. Finally, the family came to him and asked him to come back home for the following reasoning: We will forgive you and you can come back. When I asked the patient, what things there were to forgive, he told me calmly, "The fact that I am a leper. I need society to forgive me. Everyone knows I carry something that needs forgiveness or else face rejection from society."

Additionally, there have been various occasions in which people have tried to burn down the houses of [leprosy] patients or tried to burn the patients also. The last case I remember was six years ago. It was an 80-year-old woman. They set fire to her house, but she was able to escape. The community made her a little despicable shack to live in, surrounded by barbed wire so that no one could enter or leave; it didn't have a gate. These are testaments to the stigma of leprosy.

How do patients respond to hearing the diagnosis of leprosy?

There are two types of reactions. On the one hand, there are those who come with the suspicion that they have leprosy and we confirm that suspicion. First, this type of patient thinks of his family and what will happen to his children. Many start to cry. They accept that they will suffer, as long as the children do not know and do not suffer. We have

people that try to commit suicide. And when we look a little deeper, immediately after hearing the diagnosis, they feel punished by God. So, we feel the necessity to explain to them that that has nothing to do with it, with God.

On the other hand, the patients who have participated in health education talks in schools—about the treatment, about how leprosy is not a curse of God—it is incredible the positive reaction they have. They are so positive, saying "give me the medicine because I know what I have and I know that I will get better", instead of being embarrassed. They see it with completely different eyes. This confirms to me that this is the key point to managing leprosy—not just the diagnosis and treatment, but in the sense of understanding how the patient feels. This is the starting point from which to manage leprosy well. It is essential not just to teach the patients about the treatment, but to keep them calm.

How would you summarize the leprosy situation in Paraguay compared with the past and with other countries?

As far as the detection of new cases, the situation has not changed. We continue to have many new cases without achieving the reduction that we were waiting for 15 years ago with the implementation of multi-drug therapy. The detection of new cases depends a lot on the type of work implemented in each district. In the majority of places, detection of new cases works very well. We are improving in other places where we are not functioning as well. Once the patients are identified as sick, we have been commended by the World Health Organization and others on the excellent follow-up of patients.

There are very few people lost to follow-up. Follow-up of patients is done very regularly. If the patient does not come, they are found, and they finish their course of therapy.

Compared with other countries, there is a strong influence of NGOs, like the Mennonite Hospital. That means that the programs have a lot of stability that is not affected by political or financial changes in the country. Our country has a lot less leprosy than in Brazil. They treat in a more decentralized way. They continue to have problems in access and follow-up.

In Paraguay, are some groups more affected by leprosy than others?

It is notable that indigenous groups do not have leprosy. But, in the general population, there is no one group that has more leprosy. Urban and rural, and east and west seem to have the same statistics.

In Paraguay, the population of people over 45 years old has more cases of leprosy than younger age groups. Do you have any theories?

The greatest risk for exposure occurs when people start to work or go away to school. Before that, people stay close to their families. So, the greatest exposure happens in those twenty years or older. Plus, you need to consider the incubation period of leprosy. It ranges from 3-40 years. The average [incubation period] is about 15-50 years. So, if

you add 20 years at age of exposure plus the incubation period, you get about 40 years old.

Currently what is the situation of leprosy patients who live in rural areas?

In general, most patients have access to care in the medical facility that is closest to them. If they cannot go to the health centers, people go to visit them in their homes. The distance to patients' homes in our country is not an impediment to give 100% treatment.

The outpatient treatment [of leprosy] started in the 1960s. Before, it was routine to take people to places where they would live for the rest of their lives. This transformation converted the treatment of leprosy from the leper colonies to an outpatient treatment. After 1987 the treatment advanced a lot with teams going to the interior of the country so that the majority of patients have access [to care].

Why isn't the incidence of leprosy dropping, even though we have had good therapy for years and the prevalence of the disease has dropped dramatically?

We still cannot say for sure that there has been a reduction in the reservoir. The multi-bacillary patients who are treated have had months or years of opportunity to spread the bacillus. There are studies in India that show that the bacteria can stay alive on the ground for up to five months in a viable form. This could be a possible fountain of contagion. Recently, evidence has been presented that shows that there can be healthy, asymptomatic carriers of the disease. It seems reasonable that the long incubation period

and the delayed appearance of multi-bacillary cases could account for why we keep seeing so many cases. Even if we presumably treat the last leprosy patient, we could keep getting cases that this "last" patient infected in the past for the next 20-30 years. So, there is a general consensus that only infectious disease that have vaccines have been eradicated. We do not have a vaccine for leprosy.

Do you think that leprosy will be completely eradicated some day?

Judging from the situation in the world, despite multi-drug therapy, there are no secure signs that [leprosy] is really going to be eradicated.

Have you ever been scared of contracting leprosy?

I have dreamed various times that I had leprosy and I have woken up very upset. But, the illness itself has not really frightened me too much, nor the skin lesions, nor taking the treatment. What really scares me is having leg ulcers and neuritis secondary to reactions—that does worry me. But, if we make an early diagnosis and proper treatment, no one should be terrified of this disease.

What should be the fields of research for the future?

I think more research should be done in the realm of reactions. I would not focus on earlier diagnostic tests. We are already doing diagnosis at an early stage. We do not

have microbial resistance. But the reactions—we will probably need to find a way to eliminate the remnants of the bacteria so that the immunologic reactions do not occur. This is the process that leads to nerve problems. Even without significant clinical manifestations, the nerves atrophy and leave permanent sequelae. The medical management of this condition with only steroids is often insufficient. Then, we must watch the patients develop deformities, even after doing nerve surgery and giving them steroids.

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