Historic aspects of human susceptibility to leprosy and the risk of conjugal transmission

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Estimates of genetic susceptibility to leprosy were made in the past from observational reports in familial settings using descriptive epidemiologic data. Risk of conjugal transmission of leprosy (from one spouse to another) has been estimated between 1-10% and is thought to occur in 3-5% of spouses exposed to untreated lepromatous disease in the partner. Risk of secondary transmission is presumed higher in other family members than for the conjugal partner. This belief has become dogma to many leprologists who may no longer know the basis for this estimation. This article reviews the historic epidemiologic descriptions of risk for leprosy transmission in married couples compared to other family members. Although uncommon, conjugal leprosy occurs and at higher rates in populations with traditional familial intermarriage and consanguinity.

Key words: leprosy - genetic susceptibility - consanguinity

Conventionally accepted wisdom is that only a small minority of the human population is capable of sustaining infection by *Mycobacterium leprae*, unlike the universal susceptibility of humans to other members of Mycobacteriaceae. Also accepted is the belief that most humans are immune from leprosy by some yet undefined mechanism. While most modern leprologists have accepted this teaching given by masters who have gone before (Badger 1964, Trautman 1984, Noorden 1994), few know the origins of this observation.

The primary source of human leprosy is transmission from other humans. The household has been considered as the primary location for spread of this infection and particular attention has been given to familial contacts. While most family members share genetic similarity, as well as the opportunity for prolonged close contact, a special type of household contact is that of conjugal partners. Married couples usually share the same bed and have prolonged intimate contact that might allow transfer of organisms between the pair. As an untreated lepromatous patient sheds millions of organisms daily, particularly from oral and upper airway fluids, any bed partner should be exposed at a higher rate than other members of the family not sharing such close contact. However the rate of leprosy transmission between spouses has long been held to be lower than that found in other persons living in the same household.

Most married couples are not closely genetically related, in contrast to other household members who may be parents, siblings or children. As a rule, conjugal partners are assumed not to be blood relatives (Aycock 1948). However in some cultures marriage between first-cousins is an accepted practice and has been estimated as high as 43% in leprosy cases in India (Lyons et al. 2009). While consanguineous marriages may be culturally supported, the practice may result that some populations are more at risk of certain infections due to increased prevalence of genetic susceptibility.

Transmission requires an infective organism, sufficient inoculum transferred to a susceptible host and time for incubation in the host before disease is reproduced as a secondary case. Interruption of transmission can happen anywhere along this process where the conditions are not conducive. Assuming that a conjugal bed partner of an untreated lepromatous patient is the most highly exposed member of a household and therefore is most at risk for secondary infection, the rate of leprosy in a spouse should be proportional to the risk of susceptibility in a population. This assumption is made even though the mycobacterial load of the spouse, the partner's contact time with the spouse and the incubation period in the partner, cannot be controlled in any descriptive epidemiologic studies.

Converse to the rate of infection and susceptibility is the widely-held assumption that over 90% of the general human population is naturally immune to infection by *M. leprae* (Trautman 1984). The rate of uninfected conjugal partners should be proportional to the rate of natural human immunity to leprosy. Many factors, such as hygiene, standard of living, nutrition, childhood, pregnancy and various immunodeficiencies may affect the likelihood of transmission and of expression as clinical disease. The absence of leprosy in spouses of long-term and untreated patients as described in classical studies supports the observation that most humans are not able to acquire leprosy and therefore must have some form of natural immunity. Unfortunately we do not yet know of any immune marker that can reliably differentiate those members of the human population susceptible to leprosy infection from those naturally immune.

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MATERIALS AND METHODS

An extensive literature review of classical leprosy epidemiologic studies was performed, concentrating on conjugal transmission as described in the pre-antibiotic period. Primary sources were obtained as much as possible. These included original articles and texts available from medical library sources and personal archives of historic publications. Leprosy transmission rates for conjugal partners and other familial relationships were cited from the various original authors, with relevant descriptive commentary noted when available. This review could not control for the detail or specificity of the authors' calculations or descriptions. The articles and texts reviewed were evaluated in the context of epidemiologic descriptions of natural history prior to the era of modern antibiotics.

RESULTS

Estimates of leprosy in conjugal partners described in the medical literature ranged from 0.3-32%, as listed in Table I. In a 1922 address on leprosy, Rogers (1922) cited a conjugal rate of 4-5% in Hawaii, but described a rate of 12.12% in his personal case series of 700 patients. In a 1964 description of cases in Louisiana, Badger (1964) cited a conjugal rate of 4.8% occurring in nine of 185 couples. Many authors simply described conjugal leprosy as "rare" without specifying any rate (Aycock 1948, Rao et al. 1975).

Various descriptive studies from India estimated conjugal rates from 0.61-5.5% (Ali 1965, Kaur et al. 1975, Swain et al. 2004, Jindal et al. 2009). Jindal et al. (2009) compared a transmission rate of 0.61% in spouses to a rate of 9.20% in the rest of the family. Conjugal rates in Japan were described from 0.3-3.8% (Kitasato 1960, Hayasi 1965). Worth (1968) reported 37 spouses in Hong Kong followed for 10 years: three individuals (8.1%) developed leprosy, although the consanguinity of the couples was not stated. A Brazilian study in 1957 found conjugal transmission in 7.8%, occurring in 50 of 638 cases (Quagliato 1957). Meléndez et al. (2006) described a conjugal rate of 5.4% in Columbian patients, with consanguinity in two of 26 couples studied; furthermore the pairs were married five-40 years before the second spouse developed clinical symptoms. Chaussinand et al. (1960), in France, reported a single case in which the spouse had five years of marital exposure before clinical symptoms developed. In a large series of 5,626 cases from Mexico between the years 1953-1986, Aguirre-Negrette and Ramirez-Soltero (1990) described 90 men and 44 women who were diagnosed with leprosy presumed transmitted from their conjugal partners.

TABLE I

Rates of conjugal leprosy as described in historic epidemiologic surveys

Location	Year	Reference	Conjugal leprosy rate (%)	Comments
Hawaii	1922	Rogers (1922)	4-5	No details in text.
Not specified	1922	Rogers (1922)	12.12	Eighty-five of 700 cases followed.
Louisiana	1964	Badger (1964)	4.8	Nine of 185 couples.
India	1965	Ali (1965)	5.5	One hundred and six of 1936 spouses.
India	1975	Rao et al. (1975)	Rare	No conjugal rate specified (6.8/100 person year secondary attack rate in all family contacts).
India	1975	Kaur et al. (1975)	1.04	Seventeen of 1,623 cases.
India	2004	Swain et al. (2004)	1.39	One of 72 cases.
India	2009	Jindal et al. (2009)	0.61	One of 163 cases, vs. 9.20% for familial (9 of 163 cases).
Japan	1960	Kitasato (1960)	3.8	No details available.
Japan	1965	Hayasi (1965)	0.3	Twenty of 6,000 cases.
Hong Kong	1968	Worth (1968)	8.1	Three of 37 spouses, followed 10 years; consanguinity of couples not described.
Brazil	1957	Quagliato (1957)	7.8	Fifty of 638 cases.
Columbia	2006	Meléndez et al. (2006)	5.4	Twenty-six couples, two consanguineous, five-40 years married before symptoms in second partner.
Mexico	1990	Aguirre-Negrette and Ramirez-Soltero (1990)	3	One hundred thirty-four of 5,626 cases between 1953-1986 (90 men, 44 women).
France	1960	Chaussinand et al. (1960)	-	Single couple described; married five years before symptoms in partner.
Libya	1998	el-Orfi et al. (1998)	32	Eight of 17 couples with history of first-cousin consanguinity.
Libya	1998	el-Orfi et al. (1998)	2.87	Fifteen of 254 couples with no history of consanguinity.

Of particular interest is a study of conjugal leprosy by el-Orfi et al. (1998) in Libya, who described transmission in couples in a society with an accepted practice of marriage between first-degree cousins. Among Libyan couples with no history of consanguinity, the conjugal rate of leprosy was only 2.87% compared to 32% in consanguineous couples, a difference that was statistically significant by chi-square analysis with a p-value < 0.01. el-Orfi et al. (1998) concluded that couples with the same genetic background are more prone to develop the disease than those with different genetic backgrounds.

In contrast to descriptions of conjugal exposure, were studies reporting rates of transmission in persons presumed to have no genetic risk and limited exposure. Table II displays details of a large series by Gray and Dreisbach (1961) which examined leprosy transmission in missionaries residing in Nigeria. They described 12 adults and one child (1.3%) who developed leprosy among 1,209 missionaries. The mean interval of time between arrival in country and onset of symptoms was 8.7 years. Although the racial background of the missionaries was not described in this report and a small proportion of the missionaries had come to Nigeria from areas endemic for leprosy (Asia, Africa or Australia), this study illustrated a low baseline risk for disease transmission in persons from the general community who worked with leprosy patients. In the history of the USA Hansen's Disease Program in Carville Louisiana, only two hospital employees were ever diagnosed with leprosy; and their medical histories could not separate exposure in the course of their official duties from exposure to leprosy in the local community (MP Joyce, unpublished observations).

Children share a genetic background with an infected parent, may have prolonged intimate contact including sleeping with the parent and require sufficient incubation time to develop clinical disease. Table III describes classic rates of leprosy transmission to children

TABLE II

Rates of leprosy in missionaries as described in historic epidemiologic surveys

Location	Author	Year	Missionary leprosy rate (%)	Comments
Nigeria	Gray and Dreisbach (1961)	1961	1.3	Twelve adults and one child of 1,209 missionaries residing in Nigeria. 8.7 years mean interval between arrival and onset on clinical symptoms.

TABLE III

Rates of leprosy risk in children by contact with parent as described in historic epidemiologic surveys

Location	Author	Year	Children leprosy rate (%)	Comments
Philippines	Lara and Ignacio (1956)	1956	36.2	Parents with leprosy.
Louisiana	Badger (1964)	1964	5.5	Parents with leprosy.
			6.8	Mother is index case.
			3	Father is index case.
Louisiana	Rogers and Muir (1946)	1946	2	Child less than five years old.
			12	Child five-nine years old.
			36.8	Child 10-13 years old.
Indonesia	Boenjamin (1956)	1949	46.3	Child is bed partner with parents.
		1949	6	Child is not bed partner with parents.
Hong Kong	Worth (1968)	1968	14.3	Ten of 70 children age zero-six years old, exposed to parent with LL prior to sulfone treatment, followed for seven-22 years.
		1968	11.6	Eight of 69 children exposed to parent with LL prior to sulfone treatment, followed for > 10 years
		1968	8.3	Two of 26 children exposed to parent with LL prior to sulfone treatment, followed for seven-nine years.
		1968	0	None of 35 children exposed to parent with LL, but after sulfone treatment initiated, whether or not parent was smear negative, followed for seven or more years.

LL: lepromatous leprosy.

in households where a parent was the index case. The highest rate of transmission from an infected parent to a child was 36.2%, as described by Lara and Ignacio (1956) in the Philippine. Badger (1964) described a rate of transmission to children in Louisiana of 5.5% in 1964 and also described an increase rate if the mother was the index case (6.8%) compared to the father (3%), possibly indicating more direct contact of a child with the mother in a family situation.

Risk of transmission to children in familial contact also increases over time as described by Rogers and Muir (1946). Citing cases in Louisiana, children of leprosy-affected parents were diagnosed with the disease in only 2% if less than five years old, but 12% if five-nine years old and 36.8% if 10-13 years old. This observation illustrates the need for prolonged observation of exposed children who may take decades to develop clinical disease. In another descriptive study by Boenjamin (1956) in Indonesia in 1949, children who slept in the same bed with their parents developed leprosy at 46.3% whereas children who did not sleep in the same bed had a rate of only 6%.

The rates of leprosy transmission to children increase with a parent's infectivity prior to treatment and with the length of time a child is observed. Worth (1968) reported that children in Hong Kong exposed to a parent with untreated lepromatous leprosy (LL) developed the disease themselves even after the parent was started on sulfone treatment. In this study children exposed to their untreated parent developed the disease in 8.3% cases if followed for seven-nine years and 11.6% if followed for greater than 10 years. Very young children, less than six years old, exposed to a parent with untreated LL, developed the disease in 14.3% cases if followed for up to 22 years. However, if the parent has started sulfone therapy, whether skin smears were bacteriologically negative or not, none of 35 children developed disease even when followed for greater than seven years.

DISCUSSION

These descriptive epidemiologic studies demonstrate that a common genetic background combined with close contact and prolonged incubation time all contribute to higher rates in family members. Assuming that risk of leprosy transmission is related to intensity of possible exposure, a marriage partner should be the family member with the greatest risk to acquire the infection. However, leprologists have long observed that rates of secondary infection are lower in spouses than in blood relatives. The risk of conjugal transmission of leprosy has been estimated at a rate of 3-5%, consistent with this review of the medical literature. Furthermore, risk to the spouse may increase greatly with certain exposures. The duration of a marriage, sharing of the conjugal bed and particularly a marriage between consanguineous partners increase the likelihood that the unaffected spouse may acquire the infection.

As shown in these papers, when children are exposed to an infected parent, their rates of acquiring leprosy are higher than that of the spouse, indicating an increased risk due to genetic similarity with the parent. Children are particularly at risk if they are of very young age and have prolonged intimate exposure to an untreated parent by sharing a communal family bed. In contrast, historic descriptions of risk in genetically-unrelated missionaries and hospital employees show their rates of acquiring leprosy are extremely low.

The converse to leprosy rates in exposed family members supports the long-held belief that a majority of the human population is not capable of contracting leprosy. Despite sufficient exposure to an infective case and time for incubation, 90-95% of spouses did not acquire leprosy in the pre-antibiotic literature. Even in marriages with high rate of consanguinity by cultural practice, 68% of couples did not experience conjugal transmission of leprosy even though the marriage partners were genetically related as first cousins.

While past master leprologists concluded from clinical observation that only 5% of the human population could sustain infection by leprosy, this review supports their expert opinion. Markers for the genetic determinants which permit acquisition of leprosy would permit identification of the susceptible human population and could provide immunologic interventions that will truly eradiate this historic disease.

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