INTERNATIONAL JOURNAL OF LEPROSY Volume 55, Number 3
Printed in the U.S.A.

An Investigation of Family Size and Birth Order as Risk Factors in Leprosy[1]

Ivoni G. Koumantaki, Klea M. Katsouyanni, Evangelia P. Kaklamani,
Irene M. Malama, Dimitri Th. Karalis, Dimitri J. Papaïoannou,
and Dimitri V. Trichopoulos[2]
with technical assistance of P. Drogari

The conditions influencing effective exposure to *Mycobacterium leprae* and the establishment of the disease, leprosy, are not well understood. Several factors have been investigated, including genetic, immunological, and environmental variables ([3–5, 7]). We have investigated the sibship size and birth order distribution of 187 patients with leprosy (114 lepromatous and 73 tuberculoid) and a control group of 528 hospitalized patients. If age at exposure to *M. leprae* is important for the development of the disease, it would be expected that patients with leprosy in general, or with a certain form of the disease in particular, would have a different frequency distribution with respect to sibship size and/or birth order than unaffected persons. We report here the findings of this analysis.

MATERIALS AND METHODS

The study includes 187 patients with leprosy who were hospitalized or seen as outpatients at the Center of Hansen's Disease of the Hospital for Infectious Diseases in Athens, Greece. The control group comprised 528 low socioeconomic class patients, in order to match the cases with respect to this factor, hospitalized in nearby general hospitals with a diagnosis other than leprosy or other infectious diseases. Patients and controls originated from various regions of the country, and there were no significant differences by place of origin (urban, semi-urban, rural). All subjects were of Caucasian origin. It should be noted that the socioeconomic status of leprosy patients in Greece is low but not as low as that found in some less-developed countries. Furthermore, selection of an appropriate control group eliminates to a substantial extent the possibility of confounding introduced by differential recollection according to sibship size. The study of all cases and controls took place during a 2-year period.

The diagnosis of leprosy and its classification according to the Ridley-Jopling scale ([9]) was based on clinical picture, bacteriologic report, and the histopathology of the lesions. Only cases with the two polar types of leprosy were considered; patients with borderline or indeterminate forms of the disease were excluded from the analysis. All 73 Hansen's disease patients with the polar tuberculoid form had a negative bacteriologic report and had no "lepra reactions" during the study period. On the other hand, among 114 patients with the polar lepromatous form of Hansen's disease, 22 had a positive bacteriologic report and 10 among them had lepra reactions. No reactions were noted among patients with the polar lepromatous form of Hansen's disease and a negative bacteriologic report.

Patients and controls were interviewed by the same person (two of the authors). In the interviews, data concerning birth order (live-born children), sibship size, years of schooling of both patient and father (believed to reflect socioeconomic status better than any other generic indicator in the population of Greece [11]), status of the father or the mother with respect to leprosy, and other demographic and medical variables were record-

[1] Received for publication on 27 May 1986; accepted for publication in revised form on 11 February 1987.

[2] I. G. Koumantaki, M.D., Lecturer; K. M. Katsouyanni, Dr.Med.Sc., Lecturer; E. M. Kaklamani, M.D., Associate Professor; I. M. Malama, M.D., Internist; D. T. Karalis, Lecturer; D. J. Papaïoannou, M.D., Lecturer; and D. V. Trichopoulos, M.D., Professor, Department of Hygiene and Epidemiology, School of Medicine, University of Athens, 11527 Athens (Goudi), Greece.

Reprint requests to Dr. Kaklamani.

TABLE 1. *Summary of observed and sibship-standardized expected frequencies of leprosy patients by birth order and form of the disease.*

	Birth order			Total
	1–2	3–4	5+	
All leprosy patients				
Observed	90	51	46	187
Expected	94.4	52.2	40.4	187
Polar tuberculoid form				
Observed	31	24	18	73
Expected	36.3	22.6	14.1	73
Polar lepromatous form				
Observed	59	27	28	114
Expected	58.2	29.5	26.3	114

ed. The interview forms were precoded, and the interviewers were pilot-trained in order to minimize potential biases.

The analysis was done by the classical Greenwood-Yule method ([6]) as well as with logistic regression procedures using GLIM ([1]).

RESULTS

Table 1 is a summary of the observed and sibship-standardized (by the Greenwood-Yule method [6]) expected frequencies of leprosy patients by birth order and form of the disease. It can be seen that there is little overall difference between the observed and the expected distribution for the total group of patients with Hansen's disease. However, there appears to be a different pattern of discrepancy between the two subgroups of patients with Hansen's disease, i.e., between patients with polar lepromatous leprosy and polar tuberculoid leprosy. Although the contrast is neither striking nor significant, it does suggest that for patients with tuberculoid leprosy there is a small deficit of cases in the earlier birth orders (31 observed vs 36.3 expected); for patients with lepromatous leprosy, there is no such deficit at the earlier birth orders.

In the simple Greenwood-Yule analysis no account was taken of two important factors: a) socioeconomic status as indicated by years of schooling ([11]), and b) status of the father or the mother with respect to leprosy. Both of these factors, as well as sibship size, birth order, and current age, were taken into account in the multivariate modeling summarized in Table 2.

The findings from the logistic analysis indicate that, after control for socioeconomic class, sibship size becomes a nonsignificant and nonconsistent predictor of leprosy or of the form of leprosy. On the other hand, the multivariate analysis supports the impression that lepromatous patients belong to the earlier birth orders in both sexes, although in neither instance does the contrast reach statistical significance.

TABLE 2. *Regression coefficients (b), standard error of the regression coefficients [SE(b)], and p values for sibship size and birth order in multivariate modeling (logistic regression).*[a]

	Sibship size				Birth order			
	b	SE(b)	χ^2	p	b	SE(b)	χ^2	p
				Men				
Contrasting								
All controls[b] All cases	−0.073	0.057	1.7	0.19	0.028	0.064	0.2	0.65
All TT cases[c] All LL cases	0.066	0.090	0.5	0.48	−0.098	0.106	0.9	0.34
				Women				
Contrasting								
All controls[b] All cases	0.026	0.071	0.2	0.65	−0.101	0.080	1.6	0.21
All TT cases[c] All LL cases	0.027	0.108	0.2	0.65	−0.133	0.122	1.2	0.27

[a] Controlling also for socioeconomic class, age of patients, and (for leprosy cases) for leprosy status of parents.
[b] 0 for controls and 1 for cases.
[c] 1 for TT cases and 2 for LL cases.

TABLE 3. *Regression coefficients (b), standard error of the regression coefficients [SE(b)], and p values for sibship size and birth order in multivariate modeling (logistic regression) excluding cases with affected parents.*[a]

	Sibship size				Birth order			
	b	SE(b)	χ^2	p	b	SE(b)	χ^2	p
				Men				
Contrasting								
All controls[b,c] All cases	−0.073	0.057	1.7	0.19	0.028	0.064	0.2	0.65
All TT cases[d] All LL cases	0.069	0.099	0.5	0.48	−0.120	0.119	1.1	0.29
				Women				
Contrasting								
All controls[b,c] All cases	0.026	0.071	0.2	0.65	−0.101	0.080	1.6	0.21
All TT cases[d] All LL cases	−0.027	0.110	0.1	0.75	−0.169	0.131	1.8	0.18
				Men and women				
Contrasting (controlling for sex)								
All TT cases[d] All LL cases	0.041	0.072	0.3	0.58	−0.130	0.086	2.7	0.10

[a] Controlling also for socioeconomic class and age. Leprosy cases (45) with affected parents were excluded.
[b] 0 for controls and 1 for cases.
[c] These results are, of course, identical to the respective results of Table 2.
[d] 0 for TT cases and 1 for LL cases.

Table 3 summarizes the Chi-square values for sibship size and birth order in the logistic regression controlling for socioeconomic class and current age, excluding the 45 leprosy cases with affected parents. The contrasts between lepromatous and tuberculoid cases, with regard to birth order, although statistically nonsignificant, are even more suggestive that lepromatous patients belong to earlier birth orders in both sexes.

Thirty-seven of the cases reported at least one of their older sibs as affected by leprosy. However, when the appropriate interaction variable was introduced in the respective model, there was no significant or suggestive evidence of such interaction.

DISCUSSION

It is known that the incidence of contagious diseases in general rises with the increase of the family size, since the probability of introduction and spread of infection is correspondingly greater ([10]). Furthermore, it is known, at least for some infections, that first-born children are usually exposed to the disease at school age; whereas later-born children are usually exposed during pre-school age ([2]). On the basis of these observations and the recent realization that leprosy is less unique among infectious diseases than was formerly thought ([5]), we attempted to investigate if sibship size and birth order are factors related to the development of leprosy in general or to a particular form of the disease.

In this study we included only patients suffering from the two polar forms of leprosy in order to avoid difficulties in classification. We also used, as a control group, patients of low socioeconomic class from general hospitals with a diagnosis other than leprosy or other infectious disease. There is no evidence that the disease of any diagnostic group in the controls is related to sibship size and/or birth order in any other way than that mediated by socioeconomic status which is an intentionally matched factor. We have focused the analysis on birth order rather than on sibship size. Both of these variables can affect age at exposure and probability of transmission of the disease. However, because of the extremely strong importance of socioeconomic factors for exposure and transmission of leprosy,

and because of the strong correlation between socioeconomic factors and sibship size, we considered it unlikely that we would have been able to completely control socioeconomic status, and we have expected a residual confounding with respect to sibship size. By contrast, the birth order association could be investigated independently of socioeconomic class and sibship size and, thus, would be reasonably free from confounding bias.

For the analysis, we have applied the classical Greenwood-Yule method ([6]) as well as multivariate procedures ([1]).

The overall results are negative. Even so, they do not disprove the existence of an infectious pattern but rather fail to demonstrate whether one does actually exist. A small deficit of cases with tuberculoid leprosy was found in the earlier birth orders. This observation could imply that cases with tuberculoid leprosy are, on the average, exposed to *M. leprae* earlier in life than are cases with lepromatous leprosy, since children born to late birth orders are likely to be infected by their older sibs. In the simple Greenwood-Yule analysis, no control group is required; therefore possible bias introduced by secular changes in parity cannot be controlled ([8]). Furthermore, no account was taken for the status of the father or the mother with respect to leprosy. Both of these factors as well as sibship size, birth order, socioeconomic status, and current age were taken into account in the multivariate modeling where 528 control subjects were included. In all comparisons, a small deficit of cases with tuberculoid leprosy was found in the earlier birth order. The results from this analysis suggest that exposure to *M. leprae* early in life predisposes to tuberculoid leprosy, although nominal significance ($p \approx 0.05$) has not been reached in either approach.

The results of this study are in agreement with descriptive epidemiological data which show that in highly endemic areas, where early exposure to *M. leprae* is the rule, the incidence of tuberculoid leprosy is much higher than in nonendemic countries ([5]). Neither observation, however, leads to any explanation of the mechanism by which early exposure to *M. leprae* leads to the more resistant type of leprosy.

SUMMARY

To investigate if early exposure to *Mycobacterium leprae* is a factor determining development of Hansen's disease in general, or of a particular form of the disease, we have studied the sibship size and birth order distribution of 187 leprosy cases and 528 hospitalized control patients.

By the Greenwood-Yule analysis, a small deficit of cases in the earlier birth order in the tuberculoid form was observed. Such a deficit was not observed in lepromatous leprosy patients.

In the multivariate analysis, where socioeconomic factors, current age, and leprosy status of the parents were taken into account, it was found that sibship size becomes a nonsignificant and nonconsistent predictor of leprosy in general or of a particular form of the disease. On the other hand, the logistic analysis supports the impression that tuberculoid leprosy patients belong to the later birth order in both sexes. Although the contrast is statistically nonsignificant in either sex, it suggests that early exposure in life predisposes to the tuberculoid form of leprosy.

RESUMEN

Para investigar si la exposición temprana al *Mycobacterium leprae* es un factor determinante en el desarrollo de la enfermedad de Hansen en general, o de una forma particular de la misma, se analizó el número de hermanos y el órden de su nacimiento en 187 casos de lepra y en 528 pacientes control hospitalizados.

Por el análisis de Greenwood-Yule, se observó un pequeño déficit de casos tuberculoides en los nacimientos de órden temprano. Tal déficit no se observó en los pacientes con lepra lepromatosa.

En un análisis multivariado donde se tomaron en cuenta factores socioeconómicos, edad actual, y estado de la lepra en los progenitores, se encontró que el tamaño de la progenie no está asociado ni con el desarrollo de la lepra en general ni con ningún tipo particular de lepra. Por otro lado, el análisis logístico apoya la impresión de que los pacientes con lepra tuberculoide corresponden a nacimientos de orden tardío, en ambos sexos. Por otro lado, aunque el contraste no es estadísticamente significativo para ninguno de los sexos, si sugiere que la exposición temprana en la vida, predispone a la forma tuberculoide de la lepra.

RÉSUMÉ

Afin d'étudier si une exposition précoce à *Mycobacterium leprae* constitue un facteur intervenant dans le

développement de la maladie de Hansen en général, ou d'une forme particulière de l'affection, on a étudié la dimension des familles et la distribution de l'ordre des naissances chez 187 malades de la lèpre et chez 528 sujets témoins hospitalisés.

En utilisant l'analyse de Greenwood-Yule, on a noté un léger déficit de cas parmi les sujets appartenant aux valeurs les plus faibles dans l'ordre des naissances, pour la forme tuberculoide. Un tel déficit n'a pas été observé chez les malades lépromateux.

Par l'analyse multivariée, prenant en compte les facteurs socioéconomiques, l'âge actuel, et la présence ou non de lèpre chez les parents, on a constaté que la dimension de la famille ne permet pas de prédire de façon significative ou cohérente l'apparition de la lèpre en général ou d'une forme particulière de la maladie. Par ailleurs, l'analyse logistique renforce l'impression que les malades atteints de lèpre tuberculoide ont plus souvent des rangs de naissance élevés. Malgré le fait que le contraste ne soit pas statistiquement significatif, ni dans un sexe ni dans l'autre, cette observation suggère cependant qu'une exposition précoce à la lèpre au cours de la vie prédispose à la forme tuberculoide de la maladie.

Acknowledgment. We acknowledge Ms Helen Toussi for her excellent technical assistance.

REFERENCES

1. Baker, R. J. and Nelder, J. A. *Generalized Linear Interactive Modelling (GLIM).* Oxford: Numerical Algorithms Group, 1978.
2. Barret, D. H., Burks, J. M., McMahon, B., Elliott, S., Berquist, K. R., Bender, T. R. and Maynard, J. E. Epidemiology of hepatitis B in two Alaska communities. Am. J. Epidemiol. **105** (1977) 118–122.
3. de Vries, R. R. P., Lai-A-Fat, R. F. M., Nijenhuis, L. E. and van Rood, J. J. HLA-linked genetic control of host response to *Mycobacterium leprae.* Lancet **2** (1976) 1328–1330.
4. Duncan, E. M., Melsom, R., Pearson, J. M. H., Menzel, S. and Barnetson, R. St.C. A clinical and immunological study of four babies of mothers with lepromatous leprosy, two of whom developed leprosy in infancy. Int. J. Lepr. **51** (1983) 7–17.
5. Fine, P. E. Leprosy: the epidemiology of a slow bacterium. Epidemiol. Rev. **4** (1982) 161–188.
6. Greenwood, M. and Yule, G. U. On the determination of size of family and of the distribution of characters in order of birth from samples taken through members of the siblings. J. R. Stat. Soc. **77** (1914) 179–199.
7. Pedley, J. C. Transmission of leprosy. In: *A Window on Leprosy.* Chatterjee, B. R., ed. Delhi: Gandhi Memorial Leprosy Foundation, 1978, pp. 54–58.
8. Price, J. and Hare, E. Birth order studies: some sources of bias. Br. J. Psychiatry **115** (1969) 633–646.
9. Ridley, D. S. and Jopling, W. H. Classification of leprosy according to immunity; a five-group system. Int. J. Lepr. **34** (1966) 255–273.
10. Taylor, I. and Knowelden, J. *Principles of Epidemiology.* 2nd ed. London: J. & A. Churchill Ltd., 1964, p. 304.
11. Trichopoulos, D. *Epidemiology; Principles, Methods, Applications.* Athens: Parissianos, 1982.