Long-Term Predictors of Recurrent Laboratory-Confirmed Giardiasis: A 10-Year National Surveillance Study

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During 2002 to 2011, 275 of 6828 children with giardiasis in Israel were reported with recurrent, over 6 months apart, episodes. The only significant multivariable-adjusted risk predictor of a recurrent episode was non-Jewish ethnicity (hazard ratio, 4.61 [95% confidence interval, 3.32–6.40]; \( P < .001 \)), also accompanied by significant interaction with lower maternal education.

Key words. epidemiology; ethnicity; Giardia lamblia; pediatric; socioeconomic status.

Giardia lamblia is found worldwide in temperate and tropical locations and, in particular, where sanitary conditions are suboptimal. Giardiasis places a heavy burden on public health diagnostic and treatment services in both developing and developed countries [1]. Higher transmission rates are found in populations characterized by low socioeconomic status (SES) and crowded living conditions [2]. In children, recurrent or persistent giardiasis might lead to serious consequences due to malnutrition, including retarded growth and development and poor cognitive function [3, 4]. Previous studies in Israel, mostly conducted before 2000, described high prevalence among children of Arab and Bedouin origin [5–7], children living in rural areas [8], and Ethiopian immigrants [9]. We hypothesized that recurrent episodes of pediatric giardiasis would be associated in the long term with modifiable environmental and socioeconomic predictors of the pediatric patient’s household, such as the number of siblings and parents’ education level, rather than with individual perinatal characteristics such as gestational age and birth weight.

METHODS
Subjects and Study Design
Since 2001, giardiasis has been a notifiable disease by law in Israel. Individual case notifications are reported by healthcare providers and clinical laboratories to the District Health Offices. The reports are processed nationally by the Division of Epidemiology and provide a basis for all incidence data and epidemiological analysis of illness among civilians. We studied the population-based national surveillance data for laboratory-confirmed (mostly by microscopic examination of the stool) giardiasis of all reported community and hospitalized cases between 2002 and the end of 2011. Furthermore, we linked this database with the National Live Birth Registry (also mandated by law) to analyze the potential exposures of recurrent giardiasis that could be related to birth or family characteristics in the pediatric patients (<18 years of age). This administrative registry had available computerized records for live births since January 1, 1993. Complete computerized records, defined in this study as fully recorded data for maternal years of education, which was generally more frequently recorded than paternal years of education, were available for live births from October 1997. The linkage between the databases was readily feasible because each resident in Israel has a unique identification number from birth, and this number appeared consistently in both databases. The study was approved by the Institutional Helsinki Committee of the Ministry of Health.
Definitions

Recurrent giardiasis was defined as having at least 2 episodes of laboratory-confirmed giardiasis during the study period (2002–2011) with a minimum of a 6-month interval between consecutive episodes, by date of disease onset. The primary outcome was dichotomized to recurrent giardiasis episodes vs 1 single episode. This definite outcome ensured a distinctive analysis of the more influential predictors for recurrent giardiasis episodes in the medium and long-term periods, in contrast to previous studies, in which recurrent episodes were practically undistinguished from persistent episodes (eg, when the minimal time lapse between recurrent diarrheal episodes was defined as 3 days [5-7]).

Statistical Analysis

The full section is available as Supplemental Material. All P value calculations were 2-tailed and considered statistically significant if P < .05. All data files were computerized and processed to contain individual anonymous records only. The linked database was analyzed using IBM SPSS, version 20.0 (Chicago, IL).

RESULTS

Epidemiology of Giardiasis in Israel, 2002–2011

During the study period, 16 436 adults and children were reported to the Ministry of Health. The average annual incidence of giardiasis in Israel was 24.2 case-patients per 100 000 population (range, 19.9 in 2011 to 28.3 in 2007). The average annual incidence by age group was the highest in children aged 1–4 (142.7 case-patients per 100 000) followed by 58.1 case-patients per 100 000 infants <1 year (Supplemental Figure 1). The average annual incidence by ethnicity was 25.0 case-patients in the Jewish population and 19.3 case-patients in the non-Jewish population per 100 000 population.

Of the 16 436 notified patients, 65% (n = 10 694) were pediatric (age <18 years) at time of first (or single) episode onset (Figure 1). Of all pediatric cases, 64% (n = 6828) patients had complete Live Birth Register data (born from October 1997) following the linkage between the databases. This linked cohort had a mean follow-up time within the 10-year surveillance period of 4.2 ± 2.7 years. A total of 275 pediatric case-patients (4.2%) had recurrent episodes of laboratory-confirmed giardiasis, and, of those, 43 pediatric case-patients (0.7%) had 3 or more episodes during the follow-up period (Figure 1). The statistically significant differences in baseline characteristics over the recurrent vs single giardiasis outcome were age at onset of first episode, maternal and paternal education years, number of siblings in household at birth, and ethnicity (Supplemental Table 1).

Cross-Sectional Correlates of Mother Educational Level >12 Years

For all patients included in the study, maternal education level’s correlates were studied in a multivariate logistic regression model (Supplemental Table 2). A working mother, mother age at birth ≥30 years, Jewish ethnicity, and having 0–3 siblings in the household on first episode (vs >3 siblings) were strongly correlated with maternal education level >12 years (all P < .001).

Kaplan-Meier Curves for Time to Recurrence of Giardiasis

Figure 2 presents the cumulative probability over time for recurrent laboratory-confirmed giardiasis, stratified by ethnicity, and the maternal education level. Patients, of both Jewish and non-Jewish ethnicity, who had mothers in the higher education stratum, had lower outcome rates of recurrent giardiasis (log-rank P for the overall comparison <.001). Patients of Jewish ethnicity of both educational strata had lower outcome rates of recurrent giardiasis, compared to patients of Arab or other ethnicities (log-rank P < .001 in the maternal education years ≤12 strata and log-rank P = .06 in the maternal education years >12 years).

Multivariate Model for Recurrent Giardiasis Outcome and Interaction-Term Analysis

The only significant predictor for recurrent giardiasis outcome in the fully-adjusted multivariate regression model (Supplemental Table 3) was ethnicity. The hazard ratio (HR) for recurrent giardiasis in the non-Jewish patients was 4.61 (95% confidence interval [CI], 3.32–6.40; P < .001). This predictor was evaluated further by inserting into the same model the interaction term between maternal education level and non-Jewish ethnicity. A statistically significant interaction was found.
between these predictors: the HR for recurrent giardiasis in the group of patients with mother education years ≤12, who were of non-Jewish ethnicity, was 2.44 (95% CI, 1.10–5.41; \(P = .03\)), whereas in the group of patients with mother education years >12, who were of non-Jewish ethnicity, the HR was 0.41 (95% CI, .19–.91; \(P = .03\); \(P\)-for-interaction = .02).

**DISCUSSION**

To our knowledge, we studied the largest cohort to date of laboratory-confirmed giardiasis, with particular emphasis on recurrent episodes in children during a long-term, 10-year, surveillance period. Our main finding was that SES, as represented by the patients’ maternal education level, was significantly associated, in the univariate and multivariate analyses, with recurrent laboratory-confirmed episodes of giardiasis: lower maternal education was a predictor of risk, whereas higher maternal education was a predictor of protection against recurrent episodes. This finding is important because SES is generally a modifiable predictor of disease, in contrast to more deterministic characteristics, such as ethnicity or birth weight.

In our study, lower maternal education level interacting with non-Jewish origin were the highest risk predictors for children with recurrent giardiasis. Previously established in a small study of 324 Arab Bedouin children in Israel, maternal education was related to persistent or recurrent *G. lamblia* infection (defined as a minimal 3-day between-episodes interval), demonstrating a significant inverse association with recurrent infections within the short 18- to 23-month follow-up of that study, from birth [5-7]. Maternal education level appears to be a strong risk factor for recurrent infection, and, apart from being a correlate of SES [2], it could also be an indicator for the household overall hygiene level, food preparation habits, and utensil storage. In households with reduced sanitary conditions, the risk or the incidence rate of giardiasis in infants was higher [10].

In previous studies in Israel, researchers found that *G. lamblia* was present in as high as 53% of the study population, and that 20% had recurrent infection within the 2-year follow-up period [5-7]. Even higher reinfection rates were found in longitudinal studies in Brazil and Peru, with reinfection rates of 46% and 87%, respectively [2, 11]. However, these studies were all of much smaller cohort sizes, had shorter follow-up periods, focused on a limited age range, and defined disease recurrence with significantly shorter intervals (cross-sectional [2]; 3 days [5-7] or up to 1 month [11]) between diarrheal episodes than our study.

Our study has limitations. Incidence of giardiasis could possibly be underestimated due to the underdetection of the disease at the clinical level or underreporting at the epidemiological surveillance level. Not all infected persons are symptomatic, particularly children, or persons who are symptomatic do not always seek medical care. In addition, healthcare providers do not always include laboratory diagnostics in their evaluation of nonbloody diarrheal diseases [12], and case reports are not always completed for positive laboratory results. However, because our groups of comparison were those children with recurrent giardiasis vs those with a single episode, any detection or reporting bias would affect both groups in a nondifferential manner and would therefore even weaken the strength of the associations found in our study.

Giardiasis episodes in our study were laboratory-confirmed, and therefore it is less likely that inequality in access to clinical and laboratory diagnostic services served as a mediator on the pathway between the observed significant associations. In addition, the rate of hospitalizations and the mean gestational age at birth were similar between
Jews and non-Jews. Thus, in respect to these indices of possible health inequalities, there were no statistically significant discrepancies.

In conclusion, modifiable socioeconomic predictors of the household, rather than individual ones (such as gender or birth weight), may contribute significantly to recurrent episodes of pediatric giardiasis. Consequently, health promotion interventions focused on providing public education regarding methods of prevention, and interruption of transmission (such as environmental and hygiene control measures) should receive increased emphasis.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Supplementary Data

Supplementary materials are available at the Journal of The Pediatric Infectious Diseases Society online (http://jpids.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copy-edited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

References