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VISCERAL LARVA MIGRANS IN FRENCH ADULTS: A NEW DISEASE SYNDROME?

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Visceral larva migrans is apparently an endemic disease among adults in southwest France. Thirty-seven adults living in the Midi-Pyrenees region of France were confirmed as having visceral larva migrans based on an increased specific antibody titer to *Toxocara canis* as detected by enzyme-linked immunosorbent assay (ELISA) and by the Western blot method. The disease was characterized clinically by weakness, pruritis, rash, difficulty breathing, abdominal pain, and pathologically by allergic manifestations including eosinophilia and increased serum immunoglobulin (Ig) E levels. Conditional logistic regression analysis using a control group of 37 hospital patients with other conditions who were individually matched to patients with visceral larva migrans by age and sex revealed an increased risk for visceral larva migrans associated with hunting or living in a household with a hunter (odds ratio (OR) = 9.0, $p = 0.02$) and with living in a village of <500 persons (OR = 5.7, $p = 0.04$). Owning two or more dogs compared with owning one or no dogs increased the risk of visceral larva migrans for hunting or living in a household with a hunter (OR = 9.6 vs. OR = 4.5) and for persons living in nonhunting households (OR = 2.1 vs. OR = 1.0). These findings, however, could not be duplicated when 60 age- and sex-matched neighbors were used as a second control group.

helminths; immunoenzyme technics; larva migrans, visceral; *Toxocara*; zoonoses

Visceral larva migrans is a zoonotic disease caused by the migration or presence in human tissue of nematode larvae from lower animals. Invading larvae are commonly of species not adapted to human hosts. Therefore, within human hosts, these larvae remain immature and do not complete their life cycle. An important

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Abbreviation: ELISA, enzyme-linked immunosorbent assay.

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cause of visceral larva migrans is the second-stage larva of *Toxocara canis*, the common dog roundworm.

The typical patient with visceral larva migrans is a child one to five years of age who has a history of pica, usually geophagia, and recent exposure to a puppy (1). Clinical findings are likely to include one or more of the following: fever, hepatomegaly, asthma or respiratory impairment, central nervous system signs, and visual disturbance (2). Laboratory findings often include, but are not limited to, leukocytosis, prolonged eosinophilia, an increased anti-A or anti-B isohemagglutinin titer, and an elevated concentration of serum immunoglobulin (Ig) G and IgE (3, 4).

In 1982, Magnaval et al. (5) described 48 cases of visceral larva migrans that occurred over a one-year period of time in the Midi-Pyrenees region of France. Patients ranged in age from five to 65 years, with an average age of 49 years; 35 (73 per cent) were female. The syndrome was characterized by chronic eosinophilia (>500 cells/mm^3), generalized weakness, anorexia, weight loss, dermatologic manifestations (pruritis, urticaria), and pulmonary signs (cough, dyspnea). Repeated coprologic and serologic examinations were negative for the common causes of parasitic disease in that geographic area. A presumptive diagnosis of visceral larva migrans was based on the hematologic findings and positive serologic results of immunoelectrophoresis using an antigen prepared from the uterus of *Ascaris suum*. An epidemiologic investigation implicated consumption of raw dandelions as the possible source of infection, despite the fact that no specific etiologic agent was identified.

The object of the current investigation was to describe further the occurrence of visceral larva migrans among French adults and to report the findings of a case-control epidemiologic study conducted in the Midi-Pyrenees region of France. None of the patients in the present study had been included in Magnaval et al.'s (5) previous report.

Materials and methods

Subjects

Patients with visceral larva migrans were identified among persons referred to the Laboratory of Parasitology, Central Hospital of Toulouse-Purpan, France, between January 1979 and January 1983 for medical consultation and serologic evaluation. The primary reasons for their referral were typically persistent eosinophilia, elevated total IgE, rash, or generalized weakness, all of uncertain etiology. A presumptive diagnosis of visceral larva migrans was made if repeated coprologic examinations were negative for the presence of parasite ova and parasites and if serologic tests were nondiagnostic for the following parasitic conditions: fascioliasis by enzyme-linked immunosorbent assay (ELISA), indirect immunofluorescence, and immunoelectrophoresis; hydatidosis by ELISA and indirect hemagglutination; strongyloidiasis by indirect immunofluorescence; and taeniasis by countercurrent immunoelectrophoresis. In addition, the criteria for visceral larva migrans included a positive ELISA for *T. canis* and a positive immunoelectrophoresis assay for *A. suum*, as described later.

Two comparison groups were selected for study. A neighborhood control group was assembled by asking each patient with visceral larva migrans to suggest the names of two friends who lived within 10 km, were of the same sex, and were approximately the same age as the patient. These friends were contacted by telephone, and permission was obtained for an interview at their home on the same day that the patients with visceral larva migrans were visited. Venous blood samples were collected in a similar manner from patients and neighborhood controls at the time of the interview. In some instances, only one neighborhood control was available for a patient with visceral larva migrans.

A second control group was formed by matching each patient with visceral larva migrans with an inpatient from the general medical or surgical services at the Central

Hospital of Toulouse-Purpan. Hospital controls were individually matched to patients with visceral larva migrans by sex and age. Consent was obtained from the patients for an interview and for collection of a venous blood sample. In only one instance was permission denied by an inpatient for these procedures.

Serum samples were collected from the following: randomly selected French patients with visceral larva migrans and hospital controls; patients in the United States whose clinical signs and serologic tests were consistent with visceral larva migrans caused by *T. canis*; cynomolgus macaques experimentally infected with *T. canis* (6) or *A. suum* eggs; and patients confirmed by the Centers for Disease Control, Atlanta, Georgia, as being infected with *Schistosoma mansoni*, *Strongyloides stercoralis*, or *Wuchereria bancrofti*. Sera were evaluated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and Western blot techniques as previously described (7, 8). These methods were used to determine qualitative and quantitative differences in the pattern of reactivity of the above sera with *T. canis* larval excretory-secretory antigens.

Interviews

All interviews with patients with visceral larva migrans and with hospital and neighborhood controls were conducted from March to June 1984 by one of the investigators (J.-F. M.) after pretesting of the questionnaire. The actual interview took approximately 30 minutes and included questions concerning medical history (patients with visceral larva migrans only), education, residence and travel experience, occupation, tobacco use, animal ownership and exposures, diet, home gardening, water source, type of sewage disposal, and hobbies. For the patients with visceral larva migrans, these questions pertained to the one-year time period prior to onset of their clinical signs and symptoms. For the neighborhood and hospital controls, the time frame of reference for the interview questions corresponded to that of the patients with visceral larva migrans with whom they had been matched.

Laboratory tests

A serologic confirmation of visceral larva migrans was based on an antibody titer of >1:16 to *T. canis* second-stage larval excretory-secretory antigen by ELISA (9, 10) and on a positive reaction by immunoelectrophoresis (5) to a soluble extract of the uterus of gravid *A. suum* worms. Patients with visceral larva migrans fulfilled both criteria, whereas all control subjects were negative on both ELISA and immunoelectrophoresis testing. Blood samples used for differentiating cases and controls were those collected at the time of the interview. Blood samples collected previously from patients with visceral larva migrans at the time of onset of their clinical signs were not available for this study. Serologic tests for other parasitic infections were performed by the Laboratory of Parasitology, Central Hospital of Toulouse-Purpan.

Hematologic studies were performed by the Hematology Department and measurement of serum immunoglobulins by the Central Blood Bank, Central Hospital of Toulouse-Purpan. Specific IgE antibodies were measured as described by Brochier et al. (11). The normal reference values for all laboratory procedures were those used by the individual laboratories.

Each of the laboratory procedures was usually performed for the patients with visceral larva migrans and for the neighborhood controls without prior knowledge of the diagnosis. Because of limited resources, however, not all procedures were requested for the hospital controls.

Statistical analysis

Data were analyzed by standard methods for fixed and variably matched case-control epidemiologic studies (12, 13). For the interview data, odds ratios (OR) with 95 per cent confidence limits (CL) were calculated for each item in the questionnaire by using

the hospital and neighborhood control groups separately. Statistical significance, defined as $p < 0.05$, was determined by McNemar's test or by the maximum likelihood estimate of the odds ratio. For the laboratory data, the paired t test was used for both case-control comparisons. When there were two neighborhood controls for a patient with visceral larva migrans, the average laboratory value of the two controls was used.

A multiple logistic statistical model for matched data as described by Breslow and Day (12) and implemented by the Statistical Analysis System (SAS) (14) was used to identify questionnaire items that were independently associated with an increased risk of visceral larva migrans. Questionnaire items that were significant at $p < 0.1$ on the initial univariate matched-pairs analysis and all animal contact questions were tested for inclusion in the logistic models. For the laboratory data, a logistic multiple regression model (15) as implemented by SAS (16) was used to identify the laboratory measures that best discriminated between patients with visceral larva migrans and neighborhood controls, and between patients with visceral larva migrans with and without allergic manifestations of visceral larva migrans. The former analysis was not performed using the hospital control group because not all laboratory tests had been performed for this group.

RESULTS

Demographic characteristics

Serum specimens from 240 persons which were submitted to the Laboratory of Parasitology, Central Hospital of Toulouse-Purpan between January 1979 and January 1983 for visceral larva migrans were found positive by immunoelectrophoresis. Forty-five of these persons were subsequently referred to one of the authors (J.-F. M.) for clinical consultation. In February 1984, an attempt was made to contact these 45 patients and to obtain their consent to participate in an epidemiologic study. Five (11.1 per cent) persons could not be contacted by telephone, two (4.4 per cent) refused to participate, and one (2.2 per cent) person did not satisfy the criteria for visceral larva migrans because the ELISA test was negative. Of the 37 persons who agreed to participate, 18 (48.6 per cent) had onset of clinical signs within one year of the study, 28 (75.7 per cent) within two years, and 33 (89.2 per cent) within three years. The average time interval between onset of clinical signs and the study was 18.6 months (median 15.0 months).

The 37 patients with visceral larva migrans were individually matched by age and sex to 37 hospital controls. The mean age of the cases and hospital controls was 46.8 years (standard deviation (SD) 13.3 years, range 24–73 years) and 48.8 years (SD 14.4 years, range 19–73 years), respectively. Thirty-five (94.6 per cent) of the cases were successfully matched to hospital controls within 10 years of age. Sixteen (43.2 per cent) of the patients with visceral larva migrans and their matched hospital controls were males.

A single neighborhood control was identified for 14 patients with visceral larva migrans, and two neighborhood controls were identified for the remaining 23 cases. The mean age of the 60 neighborhood controls was 45.5 years (SD 17.4 years, range 20–75 years). Fifty-three (88.3 per cent) of the neighborhood controls were matched to patients with visceral larva migrans within 10 years of age. Of the 60 neighborhood controls, 22 (36.7 per cent) were males.

Twenty-seven (73.0 per cent) of the 37 patients with visceral larva migrans lived in the Haute Garonne Department of France (figure 1) compared with 68.3 per cent of the neighborhood and 55.6 per cent of the hospital controls. Cases and their neighborhood controls came from seven different departments in southwest France, whereas their hospital controls came from 10 different departments.

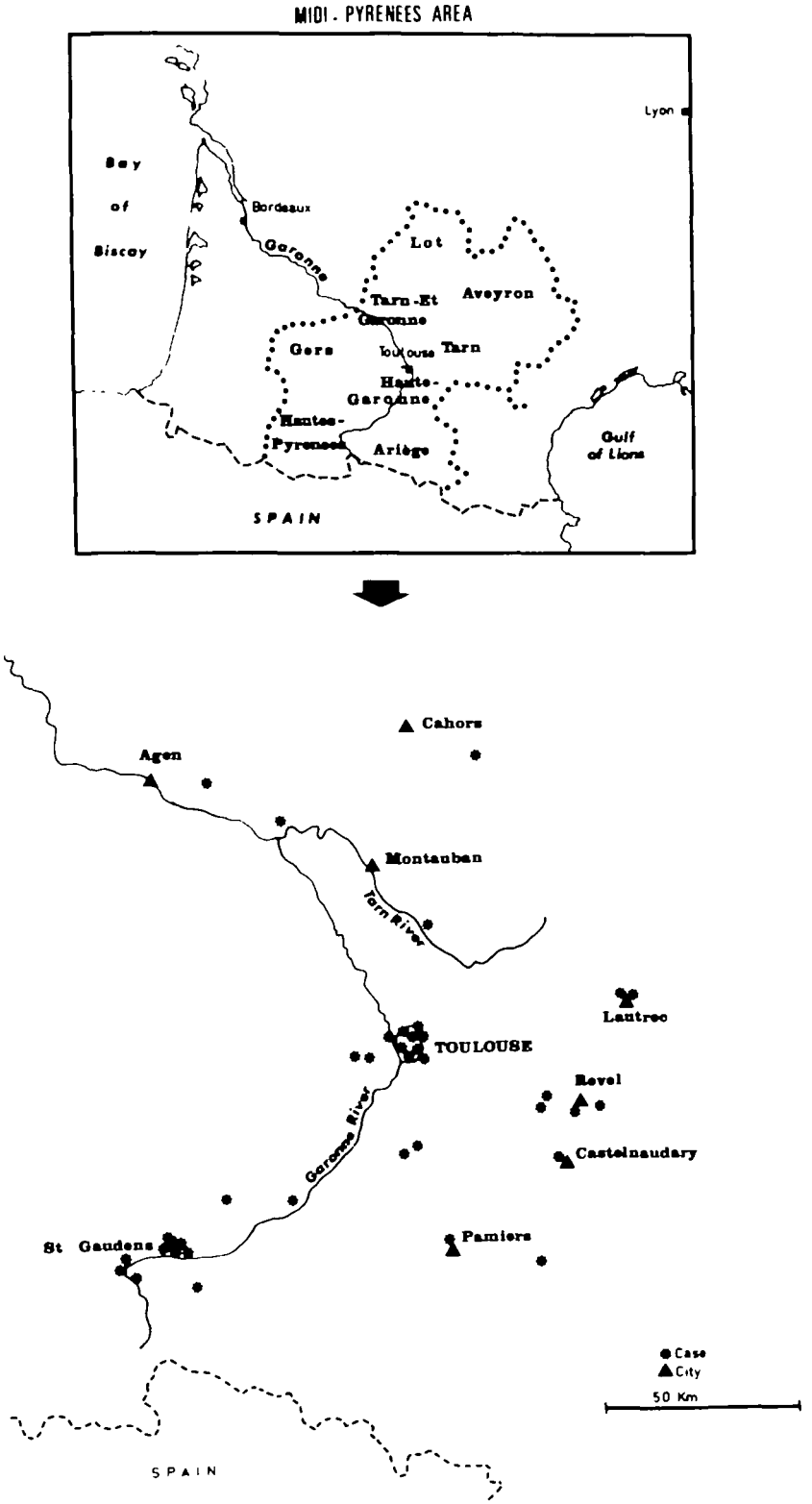

FIGURE 1. Map of southwest France indicating the distribution of 37 patients with visceral larva migrans within the Midi-Pyrenees region.

Clinical and laboratory findings

The frequency of signs and symptoms for the 37 patients with visceral larva migrans is presented in table 1. Nineteen (51.4 per cent) of the patients had allergic manifestations including pruritis, rash, or urticaria which had persisted for at least three months. Typically, the weakness and allergic manifestations were present intermittently for more than one year, despite repeated symptomatic treatment with antihistamines and corticosteroids. Sixteen of the 37 patients with visceral larva migrans were also treated with fluoromebendazole (Fluvermal, Janssen-Lebrun Laboratories, France), as described elsewhere (17), with 10 patients showing clinical improvement within three months of therapy. Results of chest and abdominal radiographs in all instances were within normal limits, except for hepatomegaly in two patients.

Laboratory findings for the patients with visceral larva migrans and both control groups are shown in table 2. Significant differences were noted between the groups, with the cases having higher eosinophil counts, higher red blood cell sedimentation rates, and higher total and specific concentrations of serum IgE, but marginally lower serum IgM levels. No significant correlations (Pearson's r, $p < 0.05$) were noted between the length of time from the onset of clinical signs in the cases to the time of this study and eosinophil count, total and specific concentrations of serum IgE, or ELISA titer. There was, however, a trend for all these values to decrease with increasing time since onset of clinical signs.

TABLE 1

Clinical signs and symptoms in 37 patients with visceral larva migrans from the Midi-Pyrenees region of France, 1979–1983

Sign or symptom	No. reporting*	% reporting
Weakness	31	83.8
Pruritis	18	48.6
Rash or urticaria	14	37.8
Difficulty breathing	14	37.8
Abdominal pain	10	27.0
Dizziness	9	24.3
Cough	8	21.6
Loss of appetite	7	18.9
Weight loss (>5% of body weight)	7	18.9
Headache	6	16.2
Diarrhea	4	10.8
Enlarged liver	2	5.4
Vomiting	1	2.7
Malaise	1	2.7
Fever	1	2.7

* Many patients reported more than one sign or symptom.

Multivariate logistic analysis of the laboratory data for 37 patients with visceral larva migrans and 59 neighborhood controls for whom complete laboratory data were available demonstrated independent associations between visceral larva migrans and eosinophil counts >400 cells/mm^3 ($p < 0.0001$), total IgE >200 IU ($p = 0.003$), and specific IgE >0.1 Toulouse Units ($p = 0.03$). Variables entered but not included in the final logistic model were white blood cell count, alpha-2 macroglobulin, sedimentation rate, and IgM concentration. The predicted probability of eosinophil counts, total IgE, and specific IgE for visceral larva migrans is summarized in figure 2. The predicted probability for visceral larva migrans when eosinophil counts, total IgE, and specific IgE were increased was 96 per cent.

Multivariate logistic analysis was performed to determine if there were significant differences in laboratory findings between those patients with visceral larva migrans with allergic manifestations and those without (figure 3). Allergic signs were predicted to occur most often ($p = 0.92$) in young patients with eosinophil counts >400 cells/mm^3 and reciprocal $\log_2$ ELISA *T. canis* antibody titers of 4–7. Allergic manifestations were least likely to occur ($p = 0.03$) in older patients with eosinophil counts ≤400 cells/mm^3 and reciprocal $\log_2$ ELISA *T. canis* antibody titers ≥8.

Risk factor analysis

Univariate analysis revealed no significant differences between cases and either control group for the following demographic and personal characteristics: religion, years of education, marital status,

TABLE 2

Laboratory findings in 37 patients with visceral larva migrans and in their age- and sex-matched controls from the Midi-Pyrenees region of France, 1979–1983

Laboratory measure*	Cases (n = 23–37)	Controls		p(n) p(h)†
		Neighborhood (n = 47–60)	Hospital (n = 36–37)	
White blood cell count (mm³)				
Mean	7,562	7,567	7,728	p(n) = 0.80
Standard deviation	2,181	1,755	3,322	p(h) = 0.79
Range	4,100–13,700	4,200–13,100	4,000–17,000	
% elevated	16.2	10.0	22.2	
Eosinophils (mm³)				
Mean	1,444	162	211	p(n) = 0.01
Standard deviation	2,891	185	202	p(h) = 0.01
Range	0–17,400	0–790	0–715	
% elevated	73.0	13.3	13.9	
Sedimentation rate (mm/hour)				
Mean	28.1	15.0	ND‡	p(n) = 0.004
Standard deviation	27.7	14.8	ND	
Range	2–104	2–86	ND	
% elevated	29.6	11.1	ND	
Total IgE (IU) (units/ml)				
Geometric mean	851	42	ND	p(n) = 0.0001
95% CL§	42, 17,431	2, 949	ND	
Range	27–8,230	2–2,129	ND	
% elevated	81.1	15.3	ND	
Specific IgE (Toulouse Units)				
Geometric mean	1.41	0.12	0.12	p(n) = 0.0003
95% CL§	0.001, 1,419	0.05, 0.31	0.02, 0.66	p(h) = 0.0002
Range	0.1–540,000	0.1–1.60	0.1–20	
% elevated	67.6	13.3	2.7	
Alpha-2 macroglobulin (%)				
Mean	2.2	1.6	ND	p(n) = 0.16
Standard deviation	2.1	1.8	ND	
Range	0.06–9.7	0.7–10.7	ND	
% elevated	32.0	4.1	ND	
IgG (mg/dl)				
Geometric mean	1,008	1,066	ND	p(n) = 0.81
95% CL§	349, 2,909	764, 1,488	ND	
Range	112–1,700	67–1,460	ND	
% elevated	13.0	0	ND	
IgA (mg/dl)				
Geometric mean	224	196	ND	p(n) = 0.13
95% CL§	115, 438	96, 401	ND	
Range	122–483	77–375	ND	
% elevated	13.0	12.8	ND	
IgM (mg/dl)				
Geometric mean	95	127	ND	p(n) = 0.06
95% CL§	34, 265	50, 326	ND	
Range	35–223	53–601	ND	
% elevated	16.7	36.2	ND	

* Cutoff for elevated level based on white blood cell count >10,000/mm³; eosinophils >400/mm³; sedimentation rate >30 mm/hour; total IgE >200 IU; specific IgE >0.1 Toulouse Units; alpha-2 macroglobulin >2.0%; IgG >1,500 mg/dl; IgA >300 mg/dl; IgM >160 mg/dl.

†p(n), p value based on paired t test of the mean value for cases and neighborhood controls. If a case had two controls, the average value of the two controls was used for that case. p(h), p value based on paired t test of the mean value for cases and hospital controls.

‡ ND, not determined.

§ 95 per cent confidence limits around the mean.

number of children, household size, type of home (farm vs. other), number of rooms or bathrooms in the home, type of waste disposal, source of water, travel outside the city, country, or continent, and smoking history. When cases were compared with hospital controls, however, the cases were more likely to live in a rural area. The odds ratio for persons living in a town or city of <500 persons (13 (35.1 per cent) cases and five (13.5 per cent) hospital controls) compared with persons living in a town or city of >2,500 persons was 3.6 (95 per cent CL 1.5, 31.8).

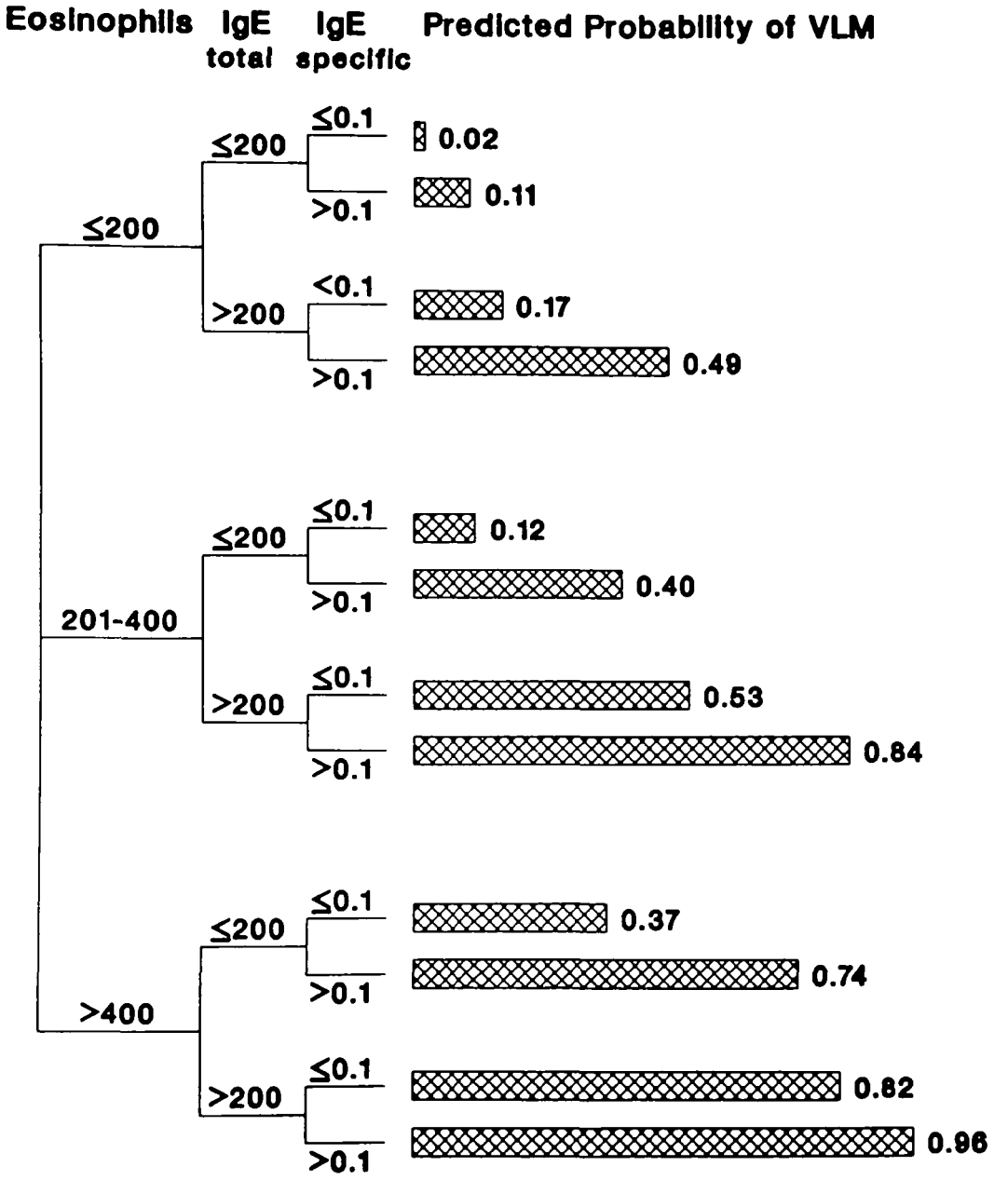

FIGURE 2. Multivariate logistic analysis of the predicted probability of three laboratory tests for visceral larva migrans (VLM). The model used data from 37 patients with visceral larva migrans and 59 age- and sex-matched neighborhood controls for whom complete laboratory data were available. The units of measurement for the laboratory tests were eosinophils (cells/mm^3), total IgE (IU), and specific IgE (Toulouse Units). Model specification: $R = 0.68$, $\chi^2_3 = 67.99$, $p < 0.001$.

Thirty-six cases for whom information on potential exposures was available were compared with each control group separately to evaluate the risk of visceral larva migrans associated with daily residential or occupational exposure to the following animals: pet or stray dogs and cats, pet birds, wildlife, sheep, pigs, poultry, rabbits, cattle,

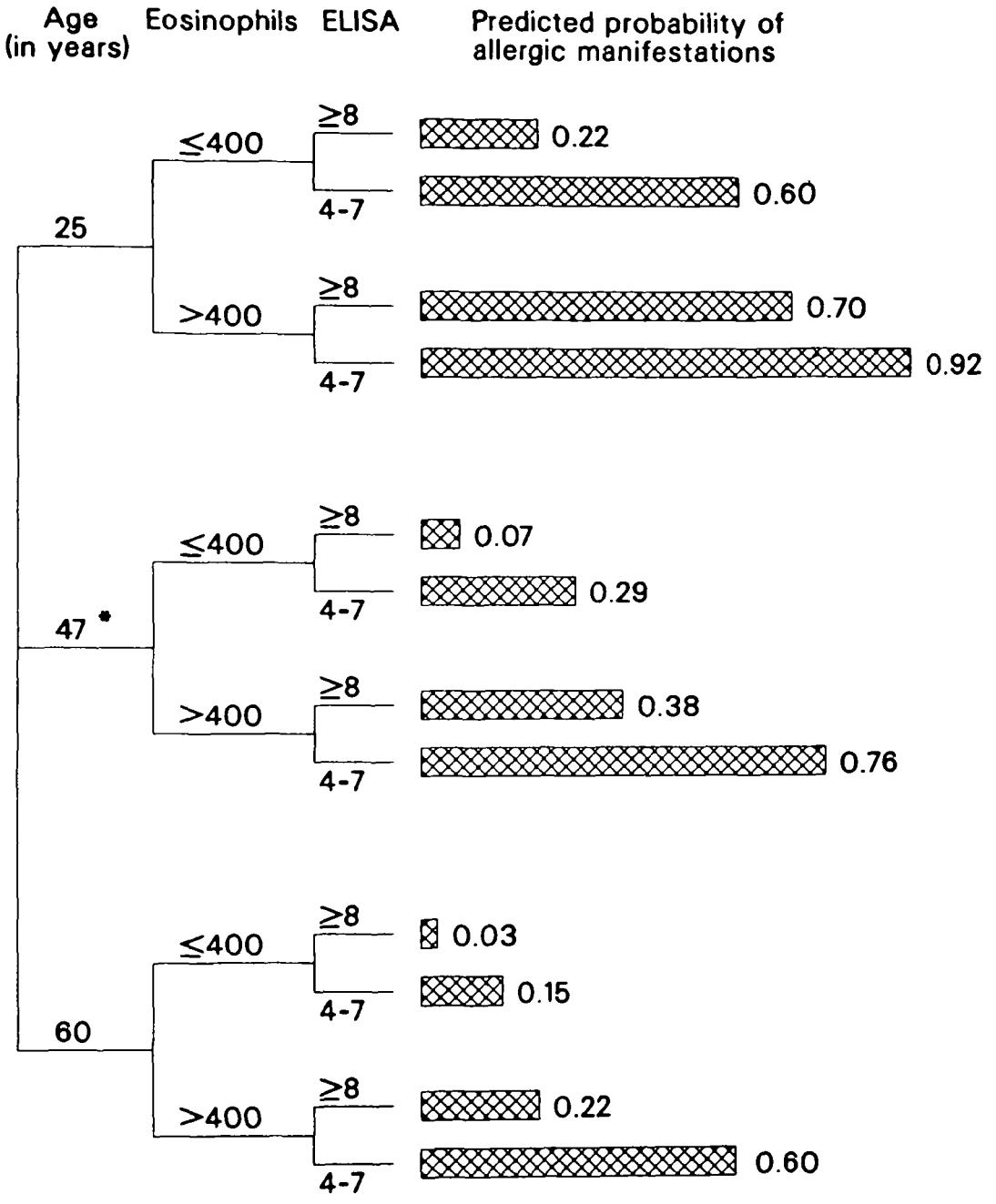

FIGURE 3. Multivariate logistic analysis of the predicted probability of the patient's age (median age 47 years), the *T. canis* ELISA (reciprocal $\log_2$ titer), and eosinophil count (cells/mm^3) for allergic manifestations (e.g., pruritis, rash, and urticaria) in 37 patients with visceral larva migrans. Model specification: $R = 0.30$, $\chi^2_7 = 10.58$, $p = 0.01$. Variables entered but not included in the final model were total IgE and specific IgE serum concentrations, white blood cell count, sex, and months since disease onset.

horses, and goats. Questions were also asked concerning whether dogs, cats, or wildlife frequently defecated in the garden. None of these animal exposures were found to be associated with a significantly increased risk of visceral larva migrans when compared with neighborhood controls. There was a decreased risk associated with

pig contact, however (OR = 0.1, 95 per cent CL 0.02, 0.6). Only five (13.9 per cent) of the cases had daily contact with pigs in contrast to 19 (31.7 per cent) of the neighborhood controls. When cases were compared with hospital controls for exposure to pigs, however, the odds ratio was 5.0 (95 per cent CL 0.4, 15.1).

When cases were compared with hospital controls, there was an increased risk of visceral larva migrans associated with daily contact with poultry (OR = 3.3, 95 per cent CL 0.9, 15.1) and owning two or more pet dogs (OR = 2.6, 95 per cent CL 0.9, 9.3), although both of these exposures were of borderline statistical significance (p = 0.06).

Diet-related risk factors were analyzed separately for an association with visceral larva migrans. These included the frequency of consumption and source of meat, fish, poultry, eggs, unpasteurized milk and cheese, and dandelions. The extent to which meat was cooked was assessed as was the presence of a vegetable garden at home and the type of fertilizer used. A question was asked concerning the frequency of hunting by the subject and other household members. The only significant finding was an increased risk of visceral larva migrans associated with hunting (OR = 5.5, 95 per cent CL 1.1, 71.9) when cases were compared with hospital controls. Thirteen (36.1 per cent) cases reported living in a household with a hunter or being a hunter compared with only five (13.5 per cent) hospital controls. The risk associated with hunting when cases were compared with their neighborhood controls was also elevated but was not statistically significant (OR = 1.8, 95 per cent CL 0.06, 5.0). The association between hunting and visceral larva migrans was stronger for males than for females in both case-control analyses (data not shown).

Conditional logistic regression analysis was used to assess simultaneously the independence and strength of several demographic factors and animal exposures on the risk of visceral larva migrans. The logistic model using the hospital control group (table 3) contained two significant variables, namely living in a town with <500 persons (OR = 5.7) and hunting (OR = 9.0). Also included was contact with pigs (OR = 11.7, p = 0.06).

Because those persons who hunted or who lived in a household with a hunter were frequently noted by the interviewer to keep several hunting dogs at home, we attempted to define further the relation between hunting, the presence of multiple dogs in the household, and the risk of visceral larva migrans. The risk of visceral

TABLE 3

Conditional logistic regression analysis for 36 patients† with visceral larva migrans and their 36 age- and sex-matched hospital controls from the Midi-Pyrenees region of France, 1979–1983*

Risk factor‡	Odds ratio	Two-tailed probability	Estimated 95% confidence limits	Discordant pairs
Hunter or hunting household	9.0	0.02	1.36, 59.6	11/2
Population <500	5.7	0.04	1.07, 30.4	11/3
Contact with pigs	11.7	0.06	0.90, 152.8	5/1

* Statistics for best fit model: 49.91 = −2 log-likelihood for the model containing no variables; 33.99 = −2 log-likelihood for the final model containing the above variables; 15.92 = χ^2 difference with 3 df, p = 0.001; 0.45 = correlation coefficient.

† Exposure variables were missing for one case.

‡ Risk factors entered but not included in the final model were contact with goats, sheep, poultry, cattle, rabbits, pet dogs, pet cats, pet birds; animals (dog, cat, or other) that defecate in garden; stray dogs or cats in the area; type of water system; type of waste removal; having at least one bathroom in the house; buying or picking dandelions; frequency of meat, poultry, and fish consumption.

larva migrans among hunters and nonhunters was found to be greater if they owned two or more dogs than if they owned one or no dogs (OR = 9.6 vs. 4.5 and OR = 2.1 vs. 1.0, respectively) (table 4).

Serologic studies

Sodium dodecyl sulfate-polyacrylamide gel electrophoresis and the Western blot procedures revealed marked similarities in the banding pattern of antigen reactivity for sera from two patients with visceral larva migrans in the United States and from six patients from France, and from monkeys experimentally infected with *T. canis* or *A. suum* (figure 4). In contrast was the distinctly different banding pattern observed with sera from patients infected with other helminth parasites.

DISCUSSION

In 1982, Magnaval et al. (5) reported the occurrence of a visceral larva migrans syndrome in 48 adults from the Midi-Pyrenees region of France. The diagnosis of visceral larva migrans was based on clinical manifestations, laboratory findings, and an elevated antibody titer against soluble antigens derived from the uterus of gravid *A. suum* worms. In this report, we described an additional 37 cases with similar characteristics. Visceral larva migrans of adults in this region today continues to be diagnosed at a frequency of about three new cases per month. The pattern of occurrence suggests that visceral larva migrans is an endemic disease in the Midi-Pyrenees region. Whether it represents a new disease or a long-established problem that is only now being recognized because of advances in serodiagnostic methods is not known. Serologic surveys using blood samples collected prior to 1980 may resolve this question.

That serum antibodies to *T. canis* have previously been demonstrated in 4.8 per cent of 166 urban blood donors and 14.5 per cent of 89 rural blood donors in the Midi-Pyrenees region indicates widespread zoonotic infection with this parasite (18). This compares with a *T. canis* seroprevalence of approximately 2 to 7 per cent in adults and 3 to 23 per cent in children aged one to 11 years in the United States (19). In the United States, seroprevalence rates tend to be higher in blacks than in whites, higher in rural than in urban areas, and to increase with decreasing income and education.

Visceral larva migrans and ocular larva migrans are two distinct clinical syndromes which result from zoonotic infection with *T. canis*. Both visceral larva migrans and ocular larva migrans typically occur in children, but rarely together. There are infrequent reports of ocular larva migrans in

TABLE 4

Conditional logistic regression analysis for 36 patients† with visceral larva migrans and their 36 age- and sex-matched hospital controls from the Midi-Pyrenees region of France, 1979–1983*

Risk factor‡	Odds ratio	Estimated 95% confidence limits	No. of cases	No. of controls
Hunt/2+ dogs	9.6	5.2, 17.5	8	2
Hunt/0–1 dog	4.5	2.5, 8.3	5	2
No hunting/2+ dogs	2.1	1.2, 3.9	8	5
No hunting/0–1 dog	1.0		15	27

* Statistics for best fit model: 49.91 = −2 log-likelihood for the model containing no variables; 41.06 = −2 log-likelihood for the final model containing the above variables; 8.85 = χ^2 difference with 1 df, $p = 0.003$; 0.37 = correlation coefficient.

† Exposure variables were missing for one case.

‡ Risk factors entered but not included in the final model were contact with poultry, pigs, rabbits; hunt and/or eat game; own two or more dogs; population size.

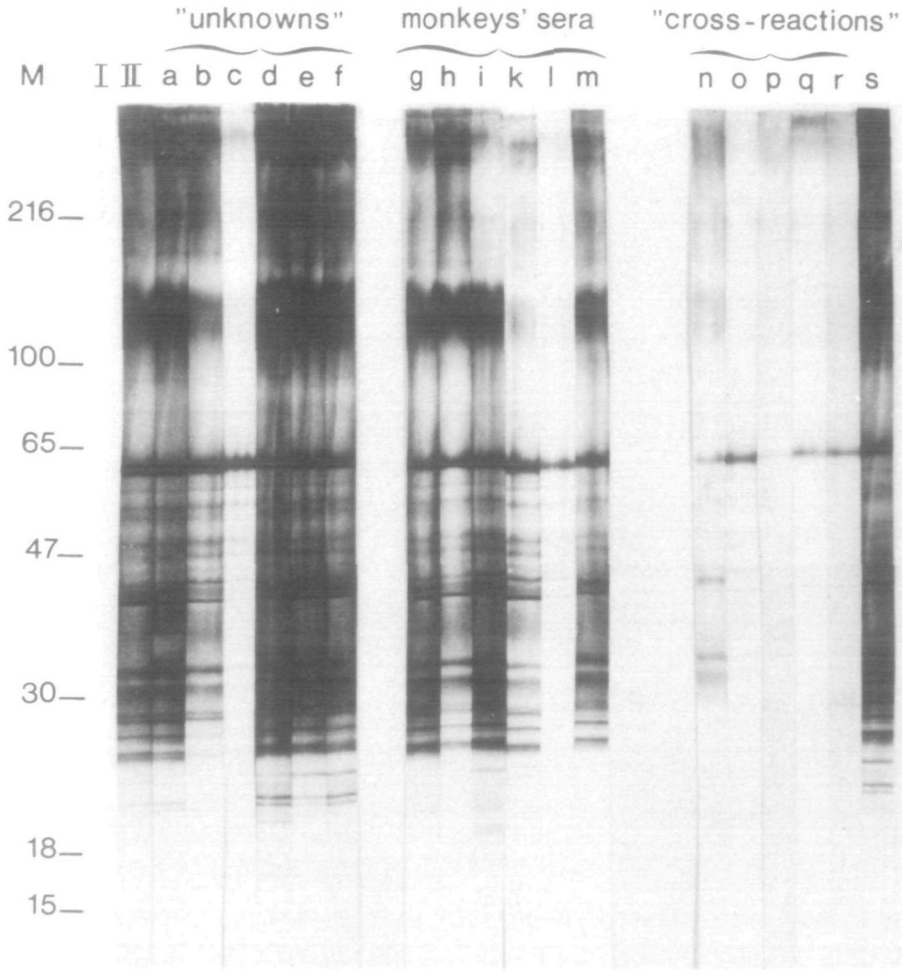

FIGURE 4. Western blot method of testing sera from six French patients with visceral larva migrans (a–f), from monkeys experimentally infected with *T. canis* (g, h, i, k) or *A. suum* (l, m), and from persons infected with another helminth parasite: *S. mansoni* (n), *S. stercoralis* (o, p), or *W. bancrofti* (q, r). Also included are a negative control serum from a healthy child (I) and sera from two children (positive controls) (II, s) in the United States who had visceral larva migrans due to *T. canis*. The test antigen was 0.3 μg of total protein of *T. canis* in vitro derived from excretory-secretory products. Column M indicates the protein standards in kilodaltons.

young adults (20). Risk factors for visceral larva migrans and ocular larva migrans in children include geophagia and the presence of puppies in the household (1). In contrast, visceral larva migrans in the Midi-Pyrenees region of France is a disease of adults, and pica and exposure to puppies are not recognized risk factors. Also, ocular larva migrans was not recognized in any of the 37 French patients with visceral larva migrans. This raises the question of whether *T. canis* is the etiologic agent of visceral larva migrans in French adults. Our study provides significant clinical, epidemiologic, and serologic evidence to implicate *T. canis*.

The allergic manifestations including eosinophilia and respiratory distress associated with toxocariasis are products of an immune-mediated inflammatory response to larvae migrating in tissues and of the formation of multiple eosinophilic granulomas, many of which contain entrapped larvae. A definitive diagnosis of toxoca-

riasis is based on demonstration of larvae in granulomas. Although histopathologic studies have not been performed on French patients with visceral larva migrans, the frequent occurrence of pruritis, rash, urticaria, respiratory problems, hepatomegaly, cough, eosinophilia, and elevated IgE levels is consistent with an underlying parasite-induced allergic mechanism. In this regard, it should be noted that for French patients with visceral larva migrans with high specific IgG ELISA antibody titers to *T. canis* and eosinophil counts >400 cells/mm^3, the predicted probability of allergic manifestations was only 38 per cent. In contrast, for patients with lower IgG ELISA antibody titers to *T. canis* and eosinophil counts >400 cells/mm^3, the predicted probability of allergic signs was 76 per cent. In addition, allergic manifestations were more likely to occur in younger patients. One explanation for these observations is that *Toxocara*-specific IgG antibodies block IgE-mediated immune responses. For example, patients with chronic filariasis have serum IgG which blocks histamine release from sensitized basophils when they are exposed to parasite antigen (21).

An association of dog exposure and hunting with visceral larva migrans was demonstrated when cases were compared with their hospital controls. Ownership of two or more dogs increased the risk of visceral larva migrans in both hunting households and in households in which no one hunted. Membership in a hunting household with one or no dogs present also was associated with an increased risk of visceral larva migrans when compared with nonhunting households with one or no dogs. These two findings are indirect evidence for zoonotic transmission of *T. canis* because the more dogs present in a household, the greater the opportunity for contamination of the environment with infective eggs of *T. canis*. Also, very few of the hunting dogs we observed in France received routine veterinary care including treatment for intestinal parasitism, and they were usually housed outdoors. In contrast, most of the pet dogs were well cared for and kept primarily indoors. In a preliminary study (unpublished data), we found *T. canis* eggs in seven (24.1 per cent) of 29 soil samples collected from the yards and gardens of cases and in five (10.2 per cent) of 49 soil samples from similar sites around the homes of the neighborhood controls. These rates of contamination are similar to those reported in backyards and public parks in the United States (22, 23). Given these findings, one would expect a greater number of reports of visceral larva migrans in children in France, especially those with geophagia. Perhaps visceral larva migrans in children is common in France, but the referral pattern by pediatricians to the central laboratories is such that children with eosinophilia are not routinely tested for antibodies to *T. canis*. Also, children were not observed to interact closely with hunting dogs, which were generally not considered as family pets.

The serologic results suggest that *Toxocara* sp. is the cause of visceral larva migrans in French adults. Although the ELISA has a specificity of greater than 90 per cent for the diagnosis of visceral larva migrans and ocular larva migrans (9), the validity of the immunoelectrophoresis test using antigens derived from *A. suum* has not been thoroughly evaluated. Preliminary studies, however, indicate that the specificity of the immunoelectrophoresis test for toxocariasis is equal to that of the ELISA, but its sensitivity is lower (5, 24). The Western blot results demonstrated that sera from French patients with visceral larva migrans, sera from patients in the United States with visceral larva migrans thought to be caused by *T. canis*, and sera from monkeys with visceral larva migrans experimentally induced by *T. canis* or *A. suum* recognized a similar number and array of antigens derived from *T. canis* larvae in vitro, whereas sera from patients infected with other helminth parasites did not. This suggests that either *T. canis* or a closely related parasite such as *Toxocara cati* which shares antigenic epitopes with

T. canis is the cause of visceral larva migrans in French adults. *A. suum* is a less likely cause of French visceral larva migrans, since the ELISA is capable of distinguishing between persons infected with *T. canis* and those infected with *A. suum* (25).

A number of methodological issues deserve discussion. The cases in this study were selected primarily because they presented with some combination of rash, weakness, eosinophilia, and elevated serum IgE levels. They are probably not representative of all patients with visceral larva migrans, and they do not reflect the full spectrum of possible responses to *T. canis* infection. Also, the referral pattern of patients in the Midi-Pyrenees region to the Central Hospital of Toulouse-Purpan where there is a nationally recognized interest in this disease may explain the apparent excess of cases in adults from the Midi-Pyrenees. In 1981, however, positive serologic tests for patients with suspected larva migrans were also reported from laboratories in Grenoble (17.3 per cent of 161 sera tested), Marseilles (6.5 per cent of 92), and Paris (7.1 per cent of 85) (26).

There is an opportunity for interviewer bias in any case-control study, especially when the interviewer is one of the investigators who is not blinded as to the case or control status of the subjects. For this reason, the questionnaire was pretested and standardized to minimize subjective interpretations of the responses. That the interviewer in this study (J.-F. M.) previously reported that visceral larva migrans in French adults was associated with consumption of raw dandelions (5) and that no association of visceral larva migrans with dandelions was found in the present study argue against the occurrence of interviewer bias. In addition, other than the association of consumption of dandelions with visceral larva migrans, no specific hypothesis had been formulated prior to the study that might have biased the interviewer.

Both prevalent and incident cases were interviewed. The period of time between onset of clinical signs and the interview ranged from 17 to 76 months, and the exposures of interest were those that had occurred in the year prior to onset of visceral larva migrans. To minimize the potential for recall bias, we used the same time period of from 17 to 76 months as the reference for the matched controls. Despite this precaution, cases might still be better able to recall events associated with onset of their illness than might healthy controls (27). In addition, the problems posed in recalling events from the distant past may have produced inaccurate responses in both groups and may have masked weaker associations that were present. The same consideration might apply in attempts to correlate hematologic and serologic values with case and control status using blood samples collected so long after the onset of visceral larva migrans.

A comparison of the findings of the separate analyses of the data, one using hospital controls and the other using neighborhood controls, is indicative of overmatching in the neighborhood controls. For example, the strong association described previously for hunting and owning two or more dogs was noted when visceral larva migrans cases were compared with hospital controls, but not with neighborhood controls. A puzzling discrepancy that cannot be explained by overmatching, however, is the positive association of exposure to pigs with visceral larva migrans (OR = 5.0, 95 per cent CL 0.4, 15.1) when cases were compared with hospital controls, but the negative association with visceral larva migrans (OR = 0.1, 95 per cent CL 0.2, 0.6) when cases were compared with neighborhood controls. These seemingly disparate findings may result from the small number of cases ($n = 5$), neighborhood controls ($n = 19$), and hospital controls ($n = 1$) that reported daily exposure to pigs. These findings, however, should be further investigated because *T. canis* from dogs is capable of infecting swine (28) and because human *Toxocara* infection may be acquired by ingesting larvae in the liver or muscles of paratenic hosts (29).

Future studies of visceral larva migrans in French adults should characterize the histopathologic response and identify the causative agent in biopsy specimens. Serologic surveys are needed to determine if children and spouses of patients with visceral larva migrans are at increased risk of *T. canis* infection. Dogs in households with visceral larva migrans should be examined for evidence of intestinal parasitism, and the environment should be systematically evaluated for contamination with *T. canis* eggs. Finally, the zoonotic potential of other common helminth parasites of companion and farm animals including *T. cati*, *Toxascaris leonina*, *Toxocara vitulorum*, *Parascaris equorum*, and *Ascaridia galli* should be assessed.

In summary, zoonotic *T. canis* infection is common in the Midi-Pyrenees region of France, where it produces an endemic pattern of visceral larva migrans in adults. The clinical signs are nonspecific and commonly include weakness, pruritis, rash, urticaria, and difficulty breathing. The clinical signs in association with eosinophilia and increased serum IgE point to an underlying allergic reaction. Serologic tests and epidemiologic findings suggest that the causative agent of visceral larva migrans in French adults is *T. canis*, although other closely related nematodes cannot be entirely discounted. Ultimately, however, definitive diagnosis depends on identification of the organism in biopsied tissues. Increased awareness of visceral larva migrans by physicians should lead to more complete case ascertainment and a better understanding of the epidemiology, pathogenesis, and treatment of visceral larva migrans in France.

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