ORIGINAL CONTRIBUTIONS

THE INCIDENCE AND CLINICAL CHARACTERISTICS OF THE IMMUNE PHASE EYE DISEASE IN TREATED CASES OF HUMAN LEPTOSPIROSIS

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ABSTRACT

BACKGROUND: Uveitis is increasingly being reported from south India following epidemics of leptospirosis. The incidence of eye involvement in treated patients has not been investigated properly in prospective studies. AIMS: To determine the incidence, clinical spectrum and risk factors for Leptospiral uveitis in antibiotic-treated patients. SETTINGS AND DESIGN: A prospective cohort study conducted among the patients treated for leptospirosis at Calicut Medical College between July and November 2002 and a seroprevalence study among sewage workers. MATERIALS AND METHODS: As many as 360 patients admitted with suspected leptospirosis were studied by clinical examination, baseline ophthalmic survey, laboratory investigations and Leptospira serology (Microagglutination test – MAT; and IgM and IgG using ELISA) during the epidemic. Of the 282 seropositive and antibiotic-treated cases, 174 patients who completed 30 months of regular follow-up were analyzed. A cross-sectional serosurveillance also was performed among 50 sewage workers to determine the baseline MAT titer. STATISTICAL ANALYSIS: Univariate analysis and logistic regression. RESULTS: Thirty-two patients (18.4%) developed the eye disease during follow-up. The mean age was 43.9 years and the sex ratio was equal. Twenty-one patients (65.6%) had anterior uveitis. Only six patients (18.8%) had visual symptoms. Median duration for developing anterior uveitis was 4 weeks. Recurrent uveitis was not seen following treatment. None had vision-threatening eye disease. Clinical and laboratory abnormalities during the acute phase did not pose risk for development of the eye disease later. Forty-six sewage workers (92%) showed a MAT titer of 1/25. CONCLUSIONS: Uveitis is common following acute leptospirosis. Antibiotic-treated patients during the acute phase of illness developed only mild uveitis.

Key words: Leptospirosis, microscopic agglutination test, uveitis

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Leptospirosis is presumed to be the most widespread zoonosis in the world. The disease is seasonal, with peak incidence in summer or autumn in the temperate regions and during rainy season in the regions with a warm climate.[1] Infection to human beings is usually accidental and occurs when the individual comes into contact with water contaminated by urine of the carrier animals, like cattle, canines and rodents. Manifestations of leptospirosis range from mild nonspecific febrile illness (85-90%) to severe multi-organ disease called Weil's disease. The mortality rate in severe forms varies from 5-40%.[2]

The incidence of leptospirosis has reportedly been increasing in southern India.[3-6] In Kerala, the epidemics have been reported to peak in the period of 7-10 days following the cessation of heavy rainfall during the monsoon season.[7] More than one such epidemic usually occurs during a season.[6,7] Many of the affected patients admitted to tertiary care hospitals suffer from the severe form of leptospirosis with multi-organ dysfunction (Weil's disease).[6]

Uveitis is an important late complication of leptospirosis and may present as anterior or posterior uveitis or as panuveitis.[8-14] The other manifestations described[9-15] are hypopyon, rapid maturation of cataract, absorption of cataract, glaucoma, vitreous inflammatory reaction, optic neuritis, retinal vasculitis, retinal hemorrhage, retinal detachment and neuroretinitis. Leptospirosis is a common cause of uveitis in south India and accounts for a significant proportion of cases, which were previously labeled as idiopathic uveitis.[8]

There are no large-scale studies investigating the incidence and clinical pattern of the immune phase eye disease following acute leptospirosis. This prospective study was conducted to investigate the incidence and the clinical characteristics of immune phase eye disease and also to find out whether there is any relationship of the clinical and laboratory parameters in the acute phase with future development of eye disease, in a cohort of patients with human leptospirosis treated during the period of July to November 2002 at Calicut Medical College. A cross-sectional serological survey also was performed among the sewage workers of Calicut city to determine the immunological status of the population to find out the approximate diagnostic titer of microscopic agglutination test (MAT). The study was approved by the ethical committee of Calicut Medical College, and informed consent was taken from all the patients and sewage workers.

MATERIALS AND METHODS

The patients (12-75 years of age) admitted to the general medicine wards with at least three of the following clinical features were suspected to have leptospirosis: 1) fever, 2) muscle pain or tenderness, 3) conjunctival suffusion or hemorrhage and 4) jaundice. Their clinical features and laboratory parameters were recorded with special attention to detect the presence or absence of major organ dysfunction. All the patients were examined on the second or third day of hospitalization to detect the presence or absence of eye diseases like cataract and uveitis at the Department of Ophthalmology. Visual acuity, anterior chamber examination by naked eye and using slit lamp, intraocular pressure assessment using Schiotz tonometer and direct and indirect ophthalmoscopy were done in all cases at that

time and during the subsequent follow-up visits. Benzylpenicillin 1.5 million units six hourly by intravenous route or doxycyclin 100 mg orally twice daily (to six patients who were found to have penicillin allergy) was administered to all patients for 7 days.

Leptospirosis was confirmed by leptospiral serology (serum samples were collected between the 7th and 10th day from the onset of the febrile illness) using enzyme-linked immunosorbent assay (ELISA) for IgM and IgG antileptospiral antibodies (kits supplied by Immuno Pharmacology Research Diagnostics, Italy) and also by microscopic agglutination test (MAT) at the Defense Research and Development Establishment (DR and DE), Govt. of India, Gwalior. MAT was performed by mixing serial dilutions of the sera (starting with a dilution of 1/25) with *Leptospira* serovars *L. australis, L. autumnalis, L. bataviae, L. canicola, L. celledoni, L. cynopteri, L. djasiman, L. grippotyphosa, L. hardjo, L. hebdomadis, L. icterohaemorrhagiae, L. copenhageni, L. Pomona, L. Sarmin, L. shermani* and *L. tarassovi* (pathogenic serovars); and *L. andamana, L. patoc* and *L. ranarum* (nonpathogenic serovars).

On 25th August, a cross-sectional serosurveillance was conducted among 50 male corporation sewage workers (sewage workers are reported to be at high risk for the development of leptospiral infection) employed in Calicut city using the same MAT battery. Forty-six of these workers had a positive MAT titer of 1/25, 3 of them had titer of 1/50 (2 of them had reported having febrile illness with muscle pains in the previous monsoon season) and 1 had a titer of 1/100. Therefore, a MAT titer of 1/100 was taken as significant titer for the serodiagnosis of acute leptospirosis, because the majority (92%) among the high-risk group had low baseline MAT titers.

All the confirmed cases of leptospirosis were followed up in the ophthalmology clinic once weekly in the first month, biweekly for the next 2 months, once in a month for the next 3 months; and then once in two months for the next 6 months and once in 3 months thereafter. Those patients who did not turn up for regular follow-up were contacted by telephone calls or letters to ensure their attendance in the ophthalmology clinic on the next week of their default. The patients were also educated about the symptoms of leptospiral eye disease and were instructed to attend the clinic immediately on developing any symptoms like ocular pain, redness, photophobia, blurring of vision and floaters in between the follow-up appointments. The patients showing evidence of anterior uveitis on follow-up were treated with fluoromethalone 0.1% w/v and homatropine 2% w/v eye drops for local instillation into the eyes. These cases were followed up weekly until the uveitis subsided, and the remaining follow-up was done on their cases as described for the nondiseased.

Statistical analysis

In the MAT-positive cases, 174 patients who had completed the follow-up between July 2002 and March 2005, the various clinical and laboratory parameters in the acute phase of leptospirosis were tested for risk factors for future development of eye disease using Chi-squire test and the results were expressed as odds ratios. Binomial logistic regression also was done with the immune phase eye disease as the dependent variable. The independent variables tested were the presence of the various parameters for organ dysfunction during the acute phase of illness. Backward stepwise regression (likelihood ratio) was used to arrive at the final model.

RESULTS

Of the 360 patients tested by MAT, 282 patients showed a titer of 1/100 or more (end-point titration of MAT was not done in the majority of cases because of the technical difficulty of performing this cumbersome serological test) and were diagnosed to have leptospirosis. Of these 282 cases, ELISA test for IgM antileptospiral antibodies and IgG antibodies was positive in 255 cases (90.4%) and 26 cases (9.2%) respectively. There were 17 deaths, with a case fatality rate of 6.03%.

Of the 265 patients who were cured of acute leptospirosis, only 174 patients who completed the follow-up study for 30 months in the ophthalmology clinic were included in the final statistical analysis. Of these patients, 54% were men. Twenty-four patients showed immature cataract (10 had both eyes involved) and 5 patients showed mature cataract (4 of them also had immature cataract in the other eye) at the time of initial ophthalmic examination. Six patients had small areas of hemorrhage in the retina (all had severe thrombocytopenia with platelet counts <30,000/cu. mm), which resolved within 6 weeks. None had anterior uveitis at the time of initial ophthalmic survey.

Thirty-two patients (18.4%) developed the eye disease in the follow-up period [Table 1]. The mean age of patients was 43.9 years. Male patients numbered 16. Only 6 patients (18.8%) noticed visual symptoms. Twenty-one (65.6%) of those with the eye disease had evidence of anterior uveitis in the form of anterior chamber cells, fresh keratic precipitates and aqueous flare. Median duration of the appearance of anterior uveitis was 4 weeks (range 3-6 weeks). None of the patients developed vision-threatening eye disease. Clinical and laboratory abnormalities during the acute phase of illness did not have correlation to future development of eye disease in univariate analysis [Table 2]. None of these abnormalities showed statistical significance for future eye disease on logistic regression as well. (Six patients who developed mild asymptomatic anterior uveitis and 2 patients who showed disc hyperemia defaulted from follow-up and were not included in the final analysis).

The treatment of anterior uveitis was associated with full resolution of the disease in 1-2 weeks, and none of these patients showed evidence of recurrence of eye involvement in their

Table 1: Clinical presentations of the immune phase eye disease

Eye involvement	*Both eyes*	*Left eye*	*Right eye*
Anterior uveitis	17(53.1)	2(6.3)	2(6.3)
Retinal hemorrhage	1(3.1)	1(3.1)	1(3.1)
Branch retinal vein occlusion	None	None	1(3.1)
Panuveitis, optic neuritis and cataract formation/absorption	None	None	None

Figures in parentheses are in percentage

Table 2: The relationship of the clinical and laboratory parameters in the acute phase of leptospirosis with future development of eye disease

Clinical parameter	*% of cases*	*OR (95% CI)*	*P*
Renal failure (BU>60 mg/dl and or S. Creatinine>2 mg/dl	56.3	1.48 (0.59-3.7)	0.4
Muscle involvement	80	1.55 (0.5-5.8)	0.44
Liver enlargement	58	1.7 (0.7-4.4)	0.21
Lung involvement	8.6	0.00 (0.0-11.7)	0.43
CNS involvement	9.6	? (0.13-infinity)	?
Thrombocytopenia	65.9	0.67 (0.25-1.84)	0.39
Diabetes mellitus	10.3	2.9 (0.7-11.7)	0.08
Anemia (Hb < 10 gm/dl)	19.2	1.1 (0.35-3.25)	0.16
S. bilirubin > 15 mg/dl	19.7	2.4 (0.79-7.15)	0.08

remaining follow-up period. Cases of posterior uveitis were not severe enough to mandate treatment, and they subsided spontaneously in 1-2 months. Panuveitis, hypopyon, glaucoma, vitreous inflammation, frank optic neuritis and cataract formation or absorption were not observed in any of the patients.

DISCUSSION

Delayed development of ocular disease after recovery from the acute phase of illness is a well-known complication of human leptospirosis.[8-15] Even though animal studies suggest immunologic mechanisms related to molecular mimicry between leptospiral proteins and ocular antigens for the pathogenesis of eye disease,[16,17] there is only limited evidence to suggest the same mechanism for the occurrence of ocular disease in human beings.[13]

It is not known whether the systemic antibiotic treatment during the acute phase of human leptospirosis has any protective role on long-term complications like uveitis. In a large series,[8] the majority of patients who were presented to the clinician with severe leptospiral uveitis did not receive appropriate antibiotics at the time of their probable primary infection. All the patients in our study received antibiotics during the acute phase of their illness.

A probable explanation for the milder eye disease in our series could have been related to referral bias because the cases reported by Rathinam *et al.*[8] were from the largest ophthalmic referral center in south India. However, the milder eye involvement in our study might be related to the earlier clearance of leptospiremia due to antibiotic treatment, but this hypothesis can't be proved without a double-blind controlled trial, which would be unethical to be performed in patients with proven acute leptospirosis.

Recurrent uveitis is reported to be common in leptospirosis.[8] None of the cases in our series had recurrence of eye disease after the initial involvement and its successful treatment. Recurrent uveitis in leptospirosis is more common with panuveitis cases,[8,10] which were not seen in this study. Rapid maturation/absorption of cataract was not observed in any of the patients as reported by others.[15] This might be due to the smaller sample size of the patients with uveitis in our study. Even though six patients had mild retinal hemorrhage during the acute phase of their illness, all had severe thrombocytopenia (<30,000/cu. mm), which would explain the bleeding into the retina. Optic disc edema, retinal vasculitis and hard exudates were not observed during the acute phase of their illness in any of the patients in our series, as were observed by Martins *et al*.[18]

Risk factors for mortality in patients with severe leptospirosis were related to severe organ involvement and laboratory abnormalities (hematological and biochemical) in many studies.[6,19-22] These observations prompted us to analyze whether there was any such relationship of organ involvement and abnormalities in the laboratory parameters during the acute phase of leptospirosis with future development of eye disease. But none of these abnormalities during the acute phase of illness showed any statistically significant relationship with future development of eye disease, either in univariate analysis or logistic regression.

The sex ratio was equal in our group of patients with the eye disease, even though there was a slight male preponderance in the group analyzed. Male preponderance of leptospiral eye disease in an earlier large series[8] may be related to the much higher incidence of leptospirosis in males due to occupational exposure.

Limitations of the study

1) Culture and isolation of *Leptospira* could have helped us to determine whether there had been any specific relationship of the infecting serovar with future development of uveitis.
2) End-stage titration of sera by MAT was not done in majority of the cases. End-stage MAT titers of the sera might have helped us to determine the dominant serovars in the region with reasonable specificity, though isolation of the species by culture would be ideal for the serovar identification.
3) MAT performed on paired sera showing fourfold rise in titer is the gold standard test for serodiagnosis of leptospirosis. Paired sera could not be tested in our study. But single serological titer of 1/100 gave reasonable sensitivity for diagnosis of acute leptospirosis in areas with low endemicity.[23] Moreover, the majority of the patients were IgM positive (new infections), and only a minority showed positive IgG (old infections), indicating a low endemicity of leptospirosis in the region.
4) Other causes of uveitis were not investigated in this study. None of the patients in this study had uveitis at the time of their acute leptospiral illness and hence we presume that uveitis resulted from leptospirosis. In spite of all these limitations, results of this large study might prompt future researchers to investigate further on this dreaded complication of human leptospirosis.

Strengths

This is the largest study ever done in the world and the first one from India to look into the incidence and clinical pattern of uveitis in treated cases of human leptospirosis.

CONCLUSIONS

Delayed development of eye disease is a common complication of human leptospirosis. Early detection of this complication by screening of patients and by patient reporting on development of the ocular symptoms might reduce the chance of the threat to eyesight because the clinician can initiate timely and appropriate treatment. The presence of organ involvement and abnormalities in the laboratory parameters during the acute phase of leptospirosis has no relationship with future development of the eye disease. The possibility of reduction of ocular disease in the immune phase, because of antibiotic treatment in the acute phase of leptospirosis, is to be studied further.

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