

Sex-related Different Efficacy of Chemotherapy on Human Strongyloidiasis in Okinawa, Japan

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Abstract

Sex-related different efficacy of anti-*Strongyloides* chemotherapy has been demonstrated in a prognostic study on 223 patients with uncomplicated strongyloidiasis. The efficacy of treatment with pyrinium pamoate and albendazole was found to be significantly low in males as compared to that in females. The cure rates after pyrinium pamoate treatment, when assessed by stool examination 1 year after treatment, were 34.6% in males and 59.6% in females. On the other hand, the efficacy of albendazole treatment was 60.8% in cure rate for males and 77.5% for females. The difference between males and females was more significant when efficacy was compared among the subjects without concurrent HTLV-1 infection; 41.4% versus 78.1% in pyrinium pamoate treatment and 63.5% versus 92.3% in albendazole treatment. These results suggested that the obstinacy in males might play a part in significantly high prevalence of strongyloidiasis among males in Okinawa.

Key words: strongyloidiasis; chemotherapy; pyrinium pamoate; albendazole; sex difference; HTLV-1.

Introduction

Human strongyloidiasis caused by *Strongyloides stercoralis* infection is an opportunistic parasitic disease. Okinawa Prefecture, Japan, has been known as the only area where *Strongyloides* infection is currently highly prevalent (Asato *et al.*, 1992), while other parasitic infections have been almost entirely eradicated in recent years. One of the current epidemiological features of the parasitic disease in this area is that the majority (more than 90%) of cases are in middle and upper age brackets over 40 years old. From the above fact, it seems that new infection from the environment rarely occurs among inhabit-

ants in present-day Okinawa (Sato, 1986; Sato *et al.*, 1990), so that the majority of recent cases might be a long-standing chronic infection. Another epidemiological feature is that the parasitic infection is significantly prevalent in males than in females (Sato, 1986). One of the possibility for the high prevalence in male subjects may be that males have had frequent opportunities for the infection in their life style. It is also possible to consider that males were more susceptible to the infection than females (Muller, 1992), as known in experimental infection models with *S. ratti* and rodent hosts (Katz, 1961, 1963; Dawkins *et al.*, 1980).

In the present study, the authors represented sex-related difference of therapeutic effect on strongyloidiasis patients in Okinawa.

Subjects and Methods

Subjects

A total of 223 (126 males and 97 females) patients with *Strongyloides* infection were studied.

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They were diagnosed by stool examination in a mass survey in Okinawa. The age of the subjects ranged from 39 to 86 years (mean=66.0±8.9). They were asymptomatic or mildly symptomatic.

Treatment

With pyrinium pamoate suspension (Poquil®; Warner Lambert, U.S.A.), 109 subjects (52 males and 57 females) were treated. The drug was administered at the dosage of 5 mg/kg of body weight daily for 3 consecutive days. The remaining 114 subjects (74 males and 40 females) were treated with albendazole (Zentel®; Taianjin Smithkline and French Laboratories Ltd., S.A., Puteaux, France). They received 2 courses of treatment (400 mg/day for 3 days) at an interval of 2 weeks.

The follow-up stool examinations for the both groups were performed on 2 weeks, 6 months and 1 year post treatment, and the final cure rate was determined by follow-up examination on 1 year after treatment.

Stool examination

Stool examination before and after treatment was performed by the agar-plate culture (Arakaki *et al.*, 1988) and formalin-ether concentration method. In the former method, a fecal mass of about 3 g was placed in the center of a primary agar plate for bacterial culture and incubated at 28°C for 3 days. The larvae which emerged from the fecal mass on the surface of agar plate were searched under a

microscope and recovered to identify morphologically *Strongyloides* larvae (Koga *et al.*, 1990). The stool examinations were repeated on fecal samples collected for 3 consecutive days.

Detection of antibodies to HTLV-1

The sera of the subjects were examined for anti-HTLV-1 antibodies using a kit of indirect agglutination test (SERODIA-HTLV®; Fujirebio Inc., Tokyo, Japan) (Ikeda *et al.*, 1984).

Statistics

Statistical difference was analyzed using the χ^2 (chi-square) test. A *P* value of more than 0.05 was considered to be not significant.

Results

The results of stool examination after treatment with pyrinium pamoate are shown in Fig. 1. The overall cure rate was 47.7% (52/109). The cure rate of males (34.6%) was significantly lower than that (59.6%) of females. Among the subjects, 48 (44%) were positive for anti-HTLV-1 serum antibody, showing that they have concurrent HTLV-1 infection. The difference was more significant when the cure rate was compared between male and female subjects who were negative for concurrent HTLV-1 infection; 41.4% for males and 78.1% for females. On the other hand, the cure rate of females was decreased significantly in the group with concurrent

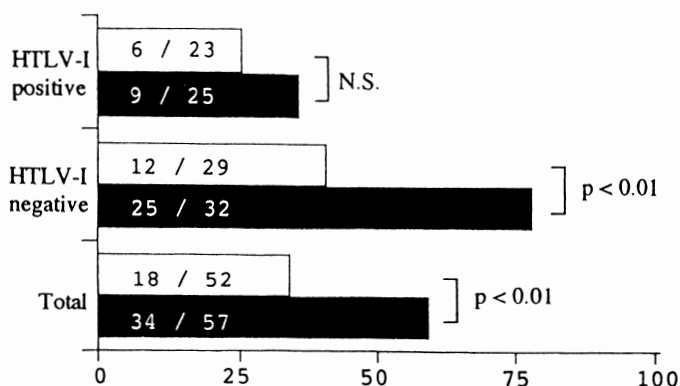


Fig. 1 Comparison of cure rate after pyrinium pamoate treatment between males (□) and females (■) with strongyloidiasis. Number inside bar: No. cured/No. treated.

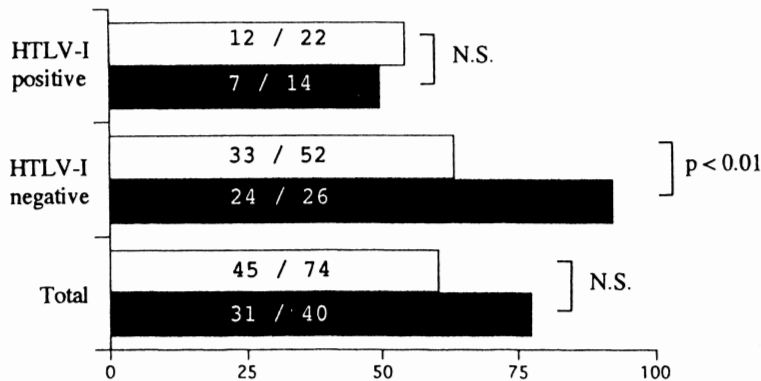


Fig. 2 Comparison of cure rate after albendazole treatment between males (□) and females (■) with strongyloidiasis. Number inside bar: No. cured/No. treated.

HTLV-1 infection, and it became to be not different from that of male patients.

Similar results after albendazole treatment are shown in Fig. 2, in which the overall cure rate of 66.7% was significantly higher than that with pyrinium pamoate. The therapeutic effect by the drug was also higher in females than in males, showing 77.5% and 60.8% respectively, although the difference was not statistically significant ($p < 0.1$). The difference between males and females became significant when the cure rates were compared among the subjects without concurrent HTLV-1 infection; 63.5% for males and 92.3% for females. The efficacy of albendazole treatment was also depressingly affected in female subjects by the concurrent HTLV-1 infection.

Discussion

It has been known that males were more susceptible than females to variety of parasitic infections and that gonad hormones may be one of the major regulators of the host susceptibility (Solomon, 1969). In the case of strongyloidiasis, it has also been demonstrated that males were more commonly infected with *Strongyloides* than females (Scaglia *et al.*, 1984; Soroczan, 1976; Walzer *et al.*, 1982). In the previous epidemiological studies in Okinawa, it has been also confirmed that males were three times more infected than females (Sato, 1986).

In their experimental model with *S. ratti* infection in mice, Dawkins *et al.* (1980) showed that male mice were ten times more susceptible than female mice when assessed by fecal larval excretion. On the other hand, in the case of *S. ratti* infection in rats, only small sex difference could be detected around the time of worm expulsion but not at the early stage of infection (Katz, 1961; 1963). For such a sex difference in mice, it has been suggested in the gonadectomy experiment that androgen but not oestrogen may be an important regulatory factor (Kiyota *et al.*, 1984) and hormonal-phagocytic cell interplay has been implicated as an important factor in the sex-related susceptibility (Abe *et al.*, 1985).

The study described here demonstrated that chemotherapy for strongyloidiasis with pyrinium pamoate and albendazole was more effective in female patients than in males; the cure rates were significantly low in male patients as compared to those of females. The efficacy in female patients was significantly reduced to the level of male patients, when female subjects have concurrent HTLV-1 infection. In Okinawa, it has been well known that more than half of strongyloidiasis patients have concurrent HTLV-1 infection (Nakada *et al.*, 1984; Sato and Shiroma, 1989; Fujita *et al.*, 1985). Recently, the authors have demonstrated that the patients with concurrent HTLV-1 infection showed reduced efficacy of chemotherapy with various anthelmintics (Takara *et al.*, 1992; Sato *et al.*, 1992;

Toma *et al.*, 1993). In contrast to the female subjects, concurrent HTLV-1 infection did not affect markedly on the therapeutic efficacy in male subjects. These results suggest that sex difference in the therapeutic efficacy may be mediated by the similar regulatory mechanism caused by concurrent HTLV-1 infection. The investigation concerning the relation between the sex-related therapeutic efficacy and the intensity of infection is underway in the following study.

The sex difference in therapeutic efficacy may also be participated to the sex predominance of strongyloidiasis in Okinawa, as has been suspected in patients with concurrent HTLV-1 infection (Sato *et al.*, 1993). Due to the significant resistance to the anthelmintics which have long been used for mass treatment of strongyloidiasis in Okinawa, male patients might be accumulated over a long period under the sanitary condition in which new infection from environment rarely occurs.

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