

## MINI-REVIEW: THE ULTRASONOGRAPHICAL AND SEROLOGICAL CHANGES AND THEIR IMPROVEMENT AFTER PRAZIQUANTEL TREATMENT IN *SCHISTOSOMA JAPONICUM* INFECTED PATIENTS IN LEYTE, PHILIPPINES

MANAMI TANAKA

Institute of Basic Medical Sciences, University of Tsukuba, Tsukuba, Ibaraki 305, Japan

*We have identified the specific ultrasonographical (US) changes in Schistosoma japonicum infected patients with the serological changes in general liver function markers. The US examination with the following haematological and biochemical serum analysis was performed on 102 patients in Schistosomiasis Hospital, Leyte, Philippines. The US liver images were classified into 4 patterns according to the development of periportal fibrosis and the patterns of echogenic bands. Among various haematological and biochemical serum parameters of liver damage. The serum levels of total bile acid (TBA) and procollagen-III-peptide (P-III-P) correlated well with the development of hepatic fibrosis and the portal hypertension. These patients were subsequently treated with praziquantel (3 x 20 mg/kg), and the improvement of the thickening of the portal vein wall and the intensity of the echogenic band formation was detected 6 months after treatment. The significant US changes could not be detected in the patients with severe hepatic fibrosis caused in the long term infection. The results revealed that the US examination with the serum TBA level would provide a sensitive tool to monitor the severity of the infection and also the improvement occurred shortly after praziquantel treatment.*

**Key words:** *Schistosoma japonicum* – praziquantel – ultrasound – total bile acid – procollagen-III-peptide

In schistosomiasis, the extent of the disease depends on the intensity of the adult worm burden and the duration of the infection (Butterworth, 1988). However, only few parameters are available for monitoring the disease in further detail for the field survey. We have recently reported the serological and ultrasonographical (US) parameters for monitoring the infection in experimental animals according to the development of hepatic fibrosis and portal hypertension (Tanaka et al., 1989; Ohmae et al., 1991a). Especially both the serum levels of the total bile acid (TBA) and procollagen-III-peptide (P-III-P), could be reliable parameters of the improvement of these damage after administration of praziquantel.

The US examination served as a useful diagnostic tool for hepatic fibrosis in *S. mansoni* infection (Homeida et al., 1988; Abdel-Wahab et al., 1989). The echogenic changes of the periportal fibrosis could be observed as tubular or round shadows, which could not be

detected in alcoholic liver diseases or hepatitis. This technique has been used in Japan for the screening of only the old *S. japonicum* cases, because no newly infected cases has not been reported since 1978 (Tanaka et al., 1988). The typical echogenic changes found in Japan are septal formation of high echogenic bands. These changes were much different from the changes reported in *S. mansoni* cases. We performed US examinations and haematological and biochemical serum analysis in the *S. japonicum* infected patients in Philippines, and compare results before and after treatment with praziquantel (PZQ).

The present study (Ohmae et al., 1991b, c) was performed from 1989 to 1990 in the Schistosomiasis Hospital, Leyte, Philippines. All the study patients monitored (total 102 patients) were more than 15 years old and residents of Northeast Leyte, which is characterized as a high endemic area of *S. japonicum* infection. However, malaria infection has never been reported in the study area (Tanaka et al., 1984). The staffs of this hospital and Schistosomiasis Research Center practiced stool examinations and COP test for the habi-

tants in this endemic area every year, and the diagnosis of the infection was based on the eggs in feces. Egg positive cases were subsequently treated with PZQ (3 x 20 mg/kg). The duration of the infection was estimated from the records of the annual stool or COP examination and their detailed history on signs and symptoms of schistosomiasis. The patients with hepatitis B infection and/or with the long history of alcohol drinking were excluded from the further investigation.

US equipment used in the present study was the ALOKA type SSD-20, Tokyo, Japan. The examination was performed by at least two doctors. The liver image was taken by subcostal, intracostal, and sagittal scans while the patients were lying on their back. The spleen image was examined by intracostal scans during their lying on the left side.

The US liver images in *S. japonicum* infection were classified into 4 types according to the patterns of the echogenic bands, and to the grade of thickening of the portal vein wall (Ohmae et al., 1991b). Type 0 (within normal limits): no echogenic dots and bands in the liver lobes. No thickening of the portal vein wall. Type 1 (linear pattern): some linear echogenic bands. Mild echogenic thickening (< 6 mm) of the portal vein wall without narrowing of the diameter. Type 2 (tubular pattern): some bright tubular, echogenic bands. Moderate to severe echogenic thickening (> 6 mm) of the portal vein wall. Type 3 (network pattern): septal formation like a turtleback blocks. More than 3 blocks surrounded by high echogenic bands. In addition, the diagnosis of liver cirrhosis was based on the irregular rough surfaces and dull edges of the US liver images with clinical symptoms such as ascites.

After the US examinations, 7 ml of blood was taken from each patient. The white blood cell (WBC) counts, eosinophil ratio, and hematocrits were immediately determined. General liver function was studied by the following parameters; total protein; albumin; bilirubin; aspartate aminotransferase (AST); alanine aminotransferase (ALT); lactate dehydrogenase (LHD);  $\gamma$ -glutamyl transferase (GGT); choline esterase (Ch-E). Serum levels of total bile acid (TBA) and procollagen-III-peptide (P-III-P) were also measured.

The most prominent abnormality found in the liver was periportal fibrosis diagnosed by

the thickening of the portal vein wall (28 patients). Hypertrophy of the left lobe was also detected in many patients (26 cases), whereas hypertrophy of the right lobe was less common (6 cases). Atrophy of the right lobe was always accompanied with hypertrophy of the left lobe (10 cases). Ten patients were diagnosed as liver cirrhosis by the US examinations and their clinical symptoms. Most of types 0 and 1 (normal to mild changes) were observed in younger group, under 40 years of age. Nineteen patients out of 29 in type 0 were less than 30 years old, and estimated within 3 years of the infection on the bases of the records of the annual stool examination. On the contrary, mean age of the patients became higher in types 2 and 3, according to the progress of the liver damage. Typical network patterns in type 3 were observed in 11 patients who were estimated at least 4 years after infection.

Splenomegaly was observed in 69 patients. However, the severity of splenomegaly did not correlate with the age of the patients. Dilatation of the splenic vein was found in 63 patients. Collateral vessels determined as spleno-renal shunts or recanalization of the umbilical vein were observed in 27 patients. There were no esophagogastric varices found by the US examinations.

As for serological tests, the serum level of TBA gradually increased with the extent of the liver damage evaluated and classified according to the US liver patterns. The titers of TBA in patients of types 2, 3, and liver cirrhosis were significantly higher than those of controls ( $P < 0.01$ ). Furthermore, the levels in the patients of types 2, 3, and liver cirrhosis showed a significant increase even compared with those of type 1 ( $P < 0.01$ ). P-III-P levels showed the similar elevation of the titers in patients of any stage, however, not so sensitive as the elevation of TBA levels. There was no correlation between the severity of splenomegaly and the serum levels of TBA or P-III-P. The levels of TBA increased significantly in the patients with dilatation of splenic vein ( $P < 0.01$ ).

After PZQ treatment, mild hepatic fibrosis classified into types 0, 1, and 2 were significantly improved (Ohmae et al., 1991c). The number of the patients in type 1 and 2 decreased, and moved to be in normal range 6 months after treatment. However, such improvement could not be detected in the study



patients with severe hepatic fibrosis. The network pattern of the echogenic bands did not change even one year after the treatment.

The extent of splenomegaly were drastically decreased after PZQ treatment. This improvement could be well detected in the patients without the production of collateral vessels. On the other hand, severe splenomegaly with the production of collaterals were not significantly improved even 1 year after treatment. The similar results were obtained when the serum TBA level was used as a parameter.

These results indicate that PZQ treatment could improve the mild hepatic fibrosis and changes in the portal system within 6 months. The improvement of the damage caused in the organs could be well detected by the US examinations, and the serum TBA level were the sensitive marker to evaluate the efficacy of PZQ. These observations had good correlation with the results obtained in experimental animals (Tanaka et al., 1989, Ohama et al., 1991a). The similar improvement in echogenic bands and/or periportal fibrosis has been reported after PZQ treatment in *S. mansoni* infected patients (Homeida et al., 1991). However, by the US examinations, the severe hepatic fibrosis classified as type 3 found in reinfected patients were not improved. The efficacy of PZQ seems to have a certain limitation in the severe damage caused in the organs in the course of a long-term infection.

We have screened various haematological and serological markers which might have a good correlation with the clinical feature of the infection. As a conclusion, the serum TBA level was proved to be most sensitive markers. Although the serum level of P-III-P is known as a good markers of fibrogenesis, the fibrogenesis in schistosomiasis japonica seems to be more limited to the portal area than the other liver diseases. Recently, the kit for analyzing the serum TBA level is commercially available, whereas the other tests can be detected by radioimmunoassay.

The changes in the portal systems could be also improved by PZQ administration. However, no change was detected both by the US examination and the serum TBA level in the patients with severe splenomegaly and already with the production of collaterals. This observation would suggest that the damage in the portal systems were also irreversible when the

intensity and the duration of the infection exceeded to a certain extent. The observations in the present study would provide one way of effective system to monitor the schistosome infection in field trials of a large-scale chemotherapy.

#### ACKNOWLEDGEMENTS

To the colleagues in Institute of Basic Medical Sciences and Institute of Clinical Medicine, University of Tsukuba, and to the colleagues in Schistosomiasis Hospital, Leyte, Philippines, for their valuable collaboration during the field survey and writing the manuscript. The present study was performed as a part of a collaborative project of the Schistosomiasis Control Service, Ministry of Health, Philippines and Sasakawa Memorial Health Foundation, Japan, for Schistosomiasis Control in the Philippines.

#### REFERENCES

- ABDEL-WAHAB, M. F.; ESMAT, G.; MILAD, N. M.; ADEL-RAZAK, S. & STRICKLAND, G. T., 1989. Characteristic sonographic pattern of schistosomal hepatic fibrosis. *Am. J. Trop. Med. Hyg.*, 40: 72-76.
- BUTTERWORTH, A. E., 1988. Control of schistosomiasis in man, p. 43-60. In *The Biology of Parasitism* Alan R. Liss, Inc., New York.
- HOMEIDA, M. A.; ABDEL-GADIR, A. F.; CHEEVER, A.; BENNETT, J.; ARHAB, B.; IBRAHIUM, S.; ABDEL-SALAM, I.; DAFALLA, A. & NASH, T., 1988. Diagnosis pathologically confirmed Symmers' periportal fibrosis by ultrasonography: a prospective blinded study. *Am. J. Trop. Med. Hyg.*, 38: 86-91.
- HOMEIDA, M. A.; TOM, I. E.; NASH, T. & BENNETT, J., 1991. Association of the therapeutic activity of praziquantel with the reversal of Symmers' fibrosis induced by *Schistosoma mansoni*. *Am. J. Trop. Med. Hyg.*, 45: 360-365.
- OHMAE, H.; TANAKA, M.; NARA, T.; UTSUNOMIYA, H.; TAGUCHI, H.; IRIE, Y. & YASURAO-KA, K., 1991a. Serological and ultrasonographical parameters of praziquantel treatment on hepatic fibrosis in *Schistosoma japonicum* infection. *Am. J. Trop. Med. Hyg.*, 45: 350-359.
- OHMAE, H.; TANAKA, M.; HAYASHI, M.; MATSUZAKI, Y.; KUROSAKI, Y.; BLAS, B.; PORTILLO, G.; SY, O. S.; IRIE, Y. & YASURAO-KA, K., 1991b. Ultrasonographic and serological abnormalities in *Schistosoma japonicum* infection in Leyte, Philippines. accepted to *Am. J. Trop. Med. Hyg.* (in press).
- OHMAE, H.; TANAKA, M.; HAYASHI, M.; MATSUZAKI, Y.; KUROSAKI, Y.; BLAS, B.; PORTILLO, G.; SY, O. S.; IRIE, Y. & YASURAO-KA, K., 1991c. The improvement of ultrasonographical and serological changes in *Schistosoma japonicum* infected patients after praziquantel treatment. accepted to *Am. J. Trop. Med. Hyg.* (in press).

- TANAKA, H.; TSUJI, M.; TSUTSUMI, H. & MINAI, M., 1984. The present status of schistosomiasis in Japan. *Sou. Ea. Asi. J. Tro. Med. Pub. Hlth.*, 15: 475-477.
- TANAKA, M.; OHMAE, H.; UTSUNOMIYA, H.; NARA, T.; IRIE, Y. & YASURAOKA, K., 1989. A comparison of antischistosomal effect of levo- and dextro-praziquantel on *Schistosoma japonicum* and *S. mansoni* in mice. *Am. J. Trop. Med. Hyg.*, 41: 198-203.
- TANAKA, M.; IRIE, Y.; YASURAOKA, K.; SATOH, A.; MATSUMOTO, S.; HAKUTA, Y.; NAKAMURA, A.; KAWAI, M. & EBIHARA, M., 1988. Chronic schistosomiasis japonica cases in the Tone River Basin, Honshu, and its early diagnosis. *J. Jpn. Assoc. Inf. Dis.*, 62: 156-163.