α,-Antitrypsin and survival in hepatocellular carcinoma

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Summary. The association between serum levels of α,-antitrypsin (α,AT) at the time of diagnosis and survival was studied in a group of 78 patients with confirmed hepatocellular carcinoma (HCC). All 78 patients were followed until the time of death, which occurred in all instances from HCC, with a median time of 6 months and a range of 1–117 months. Cox’s proportional hazards model was utilised in the analysis controlling for sex, age, HBsAg status and logarithmically transformed values of α,-fetoprotein (α-FP). Older patients and patients positive for HBsAg have suggestively higher fatality rates (0.05 < P < 0.10) whereas in these data sex and AFP levels were not important prognostic factors. Increased levels of serum α,AT at the time of diagnosis of HCC were statistically significantly (P < 0.05) related with shorter survival, patients with higher serum α,AT by 200 mg 100 ml⁻¹ having an expected survival time shorter by about 25%.

α,-Antitrypsin (α,AT) is the main protease inhibitor in human serum and its most important biological function is to inactivate a variety of proteolytic enzymes, particularly leukocyte elastase (Harpe, 1983; Cohen, 1986). Individuals who are homozygous for the Z allele are at an increased risk for hepatocellular carcinoma (HCC) (Eriksen et al., 1986), but there is no convincing evidence that individuals who are heterozygous for the Z allele, and other alleles associated with α,AT deficiency, are over-represented among cases of HCC (Govindarajan et al., 1981; Sparos et al., 1984; Eriksen, 1985; Marwick et al., 1985; Schneider et al., 1986). Interestingly, several authors have confirmed the observation of Kew et al. (1978) that HCC cases have elevated levels of serum α,AT, an increase which is found across several α,AT phenotypes (Chio & Oon, 1979; Matsuzaki et al., 1981). In 1984 we reported the results of a relatively large epidemiological study in Greece exploring, among other issues, the association between α,AT levels and HCC, by hepatitis B virus (HBV) serological status (Sparos et al., 1984). Since then, we have been able to follow, until the time of death, 78 out of the 80 cases with HCC included in that study, and we report here the findings concerning the association between serum levels of α,AT and survival of these patients.

Patients and methods

In the original study (Trichopoulos et al., 1978) 80 HCC patients were included, but two of them were lost to follow-up. The disease was histologically confirmed in 47 cases and by diagnostically high α,-fetoprotein (α-FP) values in the remaining 31 cases. All patients were Caucasian, of Greek nationality and residence, hospitalised in one of eight large hospitals in Athens during a 15-month period in 1976 and 1977. Among these patients 67 (87%) were males, and the average age was 63 years. Hepatitis B serological markers and α-FP levels were determined by radioimmunoassay (Trichopoulos et al., 1978, 1980). Serum levels and phenotypes of α,AT were determined by radial immunodiffusion and electrophoresing in acrylamide gel, respectively (Vesterberg, 1973; Chapuis-Cellier, 1975). All α,AT determinations were performed in the Department of Clinical Biochemistry of the Hospital ‘Edouard Herriot’ in Lyon, France (Sparos et al., 1984). All serologic determinations refer to the time of the HCC diagnosis and were performed blindly.

An effort was made, by ourselves, to follow regularly all HCC patients, but two of them were lost immediately after their first hospitalisation. The remaining 78 were followed by letters, telephone calls and, eventually, personal visits until their death, which occurred at times between 25 days and 117 months after diagnosis. All these patients died from HCC, according to their relatives, doctors and death certificates.

The statistical analysis was done by Cox’s proportional hazards model (Cox, 1972), using survival time (there were no censored observations), sex (male = 1, female = 2), age (in decades), HBsAg status (negative = 1, positive = 2), serum α,AT levels (in 100 mg 100 ml⁻¹) and serum α-FP levels (in ng ml⁻¹ after log transformation) as model variables. Cox’s model allows the estimation of the patients’ instantaneous fatality rate ratio (and associated confidence intervals), contrasting two particular values of any particular variable, while controlling for the potential confounding effects of the other prognostic risk factors in the model. In the present situation, in which there are no censored observations, Cox’s model is conceptually equivalent to standard multiple regression models, with survival time as dependent variable. Cox’s model was chosen because it generates epidemiologically interpretable parameters like the rate ratio, and is frequently utilised in exposure based studies and clinical follow-up investigations.

Results

Among the 78 HCC cases, 39 (50%) were positive for HBsAg. The distribution of the 78 HCC cases by α,AT phenotypes was as follows: M,M; M,Mr; Mr,Mr; Mr,Mr; Mr,M; Mr; Mr; Mr and 0 other. The mean value of α,AT was 616 mg 100 ml⁻¹ with 95% confidence intervals (CI) 579–652 mg 100 ml⁻¹; the geometric mean value of α-FP was 8,268 ng ml⁻¹ with 95% CI, 3,791–18,034 ng ml⁻¹. The median survival time of HCC patients was 6 months, with a range from 25 days to 117 months.

Table I summarises the results derived from the application of the proportional hazards model on the survival data of HCC patients.

There is evidence that the fatality rate from HCC is higher among older persons and among patients who are positive for HBsAg, whereas neither sex nor α-FP levels are prognostic indicators in these series. There is a moderately strong positive correlation between serum levels of α,AT and fatality rate from HCC, an increase of 100 mg 100 ml⁻¹ corresponding to an increase of death rate of 15% (P = 0.05).

Discussion

α,-Antitrypsin is under genetic control, and more than 30 codominant alleles at a single chromosomal locus have been
identified (Cox, 1978; Morse, 1978; Kuhnl & Spielmann, 1979; Buffone et al., 1983; Dykes et al., 1984). The association between α1AT and HCC is complex and intriguing, and may reflect both the pathophysiological role of α1AT (Eriks- 

| Variable | Category | Rate ratio | Unit | 95% confidence interval | P (two-tailed) |
|----------|----------|------------|------|------------------------|---------------|
| Sex      | male     | Baseline   | n.a. | (0.48 - 1.87)          | >0.50         |
| Age      | male     | Baseline   | 0.95 | (0.9 - 1.0)            | ~0.07         |
| HbA1c    | normal   | Baseline   | 0.99 | (0.9 - 1.0)            | ~0.09         |
| α-FT     | continuous | 1 log unit | (10-fold increase) | (0.83 - 1.17) | <0.05        |
| α1AT     | continuous | 100 mg 100 ml-1 | (1.01 - 1.32) | <0.05        |

Proportional hazards model derived fatality rate ratios associated with serum levels of α1AT and other variables. All rates ratios are mutually adjusted. *Not applicable.

Table I Survival of 78 patients with HCC

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