Autoimmune hepatitis
Life, death and in-between

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av medicine doktorsexamen framläggs till offentligt försvar i Hörsal B, byggnad 1D, 9tr, Norrlands Universitetssjukhus, fredagen den 2 juni, kl 09:00.
Avhandlingen kommer att försvaras på svenska.

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Background
Autoimmune hepatitis (AIH) is a chronic autoimmune liver disease that is overrepresented in women (75% of cases). Studies have described a 10-year survival after diagnosis near to that of the general population, but less is known about the long-term survival. The inflammation in AIH causes fibrotic tissue to form in the liver and about 1/3 of AIH patients have cirrhosis at diagnosis. Studies have shown that treatment of the underlying liver disease can reverse fibrosis, and sometimes even cirrhosis, but only a few studies have examined the response to treatment in AIH. AIH affects all ages and some women will have cirrhosis during pregnancy, which is a risk factor for an adverse outcome. Cirrhosis is also a risk factor for hepatocellular carcinoma (HCC), but the true risk for HCC in cirrhotic AIH patients is not known.

Aim
To study the epidemiology of AIH in Sweden, the causes of death and the risk of cancer for AIH patients, the efficacy of medical treatment on fibrosis and cirrhosis, and outcomes for the mother and child in pregnancy.

Material and methods
A cohort of 634 AIH patients was established at the Swedish University hospitals. Prevalence and incidence were calculated, and a relative survival analysis was performed in which survival after AIH diagnosis was compared to that of the general population. Causes of deaths were retrieved from the Cause of Death Registry. The Cancer Registry was used to calculate standard incidence ratios (SIR) and compare cancer risk to that of the general population. Two hundred fifty-eight liver biopsies from 101 patients were analyzed by a single pathologist and classified according to the Ishak grading and staging system. Liver histology was stratified according to the temporal changes of fibrosis stage, and groups were compared. A questionnaire was answered by 138 women with AIH about medication, pregnancies, disease behavior during and after pregnancy, and pregnancy outcomes.

Results
The incidence and prevalence of AIH were 1.2/100 000 and 17.3/100 000 respectively. The relative survival started to decline after 4 years compared to the reference population, and was even more pronounced after 10 years. Men were diagnosed (33.5 years versus 48.0 years, p<0.001) and died (59.7 versus 75.4 years, p=0.002) at a younger age than women. Patients with cirrhosis at diagnosis had an inferior survival (p<0.001). Liver-related death was the most common cause of death (32.7%). Among AIH patients a higher incidence of cancer was found compared with that of the general Swedish population, SIR of 2.08 (95% Confidence Interval (CI) 1.68-2.55). SIR for non-melanoma skin cancer was 9.87 (95% CI 6.26-14.81) and hepatobiliary cancer was 54.55 (95% CI 19.92-99.99). HCC was found in 4% of the cirrhotic patients and the incidence rate was 0.3% per year. A reduction of fibrosis stage from first to last biopsy was common (62.4% of patients) and patients on a continuous glucocorticoid medication more often had a decreased fibrosis stage than those with withdrawal attempts (p=0.002). One hundred children were born by 58 women with AIH, of which 23 women had 43 children after diagnosis of cirrhosis. Malformations were reported in 3%, and pre-term births (<week 38) in 22% of the pregnancies. Cirrhotic women gave birth without more complications than others, but with a higher frequency of caesarean sections than non-cirrhotic women (p=0.047).

Conclusion
Contrary to previous reports, AIH patients' life expectancy was significantly inferior to that of the control population already 4 years after onset of disease, and liver disease was the most common cause of death. AIH patients had an overall enhanced risk for cancer, mainly from an increased risk of non-melanoma skin cancer and HCC. However, the annual risk of HCC was only 0.3% in cirrhotic patients. Histological improvement of liver fibrosis was common in AIH. The proportion of pre-term births was high, but overall pregnancy and childbirth appear to be safe in AIH, even in compensated cirrhosis.