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Screening for hepatocellular carcinoma in acute intermittent porphyria: a 15-year follow-up in northern Sweden

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Abstract. Innala E, Andersson C (Umeå University, Umeå, Sweden). Screening for hepatocellular carcinoma in acute intermittent porphyria: a 15-year follow-up in northern Sweden. *J Intern Med* 2011; **269**: 538–545.

Objectives. To evaluate the benefit of screening for hepatocellular carcinoma (HCC) in gene carriers of acute intermittent porphyria (AIP) and estimate the annual incidence of HCC in this group.

Subjects. All *AIP* gene carriers aged ≥55 years from the northernmost county in Sweden, Norrbotten, were invited for screening in this prospective study every 1–1.5 years during the period 1994–2009. We registered all HCC cases amongst *AIP* gene carriers in the northern region of Sweden (four counties). We compared gene carriers with repeated screening intervals of <2 years (Group A) with controls (Group B; i.e. gene carriers who had never been screened, those screened for the first time or screened at intervals of >2 years, or dropouts). The screening included radiological examination of the liver and relevant laboratory tests.

Results. A total of 62 AIP subjects participated in the study, comprising 33% of the total AIP population aged >55 years in the northern region of Sweden. HCC was diagnosed in 22 AIP subjects (12 men and 10 women), mean age 69 (59–82) years. Amongst these subjects, 73% had experienced prior AIP attacks. The incidence rate ratio for HCC was 64 (52 in men and 93 in women). There were no cases of hepatitis B/C or alcohol abuse. Liver cirrhosis was rare. Liver resection could be performed in most subjects in Group A. Fourteen patients died of HCC, one in Group A and 13 in Group B. Compared with those who were not screened regularly, screening was associated with improved 3-year and 5-year survival (P = 0.005 and 0.038).

Conclusions. Screening for HCC in carriers of AIP enables early diagnosis and a choice of potentially curative treatments with improved prognosis. We recommend annual screening using liver imaging for *AIP* gene carriers >50 years of age.

Keywords: acute intermittent porphyria, hepatocellular carcinoma, screening, surveillance.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common neoplasia and the third leading cause of cancer death, with approximately 600 000 annual deaths worldwide [1]. The highest annual incidence of HCC is found in certain regions of Asia and in sub-Saharan Africa with 50–100 cases per 100 000 population – male-to-female ratio (m : f) 2–3 : 1. The reason for the male preponderance is not clear. The major known risk factors for HCC are viral (hepatitis B and C), toxic (alcohol and aflatoxins), metabolic (diabetes, nonfatty liver disease and haemochromatosis) and immune (autoimmune hepatitis and primary biliary cirrhosis) [1]. Liver cirrhosis is present in 80–90% of patients with HCC and is the largest single risk factor [2]. A relatively low incidence of HCC, <5 cases per 100 000, is found in Scandinavia, Canada and the United States [1]. The highest prevalence of HCC is found amongst those aged over 65 years [1]. In Sweden, the annual incidence of HCC is 4.3 per 100 000 (m : f 5.8 : 2.8) [3], and the corresponding rate for those over the age of 50 is 11.4 per 100 000 (m : f 15.4 : 8.0) [3]. This is similar to the rate in the northern region of Sweden alone. In Sweden, the prevalence of hepatitis B and C virus (HBV and HBC) infections is low.

The prognosis of HCC is extremely poor if untreated. Early detection and various treatment options have led to marked improvement in the outcome of patients with HCC over the past three decades [4].

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Surveillance programmes for specific groups at high risk of HCC are currently recommended [5].

An association between acute intermittent porphyria (AIP) and HCC was reported for the first time in 1984 [6] and has since been confirmed [7–9]. An association with other acute porphyrias, such as hereditary coproporphyria [10] and variegate porphyria [8, 11, 12], has also been reported.

Our finding of a 100-fold risk of developing HCC in *AIP* gene carriers from a population-based mortality study from northern Sweden with a very high prevalence of AIP [13] was the incentive for this screening programme. The aim of this study was to evaluate the benefit of screening for HCC in gene carriers of *AIP*; to our knowledge, this is the first such study. We also estimated the annual incidence of HCC in this patient group.

Material and methods

Participants and study settings

We started the screening programme in 1994 with a follow-up of 15 years until 2009. All DNA-diagnosed *AIP* gene carriers above the age of 55 years, living in the county of Norrbotten (the northernmost county in Sweden with a total of about 250 000 inhabitants), were invited at intervals of 1.0–1.5 years to take part in the screening programme. All patients with AIP from the northern region of Sweden with a diagnosis of HCC during these 15 years were registered in the study. The northern region comprises the four most northern counties in Sweden with a population of about 900 000. In a few cases, physicians from the northern region, outside Norrbotten, had detected HCC in patients with AIP through radiological screening, and these HCC cases were included in the study. The W198X AIP mutation in the *PBGD* gene was present in 90% of the AIP population in this area [14].

Procedures

The prospective screening programme was composed of three parts: a radiological examination, relevant laboratory tests and a questionnaire. Case records were used for verification of radiological examinations, laboratory results, HCC diagnosis, treatment and outcome i.e. relapse, cause of death and survival time.

Contrast-enhanced computed tomography (CT) was most frequently used to detect HCC, followed by ultrasonography and in a few cases magnetic resonance imaging (MRI). The examinations were performed at the local hospitals. When diagnostic problems occurred, a combination of radiological methods was used. Diagnosis of HCC was based on liver biopsy or, in a few cases, on a combination of radiological imaging methods. The diagnosis was confirmed by the Swedish Cancer Registry and cross-checked with our AIP registry from northern Sweden.

Blood tests included aminotransferases, triglycerides, bilirubin, ferritin, gamma-glutamyltransferase, alpha-fetoprotein (AFP) and creatinine, and urinary tests included 5-aminolevulinic acid (U-ALA) and porphobilinogen (U-PBG). The porphyrin precursors were measured when patients were not experiencing an attack of AIP. Reference levels for U-ALA were <3.1 mmol mol^{-1} creatinine or <45 μmol L^{-1}, and for U-PBG, the levels were <1.2 mmol mol^{-1} creatinine or <11 μmol L^{-1}. Standard biochemical laboratory analyses were performed at accredited departments of clinical chemistry at the local hospitals in the region, with shared reference values. AFP was analysed at the Clinical Chemistry Department at the University Hospital of Umeå. The cut-off level of AFP for screening was 20 ng mL^{-1}. Subjects were tested for HBV and HCV at least once. HBV and HCV tests were analysed at the clinical microbiology laboratory, University Hospital of Umeå. U-ALA and U-PBG were analysed [15] at the Swedish Porphyria Centre, Stockholm.

The questionnaire focused on liver disease, alcohol consumption and occupation, and in particular on exposure to substances toxic to the liver.

In a case–control approach, we compared two groups with HCC. The screened Group A comprised gene carriers undergoing repeated screening within 1–2 years. The control Group B comprised gene carriers who had never been screened, those screened for the first time or screened at intervals of >2 years, or dropouts.

Statistical analysis

Statistical significance was calculated using chi-square and Fisher's exact probability tests for nominal variables. A value of $P < 0.05$ was chosen as the level of statistical significance. A significant difference in survival time was calculated by the Kaplan–Meier log rank test. We used spss v 11(SPSS Inc., Chicago, IL, USA) for Mac OSX for statistical analysis.

Results

About half of the Swedish *AIP* gene carriers (498) lived in the four northernmost counties of Sweden during the study period, and 180 subjects were ≥55 years old.

The eligible AIP population from the county of Norrbotten comprised 81 subjects ≥55 years old. On average, 62 *AIP* gene carriers (77%) participated in the regular screening (i.e. one-third of the whole northern region). The mean age at entry to the screening programme was 67 years (50–83 years), and 52% (32) of subjects were men. In total, 57% (35) had manifest AIP (MAIP; i.e. acute attacks had occurred during the patient's lifetime) and the remainder had latent AIP (LAIP; i.e. no attacks had been reported before initiation of the study). MAIP was more common amongst women (67%) than amongst men (33%).

HCC was diagnosed in 22 *AIP* gene carriers in the northern region during the study period; 12 were men (55%) and 16 (73%; eight men and eight women) had MAIP (Table 1). Fifteen of the patients with HCC came from Norrbotten and seven from elsewhere within the northern region; two cases outside Norrbotten were detected by screening. The most common mutation of the *AIP* gene was W198X, present in 19 subjects. Another mutation with high penetrance [14], R173W, was present in one woman with MAIP (case 5) (Table 2). The low-penetrance mutation R167W was present in one woman with LAIP and normal levels of both U-ALA and U-PBG (case 14). One man with LAIP had the I113T mutation (case 1).

A summary of patient characteristics and clinical data is shown in Table 1. HCC was almost as common in women as in men, and in six cases (27%) of HCC, the *AIP* gene carriers had not previously experienced an AIP attack (i.e. LAIP). Normal levels of both U-ALA and U-PBG were found in only two cases.

Alpha-fetoprotein was normal in all subjects in Group A and in most controls in Group B. In four subjects, the AFP level was above 200 ng mL^{-1} and they all had a tumour burden of >10 cm (Table 2). Three of these patients had terminal-stage disease. Aminotransferases were moderately increased in the five patients with increased levels of AFP.

There were no patients with alcoholism, other liver diseases or prior exposure to substances toxic to the liver.

Table 1 *Clinical data from 10 women and 12 men with hepatocellular carcinoma and AIP. Comparison between Group A with screening intervals <2 years and Group B (never screened, first screening, screening intervals >2 years or dropouts)*

	Group A Regular screening <2 years	Group B Never screened, first screening or dropout >2 years
Number	8	14
Women	3	7
Mean age at diagnosis (range)	69 (60–80)	69 (59–82)
Manifest AIP	8	8
Cirrhosis/eligible	2/6	2/11
Tumour differentiation (high/medium/low)	5/1/0	9/1/0
Hepatitis B or C	0	0
AFP >20 ng mL^{-1} [a]	0	5
U-ALA and U-PBG normal [b]	1	1
Tumour burden >7 cm	1	10
Surgery	7	4
Recurrence	3	3

AIP, acute intermittent porphyria; U-ALA, 5-aminolevulinic acid; U-PBG, porphobilinogen; AFP, alpha-fetoprotein.
[a]AFP, four missing values.
[b]U-ALA reference <3.1 mmol mol^{-1} creatinine or <45 μmol L^{-1}. U-PBG reference <1.2 mmol mol^{-1} creatinine or <11 μmol L^{-1}. One missing value

Surgery was an option for seven of eight screened patients in Group A compared with four of 14 controls in Group B ($P = 0.024$). Recurrence of HCC occurred in three of seven patients in Group A and in three of four controls (ns). All patients in the control group died during the study period. The tumour burden was greater in the control group. The cause of death was HCC in all but one subject with prostate carcinoma (case 12). Only two screened patients in Group A died; one subject died from anaplastic pulmonary cancer 1 year after successful resection of a well-differentiated HCC (excluded from statistical calculations), and the other died from HCC.

Kaplan–Meier survival analysis is shown in Fig. 1. We found improved 3-year survival in Group A compared with Group B ($P = 0.005$) as well as improved 5-year survival ($P = 0.038$).

Table 2 *Patient data, screening interval, treatment and survival data from 22 patients with hepatocellular carcinoma and acute intermittent porphyria (AIP). Comparison between Group A with screening interval <2 years and Group B (never screened, first screening or screening interval >2 years)*

Group	Case	Sex m/f	LAIP/ MAIP	Age at diagnosis	U-ALA U-PBG	AFP	Previous screening (years)	Tumour burden (cm)	Treatment	Survival months	Recurrence (years)
B1	1	m	L	65	N/+	N		5	Surgery	144	11
never	2	m	L	69	N/+	N		10	Surgery	74	1
screened	3	m	M	68	N/+	192000		>10		2	
	4	m	M	66				>10		5	
	5	f	M	64	+/+	N		>10	RF	12	
	6	f	M	76	+/+	816		>10		2	
	7	f	M	72	N/+			10		0.5	
B2 first	8	f	M	73	+/+	N		10		72	
screening	9	f	M	63	N/+	23		7		22	
B3 screening	10	m	L	66	+/+	N	3	4	Cytostatic	32	
interval	11	m	L	74	N/+	N	3	6	Surgery	23	2
>2 years	12	m	M	77	+/+	298	3.5	>10	Surgery + RF	29	
	13	f	L	59	+/+	284	2.8	>10		4	
	14	f	L	82	N/N		7	>10		2	
A regular	15	m	M	62	+/+	N	1	6	Surgery	135 + +	11
screening	16	f	M	62	+/+	N	1.5	12	Surgery	58	2
<2 years	17	m	M	60	+/+	N	1.9	5	Surgery	13*	
	18	m	M	73	+/+	N	1.5	2	Surgery	91 + +	
	19	m	M	80	N/N	N	1.9	4	Surgery	76 + +	1
	20	f	M	71	+/+	N	1.1	3	Surgery	62 + +	
	21	m	M	80	+/+	N	1.5	5		7 + +	
	22	f	M	68	+/+	N	1.5	3	Surgery	6 + +	

U-ALA, U-PBG: N = within reference levels, + = above reference levels; see Table 1 for reference levels.
AFP: N = within reference levels, <20 ng mL^{-1}.
Survival months: ++ indicates patient alive, * died from pulmonary carcinoma
m, male; f, female; LAIP, latent AIP; MAIP, manifest AIP; RF, radiofrequency ablation; U-ALA, 5-aminolevulinic acid; U-PBG, porphobilinogen; AFP, alpha-fetoprotein.

During the 15-year screening period, there were 22 cases of HCC in the northern region of Sweden in 180 *AIP* gene carriers (87 men and 93 women) ≥55 years of age. Thus, the annual incidence of HCC per 100 000 was 815 (m : f 920 : 717). The annual incidence in the same age group for the general population in northern Sweden was 12.7 (m : f 17.6 : 7.7) per 100 000. The standardized incidence rate ratio (SIR) for HCC in *AIP* gene carriers aged ≥55 years was thus 64 (95% confidence interval 40–97); m : f 52 (95% confidence interval 40–97) : 93 (95% confidence interval 45–171).

Discussion

We found that radiological screening for HCC in *AIP* gene carriers enables early diagnosis and a choice of potentially curative treatments, thereby improving prognosis. However, liver function tests and AFP were not useful in screening for HCC. We also found that carriers for AIP aged ≥55 years in northern Sweden constitute a high-risk group for developing HCC.

A strength of our study is that it is the first to prospectively estimate the incidence of HCC in AIP in a popu-

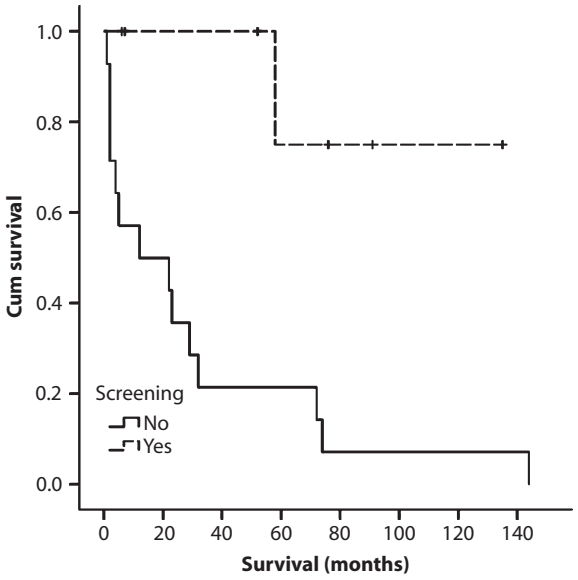

Fig. 1 *Survival time in 22 patients with acute intermittent porphyria with hepatocellular carcinoma. Dashed line, Group A, repeated screening within 1–2 years; Solid line, Group B, never screened, first-round screened, screening interval >2 years, dropouts. Case 17 (Table 2) excluded from Group A (died from pulmonary carcinoma). Log rank (Mantel–Cox) test, P = 0.004.*

lation-based investigation and to estimate the benefit of screening this patient group. The study is based on a well-characterized AIP population covering almost every adult *AIP* gene carrier in the northern region of Sweden, and it is probably the largest reported AIP population [16]. As the number of undiagnosed *AIP* gene carriers in our catchment area is small, the risk of overestimating the incidence of HCC in the AIP group is minimal. Furthermore, the patients underwent surgery at one hospital, Umeå University Hospital.

A weakness of our study could be that the founder mutation W198X of the *PBGD* gene is predominant in our *AIP* gene carriers and that this mutation is reported as severe with high penetrance [14]. This might reduce the possibility to generalize our results. Another weakness is the disadvantage of lead-time bias in surveillance studies, as surveillance detects earlier disease. Only randomized controlled studies can eliminate this bias and only one such study on HCC has been reported. The study was conducted in Chinese subjects with chronic HBV infection and showed that screening with ultrasonography twice a year reduced the 5-year mortality by 37% [17]. Nowadays, such studies are not considered possible from an ethical point of view. The best outcome measure is now regarded to be disease-free survival.

Annual incidence

The annual incidence of HCC in our study was 0.8% for *AIP* gene carriers aged >50 years; thus, 125 subjects needed to be screened to detect one case of HCC. The annual incidence of breast cancer amongst the general population of women aged >50 years in Sweden is 0.3% [3].

The annual incidence of HCC in subjects with acute porphyrias was found to be 0.16% in a French study [9] and 0.3% in a study from Switzerland [18]. In a retrospective study from Stockholm, Sweden, covering 22 years, the annual risk was calculated as nearly 1% with a relative risk of 66 compared to an age-matched population in the Stockholm area [19]. The higher annual incidence in Sweden could to some extent be explained by the presence of the high-penetrance W198X mutation in the *PBGD* gene [14]. This founder mutation is present in 90% of the AIP population in northern Sweden and in approximately 40% in the Stockholm area. The same proportions of the mutation were found amongst subjects with HCC in the two geographical areas. However, a great variety of mutations in the *PBGD* gene has been found in the larger series of AIP subjects with HCC [9, 18, 19]. Thus, specific *AIP* mutations might only partly explain the variations in annual incidence of HCC in subjects with acute porphyrias in different countries.

Incidence rate

The relative risk or SIR for HCC in *AIP* gene carriers has been estimated in several studies, and the results have varied greatly. The French study [9] reported an SIR of 36 (m : f 19 : 110). The lower figure from France, compared to the present study and the Stockholm study, [19] could be explained by the lower annual incidence of HCC. It is interesting that the risk estimates for women are similar in the French and the present studies. The relative risk reported from the first study of HCC in AIP was 83 [6], and a 61-fold risk was calculated (m : f 64-fold : 55-fold) in a study from Finland [8]. In general, the results from these studies suggest that women with AIP are at a higher relative risk of HCC than men.

Risk factors

The nine largest series, including this study, on acute porphyria and HCC comprise 104 cases (96 AIP, five variegate porphyria and one hereditary coproporphyria) [6–9, 13, 18–20]. There was a female predominance with 62% women overall. In most series, the age at diagnosis was above 50–55, with a mean of 68–69 years. However, the French study reported 50 years as the mean age at diagnosis (37–65 years). Hepatitis was only present in subjects in the French study (two of seven HCC cases), but not in the two other studies in which it was considered [19, 20], or in this study. This might to some extent explain the lower mean age at HCC diagnosis in the French AIP population. It is interesting that the presence of cirrhosis was low in all series (approximately 30 ± 10%).

The common risk factors for HCC such as being male, alcoholism, cirrhosis and HBV or HCV were not applicable in acute porphyrias. It is plausible that there is a porphyria-specific risk factor.

Porphyria-specific risk factors and pathogenesis

Further evidence of a porphyria-specific risk factor should be considered as the proportion of subjects with MAIP was 68%, calculated from pooled data from five of the large series on acute porphyrias and HCC including our study (MAIP : LAIP 52 : 25) [9, 13, 19, 20]. Furthermore, women are more severely affected by AIP than men, and the proportion of MAIP is higher in women. This corresponds to the female predominance in HCC, a reversal of the male-to-female ratio of liver cancer in general. Increased levels of U-ALA and U-PBG are more common in subjects with MAIP than in those with LAIP [16], and the increased levels of porphyrin precursors might be involved in the risk of HCC in AIP.

Various hypotheses have been suggested to explain the high prevalence of HCC in acute porphyrias [6–9, 21]. Through autooxidation of ALA, chronically increased levels of ALA in the liver could lead to the generation of free radicals and subsequently to carcinogenesis over time. Data to support this have been presented [22, 23]. Furthermore, in porphyrias, a reduced free potential (hypothetical) haeme pool could adversely affect cytochrome P450 and important antioxidants, leading to an increase in reactive oxygen species and mutation rate. The long-term effect in hepatic tissue might be liver cell injury and development of HCC caused by free radical attack on nucleic acids. The high risk of HCC in subjects with acute porphyrias is thus predictable [21].

Screening methods

Screening methods should have high sensitivity and specificity for detection of early-stage HCC. AFP was not useful as a screening tool in our study and its use for HCC screening should be discouraged according to other studies or guidelines [24, 25].

Abdominal ultrasound is currently considered the most appropriate screening technique, with a sensitivity of 60–80% and over 90% specificity in early HCC detection [26]. The specific vascular pattern, with intense contrast uptake in the arterial phase, followed by rapid washout in the portal phase, has proved to be specific to HCC. It can be examined by contrast-enhanced ultrasonography, which should be used to characterize a suspected tumour.

Repeated use of CT as a screening method is not recommended because of risks associated with irradiation. Availability problems and costs are the major problems associated with MRI as a screening method [24].

The ideal screening interval is not known, but an interval of 6–12 months has been proposed. The recommended screening interval of 6 months is mainly based on the speed of tumour growth; however, data are limited [24]. Survival time was not different in patients with cirrhosis screened at 6- or 12-monthly intervals [27].

Treatment and prognosis

Resection is the first option for a single tumour in a noncirrhotic liver, which is applicable in most cases of early HCC in patients with AIP. These patients will tolerate major resections with low morbidity because the risk of liver failure is low.

The 5-year survival rate for treatment of small tumours (stage A in the Barcelona Clinic Liver Cancer (BCLC) staging system) is 50–75%, using resection, ablation or liver transplantation [24]. Five-year survival rates after resection in a large Japanese series for HCC ≤2 cm, 2–5 cm and >5 cm were 66%, 52% and 37%, respectively [28]. Calculations of prognosis (i.e. 5-year survival rates) are mainly made in patients with HCC with cirrhosis, as noncirrhotic liver is present in only 5% of HCC in Western countries. However, the favourable outcomes from early detection of HCC

are hampered by a high incidence of recurrence: tumour recurrence complicates 70% of cases at 5 years [4]. The recurrence rate is lower after liver transplantation. In *AIP* gene carriers with HCC, liver transplantation should be considered because it is also is a cure for AIP *per se* [29, 30].

Screening recommendations

The objective of HCC screening is to decrease mortality from the disease. Before entering a patient into a screening programme, the relative risk of HCC must be considered. The relative risk is related to the incidence of HCC. Furthermore, screening should also increase life expectancy; thus, treatment results and the extremely poor prognosis for untreated cases must be considered. In patients with AIP with HCC and small tumours – usually well-differentiated HCC in noncirrhotic liver with normal function – the expected prognosis might be good.

Surveillance is currently recommended for patients at high risk of HCC; that is, certain groups of HBV/HCV carriers and those with alcoholic cirrhosis, haemochromatosis or primary biliary cirrhosis accompanied by cirrhosis. The recommendations are based on annual incidence; for example, surveillance is recommended for Asian men with hepatitis B from age 40 onward because the annual incidence in this group exceeds 0.2% [5]. AIP should be added to the list of risk factors as the reported annual incidence was 0.16–0.9% in the French, Swiss and Swedish studies, the relative risk of HCC was high, and the prognosis for nonscreened patients was poor. *AIP* gene carriers aged >50 years fulfil the Wilson and Jungner ethical principles and practice of screening for disease.

We recommend annual ultrasound screening for HCC in *AIP* gene carriers from the age of 50 and as long as therapeutic options are applicable with regard to concomitant disease and age.

Conflict of interest statement

We declare that we have no conflict of interests.

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Ethical considerations

The study was approved by the Research Ethics Committee, University of Umeå, Sweden.

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