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ORIGINAL ARTICLE

High risk of primary liver cancer in a cohort of 179 patients with Acute Hepatic Porphyria

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Abstract
Background/aims Previous studies have indicated a high risk of hepatocellular carcinoma in acute hepatic porphyrias. In this retrospective study we present the incidence of primary liver cancer and clinical characteristics in a cohort of 179 acute porphyria patients above the age of 50 years.
Methods Twenty-three cases with primary liver cancer were found either by a surveillance program or due to clinical suspicion. Standardized rate ratio was used to estimate the relative risk of primary liver cancer after indirect standardization. Survival data were calculated using the Kaplan-Meier method.
Results The mean age at diagnosis was 69 years. Hepatocellular carcinoma was found in 19 patients while four patients had cholangiocarcinoma or a combination of the two. Four patients had underlying cirrhosis. Mean tumour size was 4.3 cm in the surveillance group and 10.3 cm in the non-surveillance group (p=0.01). The overall relative risk of primary liver cancer was 86 above the age of 50: 150 for women and 37 for men. Mean survival time was 5.7 years.
Conclusion Acute hepatic porphyria carries a high risk of primary liver cancer above the age of 50 which warrants ultrasound surveillance. Sex distribution and frequency of cirrhosis differs from more common aetiologies of primary liver cancer.

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Introduction

A prospective study from the northern part of Sweden (Innala and Andersson 2011) recently showed that screening for hepatocellular cancer (HCC) in acute porphyria patients enables early diagnosis and a choice of potentially curative treatments with improved diagnosis. Other retrospective studies from Sweden and Finland (Hardell et al 1984; Lithner and Wetterberg 1984; Bengtsson and Hardell 1986; Kauppinen and Mustajoki 1988; Andersson et al 1996; Bjersing et al 1996) have shown a 60–110-fold increased relative risk of primary liver cancer (PLC) in patients with acute hepatic porphyria (AHP). A prospective French study (Andant et al 2000) found a 36-fold increase compared to age and sex matched controls. The contribution of factors such as cirrhosis or viral hepatitis has been found negligible. Despite these and several other less extensive reports, the increased risk of PLC in patients with AHP is seldom considered in comprehensive overviews on liver cancer. This association between AHP and PLC deserves more attention and AHP should be considered a risk factor of PLC together with other rare inherited metabolic disorders.

The prevalence for the three autosomal dominant acute porphyrias in Sweden varies. Acute intermittent porphyria (AIP) is the most common with a prevalence of 1:10 000 (Anderson et al 2001; Floderus et al 2002) while the prevalence for variegate

porphyria (VP) and hereditary coproporphyria (HCP) is 1:100 000 and 1:200 000 respectively (Wiman 2003). These porphyrias have low clinical penetrance and symptoms are generally triggered by endogenous or exogenous agents. Clinically, AHP is characterized by acute potentially life-threatening, attacks of neurovisceral symptoms. During acute attacks, the presumably toxic heme precursors, 5-aminolevulinic acid (ALA) and porphobilinogen (PBG), accumulate and are excreted in high concentrations in urine. Treatment measures are mainly aimed to suppress the initial enzyme in the hepatic heme biosynthetic pathway (Harper and Wahlin 2007). HCP and VP are a mixed form of porphyrias, as accumulation of coproporphyrinogen and protoporphyrinogen can also provoke erosive photodermatosis.

Recent reports on curative liver transplantation have confirmed the dominant role of the liver in the pathophysiology of AHP symptoms (Soonawalla et al 2004; Stojeba et al 2004; Seth et al 2007; Wahlin et al 2010). Late complications associated with AHP are hypertension, renal impairment, chronic peripheral neuropathy and hepatocellular carcinoma (HCC) (Anderson et al 2001). These complications are more commonly found among patients with chronic high excretion of PBG and ALA and/or recurrent acute attacks, than in latent carriers (Kauppinen and Mustajoki 1992; Kauppinen and von und zu Fraunberg 2002).

A surveillance program aiming to detect PLC in patients with AHP, including all patients above 50–55 years, was started at the Porphyria out-patient clinic at the Stockholm South Hospital in 1987 as a consequence of the reports from northern Sweden (Hardell et al 1984; Lithner and Wetterberg 1984). The present retrospective study summarizes the accumulated experience of PLC diagnosed in AHP within and outside the surveillance program 1987–2009. The patients have not been included in previous reports and they were all assessed by the same physicians (DA and ES).

The study was approved by the ethical review board, Stockholm.

Patients and methods

The AHP cohort consists of 179 patients above the age of 50; 111 women and 68 men. One hundred and fifty-eight have AIP, 12 PV, and 9 HCP. In this cohort, 23 patients have been diagnosed with PLC. Twelve patients were detected by annual radiology surveillance and five patients were referred to our clinic due to suspected relapse of acute porphyria symptoms and were diagnosed with PLC during further investigation (Table 1). Six patients (3, 12, 13, 15, 16 and 20) were referred after PLC had been diagnosed outside our clinic. The porphyria analyses were performed at the Porphyria Centre Sweden.

The surveillance program includes annual clinical examination, liver function tests, urinary excretion of porphyrin precursors and radiological examination of the liver by either ultrasound or computed tomography. Serum alpha-fetoprotein (AFP) was analysed upon PLC diagnosis. Standard work up was done to exclude concurrent liver diseases.

Tumour and adjacent liver tissue was re-examined by the same experienced liver pathologist (MB) for histopathological diagnosis when tissue was available after biopsy or tumour resection (Table 1). The specimens were Sirius stained to grade fibrosis and with haematoxylin and eosin for histological diagnosis. Fibrosis was evaluated in all cases where the tumour adjacent material was enough for grading, i.e. above 10 portal zones. Cholangiocarcinoma was classified by immunohistochemistry including cytokeratin 7. Applied tumour treatments are specified in Table 1.

Statistical analysis

The number of AHP patient years was calculated from the respective 50th birthday until April 2010 or the date of PLC diagnosis. The cancer register at the Swedish National Board of Health and Welfare provided reference population, including national age- and sex specific incidence rates. The annual Swedish PLC incidence in 2008 was 2.8 and 5.0 cases per 100 000 in women and men respectively. Over the age of 45 the annual PLC incidence in the Stockholm area was 6.2 and 11.6 cases per 100 000 in women and men respectively.

The expected number of PLC in the porphyria cohort was calculated by multiplying the incidence of PLC over the age of 45 in Stockholm by the number of patient years in the cohort.

The ratio of the observed to the expected number was used as a measure of relative risk. The crude incidence of PLC in the cohort was calculated by dividing the number of incident PLC cases observed during the study period by the number of patient years in the cohort. Survival data were calculated using the Kaplan-Meier method. Statistical analyses and graphics were performed with Microsoft Excel® software with the XLSTAT statistical software add-in. The method used for each statistical calculation is stated and p values lower than 0.05 were considered statistically significant.

Results

The 23 patients with PLC were diagnosed during two decades (Table 1). Twenty patients had AIP, two had VP and one HCP. The overall mean age at diagnosis was 68.8 years: 69.5 years (range 56–82) for 18 women and 66.2 years (range 53–75) for five men. The mean age at diagnosis was 71.3 years (range 60–82) among the 12 patients in whom the liver tumour was detected via annual surveillance

Table 1 Patient and tumour characteristics of the 23 patients with acute hepatic porphyria and primary liver cancer

Patient nr Sex	Kind of Porphyria[a] (mutation) disease activity[b]	Age at porphyria diagnosis/ age at PLC diagnosis (year)	Urinary excretion of heme precursors at PLC diagnosis (mmol/mol creatinine)		Mode of diagnosis[c]	Tumour burden (cm)	Tumour histopathology[d]	Fibrosis[e]	Treatment[f]	Survival (years)
			PBG (ref <1.2)	ALA (ref <3.1)						
1 / Female	AIP (826-2a→g) (+)	32 / 77 (2009)	3.0	3.2	Surveillance US	5	No biopsy	No biopsy	TACE	Alive (0.4)
2 / Male	AIP (499-1 g→a) (+++)	36 / 74 (2008)	35.3	13.0	Surveillance US	4	HCC; well differentiated	II	Resection	Alive (1.8)
3 / Female	VP (Mutation unidentified) (+++. cutaneous)	76 / 76 (2007)	0.7	3.9	US	13	No biopsy	No biopsy	Systemic	† (1.5)
4 / Female	AIP (345-2a→g) (+)	31 / 81 (2007)	4.2	3.0	Surveillance US	5	HCC; well differentiated	I	Resection	Alive (2.8)
5 / Female	AIP (W198X) (++)	30 / 62 (2007)	5.7	4.4	Surveillance US	3	Combined HCC –CC	II	Resection	Alive (2.8)
6 / Female	AIP (R173W) (++)	31 / 82 (2006)	9.6	7.6	Surveillance US	4	No biopsy	No biopsy	None	† (3.6)
7[i] / Female	AIP (W198X) (+++)	28 / 74 (2006)	27.1	14.4	Surveillance US	7.5	No biopsy	No biopsy	TACE	Alive (4.1)
8 / Female	AIP (499-1 g→a) (+)	22 / 65 (2006)	2.8	3.3	Surveillance US	4.5	CC	I	RT	† (3.4)
9 / Male	AIP (88-2a→g) (+)	15 / 75 (2006)	9.1	5.6	Surveillance CT	4	HCC; well differentiated	IV	RFA	† (3.5) Tumor relapse after 0.7 year
10 / Male	AIP (W198X) (+++)	53 / 68 (2005)	32.3	25.7	Surveillance US	5	CC	Not graded	Systemic	† (1.6)
11 / Female	HCP (R328C) (+)	38 / 56 (2004)	0.4	1.9	US	2	HCC; well differentiated	Cytodiagnosis	RT	† (6.2)
12[g,i]/ Female	AIP (W198X) (+)	23 / 64 (2004)	1.8	1.1	CT	6	HCC; poorly differentiated Nuclear pleomorphism	IV	Resection	Alive (5.9)
13 / Female	AIP (W198X) (+)	28 / 71 (2003)	nd	nd	CT	4	CC	Not graded	RT	† (2.2)
14 / Female	AIP (499-1 g→a) (+)	24 / 67 (2003)	0.8	1.4	Surveillance CT	3.5	HCC; moderately differentiated Clear cell	IV	Resection	Alive (7.0)
15 / Female	AIP (W198X) (+++)	64 / 65 (2001)	27.1	13.7	CT	7	HCC; well differentiated	II	RFA PEIT Systemic	† (0.8)
16 / Female	VP (1291+2insT) (+. cutaneous)	71 / 71 (2000)	1.0	2.9	US	Size and location nd	No biopsy	No biopsy	None	† (0.6)
17[i] / Female	AIP (W198X) (+)	61 / 76 (1999)	4.5	3.2	CT	7	HCC; moderately differentiated	I	Resection	† (5.4)
18[g] / Male	AIP (499-1 g→a) (+)	46 / 60 (1999)	1.8	2.9	Surveillance CT	2	HCC; moderately differentiated Pseudo glandular	II	RT	† (6.4) Tumor relapse after 6.3 years
19 / Female	AIP (207ΔT) (++)	33 / 60 (1997)	7.3	4.6	Surveillance US	size and location nd	HCC; well differentiated	Not graded	Resection	Alive (12.5)
20 / Female	AIP (499-1 g→a) (+++)	30 / 76 (1996)	63.0	6.5	US	17	HCC; moderately differentiated Acinar pattern	Not graded	Systemic	† (0.8)
21[h]/ Female	AIP (W198X) (+++)	27 / 62 (1995)	11.9	7.8	US	15	HCC; well differentiated	II	Resection RT	† (6.9) Tumor relapse after 6.3 years
22 / Female	AIP (R116W) (+++)	26 / 56 (1988)	61.6	39.7	US	19		II		

Table 1 (continued)

Patient nr Sex	Kind of Porphyria[a] (mutation) disease activity[b]	Age at porphyria diagnosis/ age at PLC diagnosis (year)	Urinary excretion of heme precursors at PLC diagnosis (mmol/mol creatinine)		Mode of diagnosis[c]	Tumour burden (cm)	Tumour histopathology[d]	Fibrosis[e]	Treatment[f]	Survival (years)
			PBG (ref <1.2)	ALA (ref <3.1)						
							HCC; poorly differentiated Nuclear pleomorphism		Resection RT and systemic	† (13.3) Tumor relapse after 8.4 years
23 / Male	AIP (W198X) (+++)	23 / 53 (1987)	118.1	61.1	US	13	HCC; moderately differentiated Acinar pattern	IV	None	† (0.3)

[a] Kind of porphyria: AIP: acute intermittent porphyria. HCP: hereditary coproporphyria. VP: variegate porphyria. Within bracklets: mutation type

[b] Disease activity:

(+) no history of acute porphyria symptoms and slightly increased urinary excretion of heme precursors

(++) sporadic episodes of acute porphyria symptoms and chronic increased urinary excretion of heme precursors during several years after diagnosis

(+++) patients in which the PLC was diagnosed in relation to acute porphyria symptoms and/or increased urinary excretion of heme precursors

[c] US: ultrasound examination

CT: computed tomography

[d] HCC hepatocellular carcinoma

cHCC-CC: combined hepatocellular-cholangiocarcinoma

CC: Cholangiocarcinoma

[e] According Batts and Ludwig

[f] TACE: transarterial chemoembolization

RT: Radiotherapy

RFA: Radiofrequency ablation

PEIT: Percutaneous ethanol injection therapy

[g] Positive alfa-fetoprotein at diagnosis

[h] See Fig. 1a-d

[i] Elevated liver function test at PLC diagnosis

nd: no data

program, while the mean age among the patients diagnosed outside the surveillance program was 66.0 years (range 53–76). The difference in age between the groups was not statistically significant (p=0.207, Mann–Whitney).

The statistical analysis in our AHP cohort (Table 2) shows a crude incidence of PLC of 0.74 %, higher for women (0.93 %) than for men (0.43 %). The relative risk of PLC for the whole cohort, expressed as standardized rate ratio, was 86 (95 % CI: 39–187); 150 (95 % CI: 60–372) for women and 37 (95 % CI: 13–105) for men. The gender difference was not statistically significant (p=0.085, Chi-square test).

In the surveillance group the relative risk, expressed as standardized rate ratio was 111 (95 % CI: 46–266); 181 (95 % CI: 63–517) for women and 64 (95 % CI: 20–198) for men. In the non-surveillance group, the corresponding risk was 69 (95 % CI: 28–167); 131 (95 % CI: 48–358) for women and 14 (95 % CI: 2–105) for men. The differences between these groups (surveillance vs non-surveillance) were not statistically significant (p=0.286, Chi-square).

The size and histopathological details of the tumours are listed in Table 1. Seven patients had well differentiated and two had moderately differentiated HCC. Three patients had an acinar/pseudoglandular pattern and two had pleomorphic growth pattern. Three patients had cholangiocarcinoma (CC), and one had combined HCC and CC with sarcomatous transformation. Four patients were diagnosed by standard radiological criteria (Bruix and Sherman 2005) without biopsy, and one declined further evaluation. In 13 of the 18 patients that underwent biopsy there was adjacent liver tissue to examine the grade of fibrosis, and only four patients had cirrhosis (Table 1). Steatohepatitis was not detected in any of the patients examined by ultrasound.

Nine patients were treated by surgical resection. Six patients were treated with radiotherapy, five by systemic chemotherapy, two by radiofrequency ablation, two by transarterial chemoemobolization and one by percutaneous ethanol injection treatment. None of the patients in this study was considered for liver transplantation due to the current experience in Sweden at the time PLC was diagnosed (Wahlin et al 2010).

The urinary excretion of PBG and ALA at diagnosis of PLC is shown in Table 1. Eight patients presented with very high concentration of urinary porphyrin precursors (Table 1, (+++)), approximately 40 times (range 10–98) the upper normal limit for PBG and 8 times (range 2–20) for ALA. This group consists mainly of patients with the largest tumour burden. Among these, three patients presented with acute porphyria symptoms, case 7, 21 and 22, Table 1, Fig. 1a-c. The remaining 15 patients had stable urinary excretion of PBG and ALA compared to previous controls, e.g. case 10 (Table 1, Fig. 1d) and had no porphyria related symptoms.

Survival data for the surveillance and non-surveillance groups are shown in Fig. 2. The mean survival time in the surveillance group was 4.8 years (95 % CI: 3.5–6.1) and in the non-surveillance group 4.2 years (95 % CI: 1.5–6.9), (p =0.153, Log-rank test). The longest survival times (12.5 and 13.3 years) were noted for two patients in whom the tumour was surgically removed.

The mean tumour diameter was smaller in the surveillance group, 4.3 cm (2–7.5) than in the non-surveillance group 10.3 cm (2–19), (p=0.01 Mann–Whitney). One patient with CC had pulmonary metastases at the time of PLC diagnosis.

Table 2 Actual and expected incidence of primary liver cancer together with calculated risk ratios in the studied cohort of 179 acute hepatic porphyria patients above 50 years of age.

	Number of patients	Patient-years	Number of PLC cases	Expected number of PLC cases[a]	Relative risk of PLC (standardized rate ratio[b])
Total	179	3111.0	23	0.27	86 (39–187)
Women	111	1940.1	18	0.12	150 (60–372)
Men	68	1170.9	5	0.14	37 (13–105)
Surveillance group	75	1252.7	12	0.11	111 (46–266)
Women	44	712.1	8	0.04	181 (63–517)
Men	31	540.6	4	0.06	64 (20–198)
Non-surveillance group	104	1858.3	11	0.16	69 (28–167)
Women	67	1228.0	10	0.08	131 (48–358)
Men	37	630.3	1	0.07	14 (2–105)

Crude incidence rate of PLC in AHP cohort>50 years: Women 928; Men 427. Overall 739

[a] The expected number of cases is standardized among the reference population according to age and sex.

[b] Standardized rate ratio is the observed number of PLC divided by the expected number of PLC

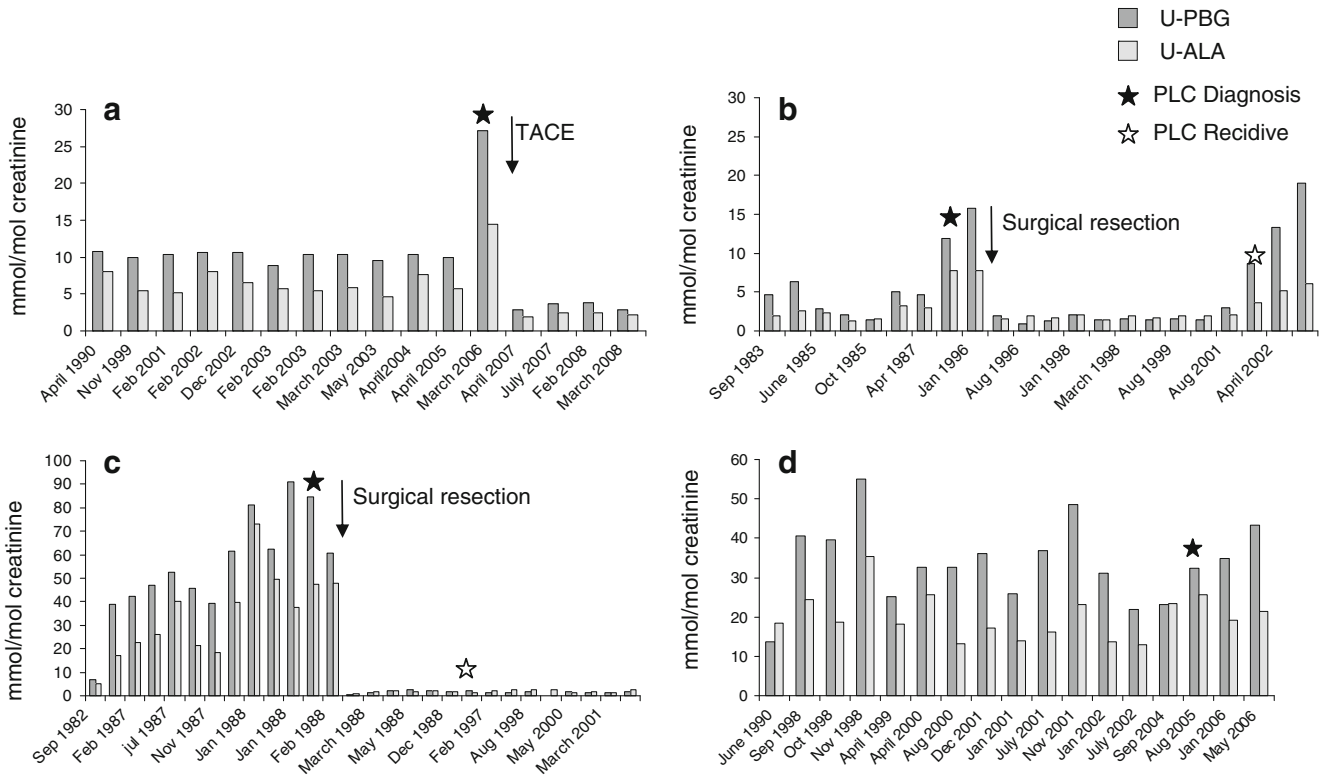

Fig. 1 (**a-d**) Urinary excretion pattern of porphyrin precursors in relation to PLC diagnosis and treatment. Reference values: U-PBG <1.2 mmol/mol creatinine; U-ALA < 3.1 mmol/mol creatinine. (**a**) Patient 7: Two years prior to PLC diagnosis a biopsy was performed of a 14 mm structure in the right liver lobe with inconclusive histopathological findings. One year later, ultrasound was conclusive with hemanginoma. The next year a HCC tumour was diagnosed in her right liver lobe. The urinary excretion of PBG and ALA was at this time importantly increased and normalized after treatment. (**b**) Patient 21: HCC diagnosis was accompanied by increased excretion of PBG and ALA and the precursors normalized after surgical resection. Seven years later, a relapse of HCC was confirmed with concomitant increase of urinary PBG and ALA. (**c**) Patient 22: HCC was diagnosed due to acute porphyria symptoms, with importantly increased urinary PBG and ALA. After 80 % surgical resection of her liver urinary excretion pattern normalized. She relapsed with pulmonary metastasis 8 years later and 2 years later HCC, which was not associated with porphyria symptoms or increased urinary PBG and ALA. (**d**) Patient 10: The patient had presented for many years with increased urinary PBG and ALA and no concomitant acute porphyria symptoms. The urinary excretion pattern remained unchanged at CC diagnosis and during treatment

Discussion

In this study we report 23 acute hepatic porphyria patients that were diagnosed with primary liver cancer during two decades, in a regional cohort of 179 patients above the age of 50 years. The annual risk for PLC in AHP was 0.74 % and the numbers needed to screen to find one case of PLC in AHP gene carriers over 50 years was 135 in our study. The overall relative risk of PLC, expressed as standardized rate ratio was 86. The results from this study are in accordance with the recent Swedish study (Innala and Andersson 2011) and reinforces previous reports (Kauppinen and Mustajoki 1988; Andersson et al 1996; Andant et al 2000) which indicate a high risk to develop PLC in AHP.

The mean age of PLC diagnosis was 68.8 which is consistent with previous Swedish and Finnish reports (Kauppinen and Mustajoki 1988; Andersson et al 1996; Innala and Andersson 2011). In the French report, the patients were considerably younger and the youngest only 37 years (Andant et al 2000). Among the 12 patients diagnosed within the annual surveillance program, the mean age of diagnosis was somewhat higher than among those diagnosed outside the program and the latter had an apparently lower risk to develop PLC; however these differences were not statistically confirmed

We found a statistically non-significant 121 % increased risk for PLC in women compared to men (p= 0.08, Chi square test). Previous Swedish, Finnish and French reports have shown a slight female dominance with an average ratio of women to men 1.2:1 (Kauppinen and Mustajoki 1988; Andersson et al 1996; Andant et al 2000; Innala and Andersson 2011).

A male dominance is present in the global incidence of HCC. Rates are typically 2–4 times higher in men than in women (Bosch et al 2004).

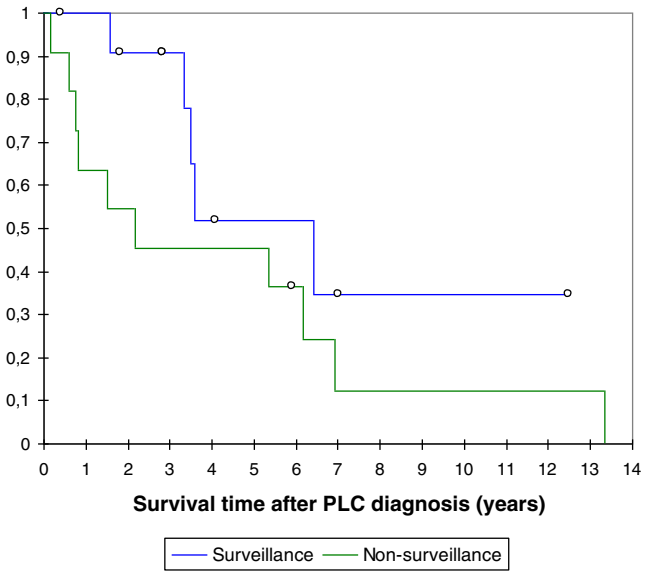

Fig. 2 Survival distribution function for the surveillance and non-surveillance groups. The mean survival time in the surveillance group was 4.8 years (95 % CI: 3.5–6.1) and in the non-surveillance group 4.2 years (95 % CI: 1.5–6.9), (p=0.153, Log-rank test)

Thus it might be concluded that the development of PLC in AHP is not related to gender but to the acute porphyria carrier condition and to age.

In our PLC group, 83 % had HCC and 17 % had CC or combined HCC-CC, while previous reports have found only HCC (Kauppinen and Mustajoki 1988; Andersson et al 1996; Bjersing et al 1996; Andant et al 2000; Innala and Andersson 2011). Whether this reflects similar pathogenetic mechanisms truly related to AHP or rather a random finding is unclear. In a Swedish paper from 1973 (Lindstedt et al 1973), to our knowledge is the first case of PLC described in AHP, the tumour and adjacent liver histopathology, investigated at autopsy described the presence of hepatocellular carcinoma combined with cholangiocarcinoma, without signs of cirrhosis in an 84 year old female with AHP. This case together with the four presented in the present study may point to a true pathogenic mechanism rather than a random finding.

As shown in Table 1, cirrhosis was found in 31 % of our assessable PLC cases, consistent with 24 % of the assessable cases in the study from Innala (Innala and Andersson 2011) and 28 % in the French study (Andant et al 2000). Since not all cases were eligible for evaluation the occurrence of fibrosis and/or cirrhosis may be underestimated in the Swedish studies. In older studies from northern Sweden (Andersson et al 1996; Bjersing et al 1996) the incidence of cirrhosis seems to be higher, but this is difficult to establish since a minority of the cases were histopathologically examined. Whether the degree of fibrosis represents a hepatotoxic effect of the porphyria condition or reflects the fact that the mean age at PLC diagnosis was nearly 70 years is difficult to answer. Theoretically, fibrosis/cirrhosis could add to the porphyrogenic risk of developing PLC in acute porphyria patients. There are few reports of biopsies performed in AHP patients without PLC. One report from 1983 including 12 AIP patients investigated by biopsy showed diverse morphologic abnormalities but no specific data of fibrosis and/or cirrhosis (Ostrowski et al 1983). Globally, HCC is associated with liver cirrhosis in 80–90 % of cases in most countries (Leong and Leong 2005). Other factors globally considered major risk factors for HCC such as viral hepatits or excessive alcohol consumption (i.e. more than 100 g weekly), were excluded in our cohort.

In our study two of the 19 HCC patients (10.5 %) had elevated serum AFP levels both below 200 ng/ml (Table 1). Treatment normalized AFP levels in both cases. Only three patients (case 7, 12 and 17) had elevated liver function tests at the time of PLC diagnosis (Table 1) but had normal levels during surveillance.

The mechanisms of carcinogenesis in AHP are still unclear but might be found in the porphyric condition. The founder mutation *W198X* is found in about 60 % of the AIP patients in the national Swedish cohort (Floderus et al 2002; Thunell et al 2006), and was the most common in previous reports from northern Sweden (Hardell et al 1984; Lithner and Wetterberg 1984; Bengtsson and Hardell 1986; Andersson et al 1996; Bjersing et al 1996; Innala and Andersson 2011). This mutation was found among 39 % of the present PLC cases, and the rest carried other AIP mutations (Table 1). Five patients have the 499-1 g->a mutation (Floderus et al 2002). It is not known whether the patients are related but there is one couple of siblings among them (cases 14 and 18, Table 1). The other mutations i.e. 345-2a->g, 88-2a->g, 207ΔT, R116W and R173W present each in one case. Three of these mutations have been reported from Sweden and two from other countries as well (Floderus et al 2002). Two patients had other forms of acute porphyria, hereditary coproporhyria and variegate porphyria, which is also reported from other studies (Kauppinen and Mustajoki 1988; Andant et al 2000; Schneider-Yin et al 2010). Thus, neither this nor other studies have found a clear correlation to a specific AIP related genotype, but it seems to be associated to the AHP gene carrier condition. Factors promoting the production of reactive oxygen species, such as heme deficiency or ALA that can cause oxidative stress, which provides a procarcinogenic microenvironment that mediates cellular and DNA damage, have been hypothesized (Batlle 1993; Thunell et al 1995; Onuki et al 2002) to be of pathogenetic importance.

Among the patients presented in this study, all had had periods of porphyria related symptoms and/or increased urinary excretion of PBG and ALA. In the patient cohort reported by Andant et al 2000 (Andant et al 2000), all seven patients with PLC had higher levels of urinary PBG and ALA compared to those not diagnosed with HCC. In the recent report by Innala et al (Innala and Andersson 2011) 16 of 22 cases were classified as manifest AIP (i.e. acute attacks had occurred during patient's

lifetime). Among the patients presented in our study, all had had periods of porphyria related symptoms and/or increased urinary excretion of PBG and ALA. At the time of PLC diagnosis, eight of our patients presented with very high urinary excretion of PBG and ALA and three of these had concomitant acute porphyria symptoms. The development of PLC coincided with a relapse of the porphyric condition in six patients (case 7, 15, 20, 21, 22 and 23, Table 1). The remaining patients presented without acute porphyria symptoms and had stable urinary excretion of PBG and ALA. Of importance is the fact that both Swedish reports (present and (Innala and Andersson 2011)) and in the French study (Andant et al 2000) the majority of AHP patients had increased urinary excretion of PBG and ALA at the time of PLC diagnosis. In our cohort the most relevant observation is that most, if not all cases, had increased excretion of PBG and ALA in urine. Although there is no clear pattern in urinary excretion of porphyrin precursors correlating to PLC diagnosis, high excretion of precursors in elderly AHP patients, or clinical symptoms of porphyria is a warning sign and these individuals should probably have shorter surveillance interval. In three of the patients treated with TACE or surgical resection, the treatment resulted in a regress of clinical and biochemical signs of porphyria (Fig. 1a-c), suggesting that porphyria symptoms may have been triggered by the hepatic tumours.

The primary objective of tumour surveillance in AHP is ultimately to decrease mortality. The prospective study from Innala (Innala and Andersson 2011) showed an improved 3-year survival ($p=0.004$) in the surveillance group compared to the not surveilled cases. In our study the mean tumour diameter was significantly smaller in the surveillance group (4.3 versus 10.3 cm, $p<0.01$). Although the size of the tumours at diagnosis in our study was in the same range as the surveilled group by Innala (Innala and Andersson 2011) we did not find a statistically significant survival advantage compared to the non-surveillance group ($p=0.153$, Fig. 2). Still, these findings and the 0.74 % annual risk of PLC warrants radiological surveillance in AHP above the age of 50.

Another objective of surveillance is early tumour diagnosis. Ideally, tumours are detected before the diameter exceeds 2–3 cm as the smaller tumour is an advantage for the application of potentially curative treatments in the surveillance group (Table 1). Whether annual or biannual surveillance should be recommended is unclear. No data is available on tumour growth rate in this or the previous studies but annual surveillance in our cohort detected tumours with a mean diameter of 4.3 cm. This suggests that a surveillance interval of 6–9 months is more appropriate. AFP adds little value to radiological surveillance.

In conclusion this and previous reports demonstrate a high incidence of PLC in AHP, primarily HCC. AHP seems to differ from the globally more common aetiologies in a number of ways, such as gender distribution, a low frequency of concurrent cirrhosis and, most likely, different pathogenetic mechanisms. No clear correlation to genotype or phenotype has been demonstrated even if high excretion of porphyrin metabolites seems to be more common among cancer cases. The porphyria specific risk factors and possible preventive strategies remain unclear. Accumulated data supports tumour surveillance in AHP above the age of 50 (Deybach and Puy 2011). The prognosis of untreated HCC is poor (Bruix and Sherman 2005). Early diagnosis combined with the wide range of therapeutic options available, most probably will improve the outcome.

The surveillance program has so far not proved a clear advantage in this patient group but the quality of the applied radiological tools have importantly improved during these last years. In the future surveillance will prove to be of same relevance in AHP as for other groups at risk to develop PLC, i.e. cirrhosis and HCV. PLC in AHP may be a global problem, but mainly reported from centres with well established routine for longstanding surveillance programs.

Conflict of interest None.

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