

Porphyrias in Norway

BACKGROUND Porphyria is an umbrella term for a group of largely hereditary diseases that are due to defective haem synthesis. The diseases have a varied and partly overlapping range of symptoms and presentations. The commonest forms of porphyria are porphyria cutanea tarda, acute intermittent porphyria and erythropoietic protoporphyria. The purpose of this study was to provide an overview of the prevalence and pathological manifestations of porphyrias in Norway.

MATERIAL AND METHOD Information on all patients registered with the Norwegian Porphyria Centre (NAPOS) up to 2012 was used to estimate the prevalence and incidence of porphyrias in Norway. Figures on symptoms, precipitating factors and follow-up routines were obtained from the Norwegian Porphyria Registry, which includes 70 % of Norwegians registered with NAPOS as having porphyria.

RESULTS The prevalence of porphyria cutanea tarda was approximately 10:100 000 and that of acute intermittent porphyria approximately 4:100 000. The total incidence of all porphyrias was approximately 0.5–1:100 000 per year. Diagnostic delay, i.e. the time passing between the onset of symptoms and diagnosis, varied from 1–17 years depending on the type of porphyria. There was wide variation in the frequency with which patients with the various types of porphyria went for medical check-ups.

INTERPRETATION The prevalence of acute intermittent porphyria and porphyria cutanea tarda appears to be higher in Norway than in most other countries. Data from the Norwegian Porphyria Registry make it possible to demonstrate differences in treatment and follow-up of porphyria patients and may be used to initiate necessary measures.

Porphyria is an umbrella term for a group of rare, largely hereditary diseases that are due to abnormal activity in the various enzymes involved in haem synthesis (1). The diagnosis in symptomatic patients is based on identification of characteristic haem precursor patterns in urine, faeces and blood. However, the symptoms and biochemical findings associated with some of the diseases overlap, which makes correct diagnosis challenging.

Some of the porphyrias present with potentially life-threatening, acute attacks characterised by severe abdominal pain and neurological and mental symptoms, while others with cutaneous symptoms in the form of vesicles and fragile skin or acute painful photosensitivity (Table 1). Two of the diseases can cause both acute attacks and cutaneous symptoms. Most porphyrias have low clinical penetrance (2). The two most commonly occurring porphyrias, porphyria cutanea tarda and acute intermittent porphyria, are inherited in an autosomal dominant fashion. Porphyria cutanea tarda also occurs as a sporadic, non-hereditary form (3).

Healthcare professionals' knowledge and experience of rare diagnoses like porphyrias will often be limited. Acute porphyrias in particular are differential diagnoses of other, far more frequently occurring diagnoses, such as appendicitis and various neurological diseases. Patients may therefore experience a long work-up before they are correctly dia-

gnosed. Early, correct diagnosis is particularly important in acute porphyrias, because guidance on safe and unsafe drugs and lifestyle can help to avert acute attacks both in those who have suffered attacks previously and in genetically predisposed individuals who have not developed symptoms (4–6).

The subject of acute porphyrias has been addressed previously in *Tidsskriftet* (7, 8), but as with many other rare diseases, there are few systematic studies based on large cohorts. The aim of this study was to use information about people with porphyrias registered with the Norwegian Porphyria Centre (NAPOS) and data from the Norwegian Porphyria Registry to provide an overview of porphyrias in Norway, focusing on incidence, prevalence, time from onset of symptoms to diagnosis, follow-up routines and quality of life.

Material and method

NAPOS has the overall responsibility for diagnosing porphyrias, and diagnoses almost all cases in Norway. When the centre was established in 1999, other laboratories that performed porphyria diagnostics were contacted, and information was obtained about patients who had been diagnosed at these laboratories.

Data such as gender, age, place of residence and diagnosis for all people registered with NAPOS up to 2012 were used to estimate the prevalence and incidence of the

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MAIN POINTS

Porphyrias are rare; about 40–60 new cases are diagnosed in Norway each year.

The time from symptom onset to diagnosis varies from one to 17 years, depending on the type of porphyria.

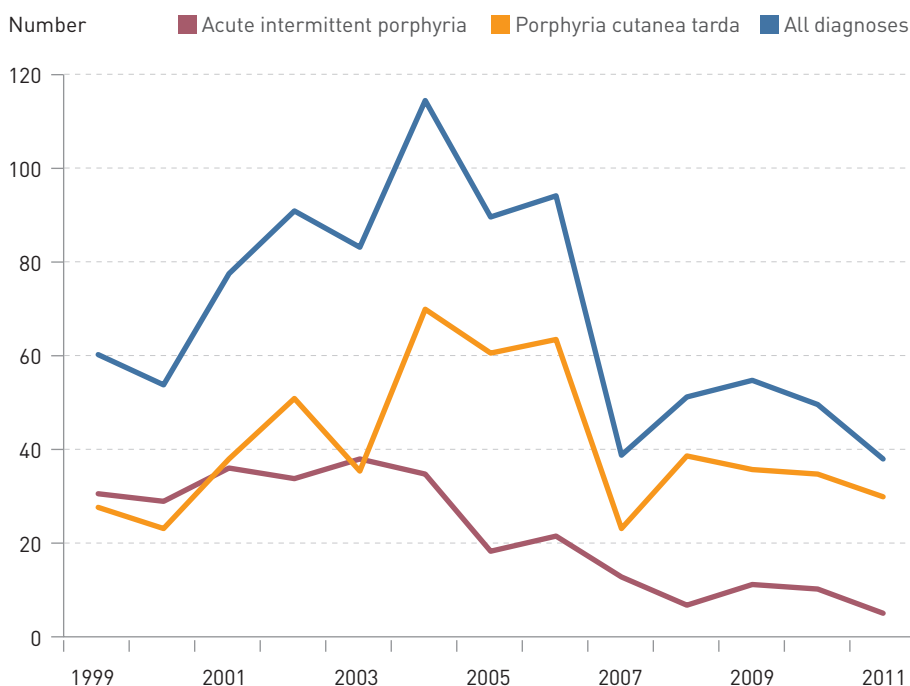
The Norwegian Porphyria Registry makes it possible to monitor trends in the diagnosis, management and treatment of this patient group.

Table 1 Overview of symptoms, inheritance and prevalence of porphyrias with 10 or more registered cases at the Norwegian Porphyria Centre (NAPOS) up to 2012

Diagnosis	Symptoms	Inheritance	Number of persons
Acute porphyrias			
Acute intermittent porphyria	Acute attacks	Autosomal dominant	326
	Symptomatic ¹		189
	Predictively identified ²		137
Hereditary coproporphyria	Acute attacks and/or photosensitivity in the form of skin fragility and blisters	Autosomal dominant	10
Variegata porphyria	Acute attacks and/or photosensitivity in the form of fragile skin and blisters	Autosomal dominant	30
Cutaneous porphyrias			
Porphyria cutanea tarda	Photosensitivity in the form of fragile skin and blisters	Autosomal dominant/ sporadic	576
	Symptomatic ¹		509
	Predictively identified ²		67
Erythropoietic protoporphyria	Acute painful photosensitivity	Autosomal recessive	32
Total			974

¹ Has or has had symptoms of his/her porphyria

² Never-symptomatic patients identified as being genetically predisposed for porphyrias

**Figure 2** Number of new diagnoses per year at the Norwegian Porphyria Centre (NAPOS) in the period 1999–2011 ($n = 896$). «All diagnoses» covers acute intermittent porphyria, porphyria cutanea tarda, variegata porphyria, hereditary coproporphyria and erythropoietic protoporphyria

different porphyrias. The diagnoses were established on the basis of diagnostic algorithms as described by Badminton et al. (4). Porphyria-related biochemical analyses were performed at the Laboratory of Clinical Biochemistry, Haukeland University Hospital, and DNA analyses were performed at the hospital's Centre for Medical Genetics and Molecular Medicine.

A distinction is made in the article between symptomatic and predictively identified porphyrias. The term «symptomatic» is used when a person has or has had symptoms of porphyria. «Predictively identified» is used when a person has been found to be genetically predisposed to porphyria, but without having had symptoms.

Information about the last place of residence registered (as of November 2011) was obtained from the Norwegian National Population Registry and population figures (as of October 2011) from Statistics Norway. Deceased subjects are not included in the prevalence figures quoted.

The Norwegian Porphyria Registry is a high quality national medical registry based on the systematic collection of questionnaires completed by patients. All patients registered with NAPOS with the diagnoses porphyria cutanea tarda, acute intermittent porphyria, variegata porphyria, hereditary coproporphyria, erythropoietic protoporphyria and predictively identified acute porphyrias are invited to participate.

When the registry was established in 2002, a questionnaire was sent to everyone with these diagnoses. Since then, the invitation and questionnaire have been sent out in connection with initial contact through the treating doctor or the genetic counsellor. Participants receive a follow-up form one or two years after the first questionnaire, and thereafter every four years.

A total of 680 persons (70% of those invited), 370 women and 310 men, were registered in the Norwegian Porphyria Registry as of February 2012. Information about symptoms, precipitating factors and incorrect treatment were obtained from the first questionnaire. Data on monitoring and follow-up routines and quality of life were based on the most recently submitted questionnaire. Most questions had multiple choice responses with the option of free text. Information on quality of life was extracted from a single non-standardised question in the questionnaires (Fig. 1). Differences in monitoring and follow-up routines for participants who had had porphyria cutanea tarda or acute intermittent porphyria for four years or more ($n = 370$) were investigated.

Descriptive analyses and simple statistical tests were conducted using SPSS Version 18.0. The chi-squared test was used to deter-

mine whether there were significant differences between the genders with respect to symptoms and precipitating factors. P-values of less than 0.05 were regarded as statistically significant. PX-Map (2009, Statistics Norway, Oslo) was used to create a prevalence map.

The Norwegian Porphyria Registry has authorisation from the Norwegian Data Protection Authority, and the study was approved by the Regional Committee for Medical and Health Research Ethics (Rek Vest).

Results

Incidence and prevalence

In the period 2000–2004, the number of porphyria diagnoses rose from year to year (Fig. 2). In particular, the number of porphyria cutanea tarda and predictively identified acute intermittent porphyria cases increased compared with previous years. From 2003 to 2006 there was also a pronounced increase in the number of predictively identified porphyria cutanea tarda cases (not shown). In the period 1999–2011, the rarer diseases, hereditary coproporphyrinuria and variegate porphyria, were diagnosed more frequently than before. For the past five years, the total number of new cases of porphyria has stabilised at an annual incidence of about 0.5–1:100 000.

Porphyria cutanea tarda is the most prevalent porphyria in Norway, with a total of 576 registered cases (Table 1), 12% of which were predictively identified without the patient having symptoms. Corresponding statistics for acute intermittent porphyria are 326 and 42%.

Prevalence was calculated at about 10:100 000 for symptomatic porphyria cutanea tarda and 4:100 000 for symptomatic acute intermittent porphyria. If cases with predictively identified genetic predisposition were included, the overall prevalence was about 12:100 000 for porphyria cutanea tarda and about 7:100 000 for acute intermittent porphyria.

Statistics for the overall prevalence of these two porphyrias distributed by county revealed large geographical differences (Fig. 3). Of genetically tested porphyria cutanea tarda cases ($n = 458$), 182 had the sporadic form and 276 the hereditary form of the disease.

Diagnostic delay

The median age of symptom onset was 54 for porphyria cutanea tarda, 23 for acute intermittent porphyria and two years for erythropoietic protoporphyria. The median diagnostic delay was one year for porphyria cutanea tarda, four years for acute intermittent porphyria and 17 years for erythropoietic protoporphyria.

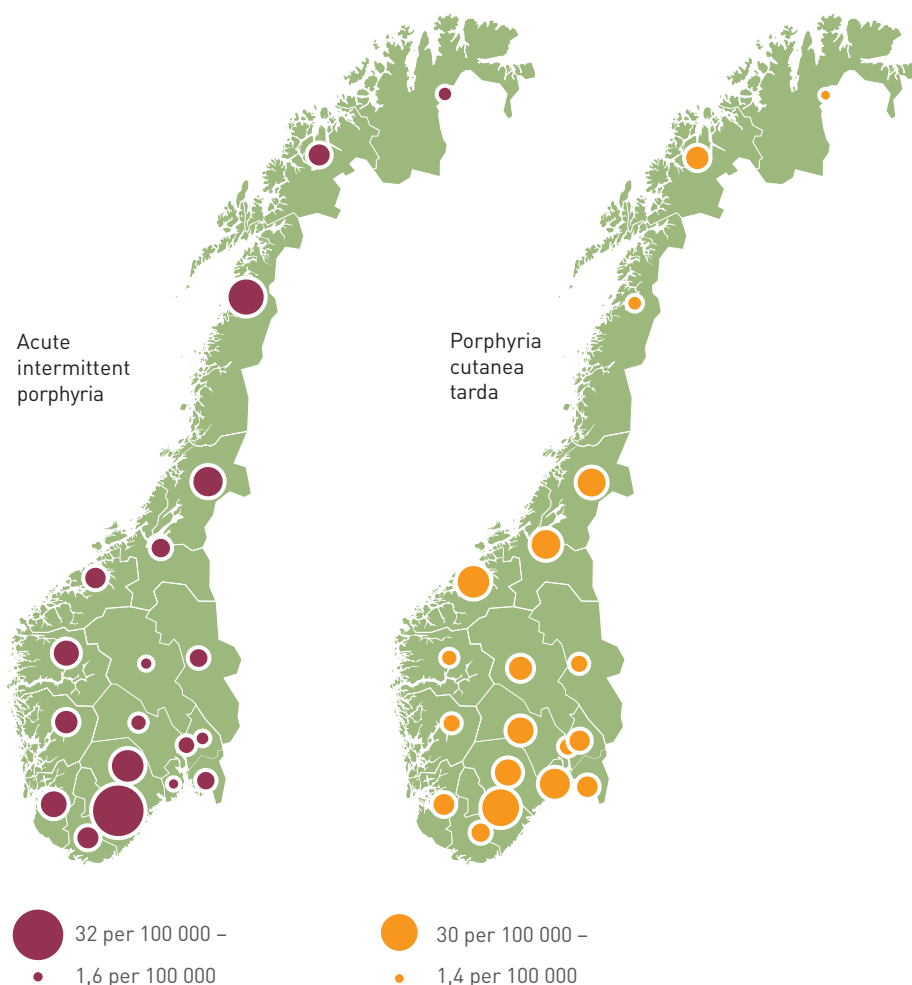


Figure 3 Prevalence by county, per 100 000 inhabitants, of acute intermittent porphyria ($n = 323$) and porphyria cutanea tarda ($n = 570$) registered at the Norwegian Porphyria Centre (NAPoS) as of 31.12. 2011, including never-symptomatic patients identified as being genetically predisposed for porphyrias

A total of 89% of the subjects with porphyria cutanea tarda and 54% of those with acute intermittent porphyria were diagnosed within 5 years of the onset of symptoms (Fig. 4). 13% of the subjects with acute intermittent porphyria and 36% of those with erythropoietic protoporphyria reported a diagnostic delay of more than 20 years. Subjects with erythropoietic protoporphyria in particular (54%), but also subjects with acute intermittent porphyria (37%) reported what they themselves believed was incorrect treatment before the diagnosis was made. A smaller percentage of the group with porphyria cutanea tarda reported incorrect treatment (20%).

Symptoms and precipitating factors

Among the subjects with acute intermittent porphyria, mental stress (63%) and physical stress (50%) were the factors reported by most subjects as precipitating attacks. Next came medicines (40%), lack of sleep (37%), alcohol (31%), working environment (27%),

hunger (27%), other illnesses (25%) and food (22%). A larger proportion of women than men reported that physical stress ($p = 0.029$) or mental stress ($p = 0.042$) had been a precipitating factor. Menstruation and the use of contraceptive pills were cited as precipitating factors by 22% and 18%, respectively, of the women.

In about 20% of the patients with porphyria cutanea tarda, alcohol was reported as a susceptibility factor. In about 10%, liver disease or iron supplement was a susceptibility factor, while 40% of the women reported that the disease was triggered by oestrogens.

The prevalence of symptoms reported to the Norwegian Porphyria Registry for the three most commonly occurring porphyrias is given in Table 2. No significant differences were found between genders.

Outpatient monitoring and follow-up

The frequency of medical check-ups varied substantially for subjects with the different

Table 2 Symptoms of acute intermittent porphyria, porphyria cutanea tarda and erythropoietic protoporphyria reported to the Norwegian Porphyria Registry

Acute intermittent porphyria (n = 134)		Porphyria cutanea tarda (n = 379)		Erythropoietic protoporphyria (n = 28)	
Symptoms experienced in acute attacks	Per cent	Photosensitivity in the form of fragile skin and blisters	Per cent	Acute painful photosensitivity	Per cent
Severe abdominal pain	93	Blisters	96	Burning/stinging pain	96
Fatigue	72	Fragile skin	86	Red/swollen skin	86
Dark/reddish urine	64	Dark/reddish urine	55	Sores/crusting	50
Muscular pain	63	Abnormal hair growth	33	Blisters	32
Muscular weakness	59	Increased pigmentation	30		
Palpitations	53				
Headache	52				
Vomiting	47				
Obstipation	46				
Mental symptoms	40				
Impaired sensation	39				
Paralysis	26				

porphyria diagnoses. Ninety-four percent of subjects with predictively identified acute intermittent porphyria, 56% of those with symptomatic acute intermittent porphyria and 33% of those with porphyria cutanea tarda never went for medical check-ups. 42% per cent of acute intermittent porphyria patients and 58% of porphyria cutanea tarda patients went for one or more check-ups per year.

Quality of life

About half the participants with symptomatic acute intermittent porphyria and porphyria cutanea tarda reported a reduced quality of life (Fig. 1). The proportion for erythropoietic protoporphyria was somewhat higher.

Discussion

After the establishment of NAPOS in 1999, the number of persons diagnosed with porphyrias in Norway increased from about 10–20 per year before 1999 to a maximum of 110 in 2004. The pre-1999 figures are uncertain, as they are based on information from different hospitals in Norway. The rarer diagnoses have also been made more frequently than previously. These increases are probably attributable to improved diagnostic methods, greater focus on and more

knowledge about the porphyrias, and the effect of family studies.

Some of the new cases of variegate porphyria and hereditary coproporphyria resulted from changes in former porphyria diagnoses, following new biochemical and genetic studies. During the same period, a number of persons who had previously been diagnosed as having porphyria had their diagnosis «removed» because it proved to be based on incorrect interpretation of analytical results.

As the porphyrias are rare, there is little reliable data on prevalence. There may also be large differences in prevalence from population to population or across geographical areas, owing, *inter alia*, to founder effects.

Porphyria cutanea tarda is the most commonly occurring porphyria in the majority of populations (1). The prevalence in our study was similar to that reported from Sweden (10 : 100 000) (9), but higher than in the UK (4 : 100 000) (4). In most populations, the hereditary form of porphyria cutanea tarda accounts for about 25% of cases (10–13). In our study we found a substantially larger percentage of hereditary cases (60%). A study from 2009 (3) showed that 74% of the hereditary cases of porphyria cutanea tarda in Norway are due to two frequently occurring mutations.

In most populations, acute intermittent porphyria is the most frequently occurring acute porphyria. Although the disease has autosomal dominant inheritance, clinical penetrance is low, and it is assumed that only 10–20% of genetically predisposed individuals will ever develop symptomatic disease. A new study examining the incidence of acute intermittent porphyria in several European countries showed a calculated prevalence (estimated on the basis of incidence in countries participating in the study) of symptomatic acute intermittent porphyria of 0.5 : 100 000 (14), which is substantially lower than our estimate (4 : 100 000) and the estimate from Sweden (10 : 100 000, but this includes predictively identified non-symptomatic cases) (15, 16).

The high prevalence in Norway and Sweden is partly due to a founder mutation originating from Arjeplog in Northern Sweden, where the estimated prevalence is 2 000 : 100 000 (15). In Saltdal Municipality in Norway's Nordland County, where this mutation also occurs frequently, the prevalence is estimated at 600 : 100 000 (7). An additional explanation may be that family screening is more easily available in Norway and Sweden, and more is known about the diseases, with the result that more patients are correctly diagnosed.

Few studies on diagnostic delay in the porphyrias have been conducted, but studies on erythropoietic protoporphyria in Sweden (17) and the UK (18) have reported 18 and 12 years' delays respectively, compared with 17 years in our study. The disease is diagnostically challenging, not only because it is very rare, but also because the clinical presentation may be a small child who cries and is agitated when exposed to the sun, without this being accompanied by distinct skin lesions (1). This study includes too few patients with erythropoietic protoporphyria to allow us to investigate whether time to diagnosis is shorter now than in the past, but the studies from Sweden and the UK have failed to demonstrate any change (17, 18).

The amount of monitoring and follow-up needed for the different diagnoses is determined by both the type of porphyria and whether the patient has symptomatic disease or is genetically predisposed without having had symptoms. With most of the porphyrias, it is possible to prevent attacks or relapses. With correct treatment and follow-up, many patients may therefore remain free of symptoms for most of their lives, and complications such as hypertension, renal failure, hepatocellular carcinoma in patients with acute porphyrias (19, 20) and liver failure in erythropoietic protoporphyria (21) can be detected early.

Despite the fact that all patients who have

had symptoms are advised to go for annual check-ups (22), over half of patients with symptomatic acute intermittent porphyria and a third of those with porphyria cutanea tarda report that they never do. In light of this information, NAPOS published detailed diagnosis-specific guidelines in 2010 for the monitoring and follow-up of porphyria patients (22).

In general, there is consistency between the symptoms reported by Norwegian patients in connection with attacks of acute intermittent porphyria and those observed in other studies (5, 23, 24). Acute attacks may be precipitated by a number of factors, such as hormonal changes (e.g. menstruation), unsafe drugs, alcohol, fasting/dieting, psychological and physical stress and other illnesses (4–6). The use of drugs (40%) as a precipitating factor was reported more frequently in our study than in studies from Sweden (20%) (5) and South Africa (10%) (6). In addition, 18% of the women in our study specifically reported contraceptive pills as a precipitating factor.

In particular, participants with acute intermittent porphyria and erythropoietic protoporphyria reported that they had a reduced quality of life as a result of their disease. These findings must be interpreted with caution, as they are not based on a validated method. A lower quality of life has previously been reported in patients with acute porphyrias compared to healthy individuals and diabetics (25).

Recent studies (17, 18) have shown that patients with erythropoietic protoporphyria have a severely reduced quality of life, which is partly explained by the long diagnostic delay, major restrictions on daily living and the fact that there are few treatment options. In light of the fact that several of the porphyrias may have long diagnostic delays, may cause severe and/or pronounced distress and are dependent on life-long follow-up, new studies are needed to assess the need for follow-up and help for porphyria patients at different stages of life.

The strength of the present study is that it provides a comprehensive overview of porphyrias in Norway, including all porphyria patients registered at NAPOS since its establishment in 1999. The study therefore encompasses many patients, despite the fact that it concerns such rare conditions. In addition, the response rate in the Norwegian Porphyria Registry is relatively high, at 70%. Non-response analyses have not been conducted, but we see that the response rate is higher for women than for men, and also for patients with erythropoietic protoporphyria. However, it must be taken into consideration that the data included in the registry are patient-reported.

There is still little systematic knowledge of the natural history of the various porphyrias and of treatment efficacy. Many patients with a rare disease report challenging encounters with the healthcare system. The Norwegian Porphyria Registry will use the systematically acquired registry data to develop and implement guidelines that may improve the clinical management of the porphyrias. A joint European porphyria registry, to be managed by NAPOS, was established recently (26). This registry will be capable of encompassing larger numbers of porphyria patients, which will result in more reliable data and in turn a better foundation for evidence-based practice.

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