

A patient-oriented perspective on porphyria

Psychosocial and health-related challenges of acute intermittent porphyria
and porphyria cutanea tarda

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Psychosocial and health-related challenges of acute intermittent porphyria and porphyria cutanea tarda

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Scientific environment

The present dissertation originated from the Norwegian Porphyria Centre (NAPOS), Haukeland University Hospital.

The PhD candidate was granted submission to the Faculty of Medicine and Dentistry at the University of Bergen (UiB) and followed doctoral training at the Department for Global Health and Primary Health Care. The candidate has also been affiliated with the Regional Strategic Research Program for Health and Social Sciences led by the Centre of Evidence–Based Practice at Bergen University College, which provided a one-month grant to write an application for full-time funding. The present project was funded in full by a research grant from the Western Norwegian Regional Health Authorities.

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Preface

My background is in nursing and is diverse, and includes experiences in somatic hospital care, home care, nursing home care and psychiatry. My introduction to the world of porphyrias began after I finished my master thesis in genetic counselling (GC) at the University of Bergen in 2007. I was then employed, and have since worked, as a genetic counsellor at the Norwegian Porphyria Centre (NAPOS). When I started working at NAPOS, I had barely heard of porphyria and I wondered how my master research could be helpful in understanding the challenges met by persons with porphyria and help me in the GC of this patient group. My master thesis was published as an article about living with an increased risk of sudden cardiac death because of long QT syndrome (LQTS) (1), a genetic condition in which the first symptom of disease can be sudden cardiac arrest.

Although the symptoms are very different, I quickly came to see several similarities between the acute porphyrias and LQTS. Both conditions are hereditary and follow an autosomal dominant pattern that is low in penetrance and has variable expressivity. These conditions are rare, their symptoms are easily mistaken or confused with other health complaints, certain medications should be avoided, and they can be fatal in some cases. Predictive testing can be beneficial because the conditions are rare and are often not recognized by health professionals. The acute porphyrias and LQTS are some of the few diseases that are tested predictively in children in Norway. Both conditions can be avoided through lifestyle advice and preventive measures, but there are no black and white solutions, and prevention of disease cannot be guaranteed.

These factors mean that these conditions pose special challenges in terms of GC, treatment and general follow-up of patients. The low penetrance and the ambiguity of symptoms can contribute to the potential for medicalization and assuming that everyday health complaints as more serious than they are. At the same time, these conditions should not be underestimated. Although rarely serious, the acute porphyrias can be lethal, and extra caution is needed when counselling this group of patients.

I became curious about the subjective experiences of persons with porphyria cutanea tarda (PCT). Surprisingly, considering that PCT is the most common form of

porphyria, hardly any research had focused on the patient perspective. Although PCT as a condition is considered undramatic, to have a good prognosis, to be easily treated and, for many, to have lifelong remission, this condition is visible and many patients experience long diagnostic delays. Through my work with PCT patients and their asymptomatic relatives, I formed the impression that PCT is not always as unproblematic as assumed.

Research activity is highly encouraged at NAPOS, although I was not accustomed to this as a nurse. Most of the research being performed at NAPOS was in the laboratory setting and there is a strong positivist research culture. Coming from a different background, I was interested in the subjective aspects of the porphyrias. This meeting of different research paradigms has influenced the design and choices made in completing this PhD project. However, I believe that taking a “mixed position” has been rewarding in that it has allowed for a broader understanding of the challenges facing people with acute intermittent porphyria and PCT, and has provided empirical findings that complement and elaborate each other. Hopefully the results are of interest and clinical value for both porphyria patients and their caregivers.

Summary

Background: To optimize patient care, follow-up and genetic counselling of persons with acute intermittent porphyria (AIP) and porphyria cutanea tarda (PCT), investigations into the subjective experiences of persons living with these conditions are warranted.

Aims: The overall objective of this thesis was to investigate the psychosocial and health-related challenges faced by people with AIP and PCT. The specific aims were: 1) to investigate the subjective experiences of adolescents and young adults who were genetically tested for AIP as minors and to identify the psychosocial consequences and how they are handled; 2) to explore the experiences of persons with PCT concerning their symptoms, treatment, prevention and follow-up; 3) to describe and compare illness perception, self-reported health complaints and psychological distress in persons with various activity of PCT and 4) to examine the associations between illness perception, self-reported health complaints, PCT symptoms and psychological distress.

Material and methods: In this thesis we used a multi-methods approach. Individual interviews were performed with 10 persons who had received a positive predictive genetic test result for AIP as minors. Three focus groups with a total of 21 persons with experience of the symptoms of PCT were carried out. The last part of the study was cross-sectional and included a questionnaire completed by 263 subjects who had PCT with active symptoms, were in a remission phase, or were an asymptomatic mutation carrier.

Results: Young persons tested genetically for AIP described few psychosocial challenges but found it difficult to become motivated to make lifestyle modifications. For some, the thought of developing an active disease was a cause for concern. AIP was experienced as a vague condition, and participants and their families attributed a range of health complaints to porphyria.

PCT was perceived as a chronic and systemic condition, and participants described a shift in their focus from skin to blood. Health complaints other than skin symptoms

were attributed to PCT. Symptoms varied greatly and, at their worst, were dramatic and described as “living in a horror movie”.

Participants with active PCT reported higher perceived illness threat, more subjective health complaints and higher degrees of psychological distress compared to asymptomatic participants. Psychological distress about PCT was however associated with perceptions of illness and total health complaints but not with PCT symptom activity.

Conclusions and implications: The results from this study show that symptoms of PCT can be dramatic and should be addressed, but asymptomatic phases can also be problematic. Separating the symptoms of AIP and PCT can be difficult for patients, and a clearer definition of an AIP attack and PCT symptoms would be beneficial. When in a phase of active disease, it is important that patients know how to implement and increase their treatment compliance while also avoiding medicalization of persons in remission or at risk of developing AIP or PCT. Patients’ perceptions of the condition should be considered, and appropriate follow-up, counselling and reassurance during clinical consultations are recommended.

List of publications

Paper I:

Andersen J., Sandberg S., Råheim M., Gjengedal E.; Psychosocial aspects of predictive genetic testing for acute intermittent porphyria in Norwegian minors. *Journal of Inherited Metabolic Disease Reports* 2011; 1:1–7

Paper II:

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Paper III:

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List of abbreviations

AIP	acute intermittent porphyria
ALA-	5-aminolevulinic acid
BIPQ	Brief Illness Perception Questionnaire
BM	biomedical model
BPS	biopsychosocial model
CI	confidence interval
CSM	Common-Sense Model of illness perception
DLQI	Dermatology Life Questionnaire Index
EPR	European Porphyria Registry
fPCT	familial porphyria cutanea tarda
GC	genetic counselling
HMBS	hydroxymethylbilane synthase
ID	interpretive description
IES	Impact of Events Scale
IPQ	Illness Perception Questionnaire
IPQ-R	Illness Perception Questionnaire Revised
IV	independent variable
NKSD	Norwegian National Advisory Unit on Rare Disorders
NAPOS	Norwegian Porphyria Centre
NPR	Norwegian Porphyria Registry
PBG	porphobilinogen

PCT	porphyria cutanea tarda
PRO	patient-reported outcome
PTSD	post-traumatic stress disorder
QoL	quality of life
SHC	subjective health complaint
sPCT	sporadic PCT
STC	systematic text condensation
UROD	Uroporphyrinogen decarboxylase
WHOQOL	World Health Organization Quality of Life instrument

Contents

Scientific environment..... 1

Acknowledgements 2

Preface 6

Summary..... 8

List of publications 10

List of abbreviations 11

INTRODUCTION 16

 1.1 Background 16

 1.2 Porphyria 16

 1.3 Acute intermittent porphyria 17

 1.4 Porphyria cutanea tarda..... 18

 1.5 Norwegian Porphyria Centre..... 19

 Table 1: Total number of patients registered at NAPOS 2014 21

 1.6 Psychosocial aspects of AIP and PCT..... 21

 1.7 Genetic testing..... 22

 1.8 Genetic counselling 24

THEORETICAL FRAMEWORK 25

 2.1 Biopsychosocial model..... 25

 2.2 The Common-Sense Model of illness perception 26

 2.3 Horowitz’s stress-response theory 27

PURPOSE OF THE STUDY..... 28

 3.1 Overall objective 29

 3.2 Specific aims 29

MATERIAL AND METHODS 29

 Table 2. Overview of study designs..... 30

4.1	Studies I and II	30
4.1.1	Interpretive description.....	30
4.1.2	Participants	32
4.1.3	Individual interviews	33
4.1.4	Focus groups.....	35
4.1.5	Analysis	37
4.1.6	Analysis paper II: Systematic text condensation.....	39
4.2	Study III.....	41
4.2.1	Study population.....	41
4.2.2	Patient-reported outcomes	42
4.2.4	The Brief Illness Perception Questionnaire.....	42
4.2.3	The Subjective Health Complaints Inventory	43
4.2.5	The Impact of Events Scale.....	44
4.2.6	Statistical analyses	45
	ETHICAL CONSIDERATIONS.....	46
	SYNOPSIS OF RESULTS	48
6.1	Paper I: Psychosocial aspects of predictive genetic testing for acute intermittent porphyria in Norwegian minors.....	48
6.2	Paper II: A skin disease, a blood disease or something in between? An exploratory focus group study of patients' experiences with porphyria cutanea tarda.	48
6.3	Paper III: Illness perception and psychological distress in persons with PCT	49
	DISCUSSION.....	49
7.1	Discussion of the results and empirical findings.....	49
7.1.1	Papers I–III: AIP and PCT.....	49
7.1.2	Paper I: AIP	52

7.1.3	Papers II and III: PCT.....	54
7.2	Methodological considerations	59
7.2.1	Credibility in the qualitative studies (Papers I and II).....	59
7.2.2	Validity and reliability in the quantitative study (paper III)	63
7.2.3	Mixing methods.....	68
	CONCLUSIONS AND IMPLICATIONS FOR PRACTICE	69
	FUTURE PERSPECTIVES.....	70
	References.....	72
	Papers I-III	
	Appendixes	
I	Interviewguide study II	
II	Instruments study III	
III	Litterature search strategy	

INTRODUCTION

1.1 Background

This thesis was designed to address the lack of formal and scientifically based knowledge about the subjective experiences of persons with acute intermittent porphyria (AIP) and porphyria cutanea tarda (PCT). AIP and PCT are the most common forms of porphyria (2), and more than 90% of the patients registered at the Norwegian Porphyria Centre (NAPOS) have one form. The aim of NAPOS is to improve the diagnostics, treatment and follow-up of patients with porphyria (3). Both AIP and PCT are diseases that, for most patients, involve large periods of remission while at the same time requiring monitoring and follow-up to prevent relapses. Some people are genetically predisposed but have never experienced symptoms, and appropriate knowledge is essential for predictive genetic testing to be beneficial to them. Because AIP and PCT affect people both when symptomatic and asymptomatic, it is important to understand how the symptomatic and asymptomatic phases of AIP and PCT are experienced by patients. Further investigations into the experiences of living with porphyria have also been recommended by patients (4) Consequently, we wanted to investigate the patients' perspectives on AIP and PCT, and to generate pragmatic and relevant knowledge that could be applied to both genetic counselling (GC) and nursing.

The following section starts with a general introduction of the porphyrias and is followed by a more specific presentation of PCT and AIP, an introduction to NAPOS and the centre's main tasks and objectives, and GC practice in Norway and at NAPOS in particular. The theoretical framework behind the patient-reported outcome (PRO) measures reported in paper III and the backdrop for the discussions are presented. The empirical findings and the methods used to obtain these findings are discussed, and the future perspectives and clinical implications are formulated.

1.2 Porphyria

Porphyria is a common denomination for a group of rare and mainly inherited metabolic diseases. Each porphyria is caused by abnormal function of different

enzymes in different steps in the haem synthetic pathway, which cause accumulation of specific porphyrins and porphyrin precursors and different symptoms (2). Seven of the porphyrias are caused by a reduced activity in the haem synthetic pathway, and the most recently described type of porphyria is caused by a gain-of-function mechanism. The porphyrias are generally classified into acute and cutaneous types. Acute porphyrias can cause attacks that typically present as abdominal pain and can be life threatening. The cutaneous porphyrias present as photosensitivity and can cause pain or skin fragility and blisters. Some of the porphyrias involve a combination of the two and may cause acute attacks while also causing cutaneous manifestations.

The porphyrias can also be defined as either hepatic or erythropoietic, depending on which organ the accumulation of metabolites occurs (2). The seven variants of porphyria in Norway are AIP, hereditary coproporphyria, variegate porphyria, PCT, erythropoietic protoporphyria (EPP), congenital erythropoietic porphyria and hepatoerythropoietic porphyria. A new porphyria, X-linked dominant protoporphyria (XLDPP) was reported in 2008. XLDPP presents with an identical phenotype as EPP but is caused by a gain-of-function mutation in the ALAS2 gene. The rate of transmission of XLDPP to subsequent generations is larger than in EPP, but there is an absence of father-to-son transmission (5). The present thesis focuses on the two most common forms of porphyria in Norway, AIP and PCT. The prevalence of symptomatic disease in Norway is estimated at 10 per 100,000 population for PCT and 4 per 100,000 population for AIP (6).

1.3 Acute intermittent porphyria

AIP presents as acute attacks of abdominal pain, nausea and/or vomiting, headache, muscle ache, muscle weakness, paresis and mild psychological symptoms. Symptoms are typically triggered by a range of common medications, hormones, alcohol, stress and fasting or low-caloric intake. Often, a combination of triggering factors is needed for symptoms to develop. AIP has a variable expressivity, which ranges from few and mild attacks to frequent and serious attacks requiring hospital admittance. Serious paralysis and respiratory failure are potentially lethal complications in AIP attacks (2, 7, 8). Treatment consists of avoiding precipitating factors, adequate nutrition, and in

severe attacks treatment with heme arginate. Liver transplantation is a curative but high-risk option for patients suffering severe recurrent attacks (9).

The incidence of symptomatic AIP in Europe is calculated to 0.13 per million per year, except for Sweden, where the numbers are higher (0.51) probably because of a founder mutation. The estimated percentage of AIP patients who will develop recurrent AIP attacks is 3–5%, when recurrent attacks are generally defined as four or more attacks per year. The number of mutation carriers developing symptoms seems to be decreasing, possibly because of improved management (10). Diagnosis of symptomatic AIP is based on detecting increased urinary porphobilinogen (PBG) and 5-aminolevulinic acid (ALA) concentrations in urine and further analysis of porphyrins in urine, faeces and blood (11). There are also indications that the majority of AIP patients in remission have increased PBG and ALA concentrations (12, p 34-35).

AIP is inherited in an autosomal manner and, as a consequence, any first-degree relative of a person with an AIP mutation has a 50% risk of having inherited the same mutation in the hydroxymethylbilane synthase (*HMBS*) gene. The condition has low penetrance, and 20–30% of mutation carriers develop symptoms, which present with varying degrees of severity (13). Because of hormonal factors, attacks occur rarely before puberty, are more common in women than in men, commonly peak in occurrence within the third decade, and occur rarely after menopause. Most individuals with symptomatic AIP have one or a few attacks during their lifetime and full recovery for the rest of their lives (2). Manifest AIP refers to the occurrence of one or more AIP attacks throughout life, and latent AIP refers to the disease identified by predictive genetic testing in a person with a genetic disposition for porphyria but without having had any symptoms. AIP thus exists in a manifest and latent form. NAPOS offers GC and predictive genetic testing to at-risk relatives of persons with a known AIP mutation.

1.4 Porphyria cutanea tarda

PCT is the most common form of porphyria worldwide (2) and is characterized by fragile, vulnerable skin and blisters on sun-exposed areas. It exists in both a hereditary

and a non-hereditary form. Both variants are triggered by factors such as high ferritin levels, high alcohol intake, oestrogens and various liver diseases. Onset of the disease is most common in late adulthood, and the median age for symptom debut in Norway is 54 years (6). PCT is characterized by elevated concentrations of uroporphyrins and heptaporphyrins in urine. Diagnosis is based on analysis of porphyrins in urine, faeces and blood in order to differentiate between the different porphyrias that can cause bullous symptoms (12, p 45-47). The established diagnostic criteria are described in the literature (11).

Treatment comprises phlebotomy to reduce hepatic iron stores and/or by administering chloroquine to increase excretion of porphyrin metabolites in urine. Treatment is usually prolonged and may require up to 15 months before clinical and biochemical remission is achieved (14, 15). Many PCT patients will remain in lifelong remission, although some will need to repeat treatment after a few years. Familial PCT (fPCT) is inherited in an autosomal dominant pattern, with a low penetrance of about 10% (16). At NAPOS, everybody diagnosed with clinically active PCT will be investigated for a mutation in the gene coding uroporphyrinogen decarboxylase (*UROD*) to determine whether they have sporadic PCT (sPCT) or fPCT. NAPOS offers GC and predictive genetic testing to family members older than 16 years who are at risk of PCT.

1.5 Norwegian Porphyria Centre

NAPOS was initiated by the Norwegian Ministry of Health and Care Services in 1999 and is situated at the Laboratory for Clinical Biochemistry at Haukeland University Hospital in Bergen. NAPOS is incorporated into the Norwegian National Advisory Unit on Rare Disorders (NKSD), whose main task is to ensure that people with rare disorders receive holistic and individually based care that cannot be expected to be provided for within the main public health-care system (17). NKSD comprises eight national Centres of Expertise on Rare Disorders, each of which is responsible for specific disorders, where patients, their families and professionals can seek help and advice.

The main objective of NAPOS is to establish better quality of services by improving and optimizing diagnostics, treatment and follow-up of all persons with porphyria in

Norway. NAPOS diagnoses almost all porphyria patients in Norway and has started the Norwegian Porphyria Registry (NPR) for this patient group. When a person is diagnosed with AIP or PCT, NAPOS issues an identification card for the person to use when seeking health-care services, which helps to avoid potential use of porphyrinogenic medications (acute porphyrias) and to ensure that appropriate treatment is initiated. NAPOS devotes considerable work to providing annual courses for patients and health personnel, updated webpages (www.napos.no) and the distribution of information letters. Research to gather relevant information is critical to the centre, and NAPOS has an active research environment with extensive international contacts that include basic, epidemiological and pharmaceutical research. A range of research is initiated by the centre, and several PhD candidates and master students are affiliated with NAPOS. NAPOS also administers the NPR and the European Porphyria Registry (EPR). The centre started a database that contains an overview of porphyrinogenic medications in 2003; the English version was launched in 2005 and is used worldwide (www.drugs-porphyria.org).

By the end of 2014, NAPOS had registered 344 persons with AIP and 690 persons with PCT (table 1). During 2014, 56 newly diagnosed persons with PCT and nine with AIP were registered (3). At the start of the present project, the corresponding number of registrants was 313 with AIP and 529 with PCT (18).

Table 1: Total number of patients registered at NAPOS 2014

Diagnosis	
Porphyria cutanea tarda (PCT)	690
Acute intermittent porphyria (AIP)	344
Erythropoietic protoporphyria (EPP)	43
Variegate porphyria (VP)	34
Hereditary coproporphyria (HCP)	12
Congenital erythropoietic porphyria (CEP)	1
Hepatoerythropoietic porphyria (HEP)	3
Total - all diagnoses	1127

1.6 Psychosocial aspects of AIP and PCT

Only a modest amount of research has focused on patients' experiences of AIP and PCT, and how the disease affects their daily life. A qualitative study of five women from Sweden concluded that AIP attacks caused the deepest despair, which included extreme pain both physically and mentally (19). Others have shown that AIP is associated with a lower quality of life (QoL) when compared with other acute porphyrias, and that for many patients, AIP has lifestyle consequences such as reduced work capacity and family size, in particular in those with manifest AIP. Depression and anxiety were more prominent in persons with AIP compared with the normal population (20, 21). A 2009 Swedish study found that one-fifth of those with manifest AIP received a disability pension (22). These findings indicate that AIP can have large psychosocial consequences for those afflicted and that growing up in a family with a member with AIP might affect relatives in a serious way. These findings also

emphasize the need for greater understanding of the psychosocial aspects of manifest AIP and the effects of living with the risk of AIP, as is the case in latent AIP.

Skin disease in general is associated with psychosocial and psychiatric morbidity and, although the direction of this association is unclear, should be taken seriously because of the association between skin disease and emotional suffering, poor adherence to dermatological treatment and impaired QoL (23). Photodermatoses are associated with psychological impact, distress and lifestyle impact (24-27), and the impact of blistering dermatoses poses a significant burden on QoL associated with shame and poor hygiene (28).

Although PCT is the most common form of porphyria worldwide (2), little has been published on the psychosocial aspects of this condition. A British questionnaire survey examined QoL in 790 persons with photodermatosis, including 12 with PCT. Although most PCT participants were probably in clinical and biochemical remission at the time of the survey and thus the results should be interpreted with caution, the authors concluded that PCT had a much smaller effect on QoL than other conditions such as EPP (29). As of August 2009, the NPR had information about 314 persons with active PCT or PCT in remission. When asked whether PCT had any impact on their QoL, 45% (n = 142) answered that PCT had a moderate to great influence on their QoL (unpublished data). We therefore felt that further information about the psychosocial and health-related challenges faced by people with PCT was needed for NAPOS and other health-care providers to optimize the care and follow-up of this patient group.

1.7 Genetic testing

Norwegian legislation defines various subtypes of genetic testing and provides the following distinctions:

- a) *genetic testing to diagnose disease*
- b) *presymptomatic genetic testing, predictive genetic testing and testing to determine whether or not a person is a carrier of hereditary disease that will only be expressed in later generations (carrier testing)*

c) *laboratory genetic testing to determine sex, with the exception of laboratory genetic testing for identification purposes* (30)

When presymptomatic, predictive or carrier genetic testing is performed, the law states that, “*genetic counselling shall be given before, during and after testing*” (30§5-5).

The Norwegian Biotechnology Act, 2003, §5-7 also states that predictive genetic investigations shall not be performed on persons younger than the age of 16 years, “*unless the test can detect a condition for which treatment may prevent or reduce damage to the child’s health*”. In such cases, “*the child’s parents or another person who has parental responsibility shall also be given genetic counselling*” (30§5-5). Before predictive genetic testing is performed, “*the person being tested must provide written consent to the test. If the person being tested is a child under the age of 16, written consent must be provided from the child’s parents or others with parental responsibility*” (30§5-4).

This is also in line with European ethical guidelines for predictive genetic testing of minors (31-33).

NAPOS routinely performs genetic testing of persons with a biochemical diagnosis of porphyria. Sequencing of the *UROD* gene is performed in patients with a clinically and biochemically confirmed PCT diagnosis. Predictive genetic testing is offered to family members of patients with a *UROD* mutation but predictive testing is performed only in persons older than 16 years.

For AIP, predictive genetic testing is offered to family members of persons with a confirmed diagnosis and a detected pathogenic mutation in the *HMBS* gene.

Symptoms of AIP are rarely seen before puberty, but a few documented cases have been reported (34-37). A predictive genetic test for AIP is expected to ensure a better prognosis for a child through avoiding precipitating factors and providing rapid diagnosis and treatment should an attack occur (38). On this basis, NAPOS offers predictive genetic testing to minors, but this is required to be accompanied by GC and written consent from the legal guardians. NAPOS does not consider very early testing as a medical necessity, and it is up to the parents of the child to decide what age is

appropriate. It is thus important to understand more completely how predictive genetic testing for AIP in minors might affect their psychosocial life.

1.8 Genetic counselling

In this thesis, as in professional work as a genetic counsellor at NAPOS, the definition of term GC is that of the American Society of Human Genetics Ad Hoc Committee on Genetic Counseling.

GC is defined as:

“...a communication process which deals with the human problems associated with the occurrence, or the risk of occurrence, of a genetic disorder in a family. This process involves an attempt by one or more appropriately trained persons to help the individual or family (1) comprehend the medical facts, including the diagnosis, the probable course of the disorder, and the available management; (2) appreciate the way heredity contributes to the disorder, and the risk of recurrence in specified relatives; (3) understand the options for dealing with the risk of recurrence; (4) choose the course of action which seems appropriate to them in view of their and their family goals and act in accordance with that decision; and (5) make the best possible adjustment to the disorder in an affected family member and/or to the risk of recurrence of that disorder” (39, p 673).

This is consistent with the view that GC is appropriate for predictive testing and for the long-term management of a disease. For NAPOS to achieve its aim of providing a better quality of services through improving and optimizing diagnostics, treatment and follow-up of all persons with porphyria in Norway, information and knowledge about the hereditary mechanisms involved are important for helping patients manage their disease. Also sPCT patients in remission or with symptomatic disease may need guidance and counselling about living with the disease and preventing future relapses. This implies that, to provide appropriate GC to porphyria patients, health-care providers need greater knowledge about the psychosocial and health-related challenges faced by patients.

THEORETICAL FRAMEWORK

In paper III, the instruments Brief Illness Perception Questionnaire (BIPQ) and the Impact of Events Scale (IES) were used to investigate the constructs of illness perception and psychological distress, and the theories behind the development of these two instruments are presented. The BIPQ is based on the Common-Sense Model of illness perception (CSM) (40). The IES was developed from the theory of the stress response by Horowitz and colleagues (41). A short introduction to the biopsychosocial model (BPS) of health (42) is presented as background for the discussion and underlying perspective of health and illness used in this thesis.

2.1 Biopsychosocial model

The biomedical model (BM) of illness, also referred to as the “disease model” or “medical model”, is based on the idea that there is a clear and direct causal relationship between a disease and its signs and symptoms (43). A “Cartesian” split between the mind and body has led to a restricted pathology model of disease that excludes social and psychological issues from the traditional disease model. The BM is relevant to acute illness or exacerbation of a chronic condition, but it does not provide a satisfying explanation of the complexity of health and illness, and research has shown that the result of illness and whether people are incapacitated by illness depend on the symptoms as well as social and psychological factors (43). In reaction to the BM perspective, the BPS was proposed by Engel in a well-known paper entitled “The need for a new medical model: a challenge for biomedicine”(42), which contended that medicine as a discipline was in crisis and that this crisis was derived from adherence to a model that was not adequate for the scientific or social responsibilities of medicine and psychiatry.

What individuals and society consider as health and the difference between being well and being ill will always be influenced by cultural, social and psychological considerations. A medical model that is based on a reductionist understanding, in which only biological factors are seen as determinants of disease, is not sufficient to meet the health needs of patients. A physician’s or health professional’s skills must

include social, psychological and biological aspects to be able to evaluate and recommend a course of action (42).

That medicine is constantly being fragmented into new specialties has made the BPS more important and relevant (44). For example, dermatological conditions are associated with emotional suffering, reduced QoL, poor treatment adherence and disability, and these associations have led to the claim that psychosocial issues and a biopsychosocial approach to management of skin disease is warranted (23). As a subgroup of dermatological conditions, and although diverse in aetiology, photodermatosis can have a high psychological impact (26), negatively influence lifestyle (27), inflict high levels of anxiety and depression (24), and cause psychological distress that is related to the patients' perceptions of illness (25). In the case of non-specific pain, it has been argued that improved patient outcomes in terms of distress require consideration of the disease characteristics as well as the psychosocial factors and that there should be a special focus on the patient's perception of illness and its effects (43).

2.2 The Common-Sense Model of illness perception

The model of self-regulation of health and illness developed by Leventhal and colleagues (45, 46), which is referred to as the CSM in this thesis, is known by many names, and is also referred to as the Illness Perception Model, the Self-Regulatory Model or the Parallel Process Model (47). Self-regulation refers broadly to humans as active agents and decision makers; compared with other living creatures, humans have the ability to exert control over their impulses and to adapt and change behaviour to attain certain goals (48). Important features of the self-regulation models include the parallel processing of both problem-focused and emotion-focused goals to successfully control the objective problem and to regulate the emotional distress. Another key theme is the distinction between abstract processes, such as factual and conceptual knowledge and concrete-experiential processes, which include perception, experiences and memories. What separates the CSM from other more general self-regulating theories (such as Lazarus and Folkman's stress-coping theory) is that the CSM applies specifically to health and illness (46). In the CSM, the emotional and cognitive

representations of illness are processed in parallel through three stages in a feedback system. The first stage is the definition or representation of the problem, the second is the planning and execution of a coping plan, and the third is appraisal of the coping response to determine whether it has brought the individual closer to the goal of coping (45).

Early research based on common sense and subsequent investigations identified five dimensions of cognitive illness representations: identity, consequences, causes, timeline and controllability. Identity refers to the ideas, label, nature and symptoms a person views as part of the disease. The consequences component refers to the seriousness of the illness and its likelihood of affecting the person physically and psychosocially. Causes refer to internal or external causes. The timeline indicates the respondent's perception of the likely duration of the health problems. Controllability refers to whether the disease is perceived as preventable, curable, or controllable (46). The key themes within the CSM are that people use common sense based on both knowledge and experience when they form representations of their illness and they test out these representations through both problem-focused and emotion-based coping. According to the CSM, the individual's beliefs about his or her condition will be influenced by factual knowledge, personal experience, social context, discourses with health professionals, the media and other people's opinions, and these beliefs may or may not be biomedically accurate (47).

2.3 Horowitz's stress-response theory

In the present study, distress is defined as two main responses to stressful life events: intrusion and avoidance. Intrusive feelings are characterized by unbidden thoughts and pangs or waves of strong feelings, such as troubled dreams or repetitive behaviour. Avoidance responses include "*denial of the meanings and consequences of an event, blunted sensation, behavioral inhibition or counter phobic activity and awareness of emotional numbness*" (41). The development of the two response subtypes was based on both field observations and clinical studies (41, 49, 50). Horowitz's stress-response theory provides an understanding of the processes involved in people's reaction to stressful events. According to this theory, a stress response comprises alternating

phases of intrusion and avoidance (41). The general pattern can be described as: 1) initial realization that a stressful event has occurred; 2) a phase of emotional numbness and denial; 3) a mixed phase of alternating between intrusive feelings and compulsive or repetitive behaviour; and 4) a working-through phase during which acceptance is initiated and there is a loss of domination by the stressful event.

The phasic relationships between intrusion and avoidance (initially described as intrusive-repetitive and denial-numbness symptoms) (51) are general responses, and every person does not necessarily enter every phase or enter the phases in a fixed sequence. A person can experience both avoidant and intrusive feelings simultaneously as a response to the same stressful event, but each may be oriented towards different aspects and meanings of the event in question. Horowitz uses the death of a spouse as an example—the bereaved may experience avoidant feelings towards the loss of a beloved one but at the same time feel intrusive thoughts that appear as emotional and angered behaviour towards the departed (51).

A key finding of both clinical field studies and experimental studies is that, after a traumatic experience, there is a compulsory tendency for symbolic repetition of some aspects of the event and that psychic trauma is more important than physical trauma in precipitating the stress response (51). Avoidant behaviour is often related to defensive and unconscious processes needed to restore emotional equilibrium and to reduce conceptual chaos. Because these processes are unconscious and not felt directly by the individual, the term “avoidance” instead of “denial” was used in later work (52). These two responses to stress are considered general and can occur in varying intensity and after stressful events of different magnitudes, and apply to both acute and chronic stress reactions (51).

PURPOSE OF THE STUDY

To facilitate and optimize follow-up and patient care, including GC and general counselling of this patient group, further information about the health-related challenges faced by persons with AIP and PCT is needed.

3.1 Overall objective

The main objective of this study was to investigate the psychosocial and health-related challenges that persons with AIP and PCT face.

3.2 Specific aims

The specific aims of the present PhD project were:

- To investigate the subjective experiences of adolescents and young adults who were genetically tested for AIP as minors and to identify the psychosocial consequences and how they are handled.
- To explore the experiences of persons with PCT concerning symptoms, treatment, prevention and follow-up.
- To describe and compare illness perception, self-reported health complaints and psychological distress in persons with various activity of PCT.
- To examine the associations between illness perception, self-reported health complaints, PCT symptoms and psychological distress.

MATERIAL AND METHODS

The present project focused on an area of expertise that has attracted only a modest amount of research. On this basis, it was considered appropriate to use an inductive and exploratory approach with qualitative methods. Research based on qualitative methods can provide independent and valuable results and can act as a hypothesis-generating approach for further studies. We wanted to perform a follow-up study that might be generalized to the population (paper III). Although all three papers can be viewed as individual and independent studies, papers II and III were designed to complement each other, and the overall design of the thesis can be defined as a multi-methods approach (53). We believed that using different methodological approaches to a research area with little prior formal knowledge would provide a solid basis for exploring the present study's objective and for contributing new insights and valuable results.

Table 2. Overview of study designs

	Method	Participants	Design
PAPER I	Qualitative study	Ten young mutation carriers for AIP tested predictively as minors	Individual interviews
PAPER II	Qualitative study	21 adults with PCT symptoms during the past 5 years	Focus group interviews
PAPER III	Quantitative study	263 persons with PCT	Cross-sectional postal survey

4.1 Studies I and II

Both studies I and II were qualitative studies that used interpretive description (ID) as a methodological approach. In study II, the analysis was inspired by systematic text condensation (STC) to aid reflexivity and transparency of the analytical process.

4.1.1 Interpretive description

ID is a research strategy developed by Canadian professor in nursing, Sally Thorne, and colleagues (54-56). The primary point of view is that health and nursing sciences are applied and practical disciplines that are not theoretical or academic by nature. The objective of ID is to offer health personnel a qualitative approach oriented towards pragmatic and practice-related research without committing to a certain theoretical position. Through an eclectic approach, knowledge that is relevant and applicable to a complex clinical setting can be created. This approach builds heavily on well-known traditions such as phenomenology, grounded theory and ethnography, while also adding something new and substantial by providing both a name and rationale for its development, instead of “watering down” or modifying and violating better-known methodological approaches developed in more academic disciplines (56). ID is a sensible qualitative approach in projects that use both qualitative and quantitative methods because it is based on pragmatic ideas and values both objective and subjective knowledge as important in the health sciences (56).

ID is an eclectic approach that allows one to break from specific genres, but some elements are emphasized. The objective in an ID study should stem from two sources: an actual practice goal and an understanding of what is known and unknown about the research area based on all sources of available empirical evidence (56, p 53). Data

collection and analysis should be performed simultaneously (i.e., the constant comparative method), so that they can influence each other mutually. One should avoid early and too-rigorous and detailed coding. The ideal aim of the analytic process is to present understanding and conceptual phenomena rather than mere descriptions, and the purpose and recipients of the research will be influential in terms of which results are emphasized and presented. By respecting the essence of various qualitative traditions but at the same time viewing method as a dynamic interplay with the researcher, method can accommodate the research, rather than vice versa. A coherent and accountable relationship between analytic technique, methodological approach, and the knowledge abstracted must be present in such a way that the end product provides relevant and meaningful results that contribute to expanding the knowledge front in the research area, and has potential implications for practice.

The fact that the health sciences are practical and not academic disciplines by nature influences how it relates to theory and philosophy, and provides challenges to the validity and credibility in qualitative research (56, 57). It is argued that one cannot know “the truth” because this will always be complex, contextual, constructed, and ultimately subjective (54). As one gives up the search for the absolute truth, one can still value knowledge as “probable truth” or as the best available at this moment. All qualitative research is deeply rooted in the contextual, although many qualitative researchers do not recognize that the disciplinary or historical context also influences their own perspectives. Acknowledging that “contextual awareness” that “we cannot see what we cannot see”, and that our “truths” are social constructions, is essential.

The objective of ID is to present knowledge that can have practice implications. In the applied sciences, all knowledge can influence clinical practice and cannot be regarded as purely theoretical. This requires careful consideration and a *pragmatic obligation*. One must therefore defend why the knowledge generated is necessary and why it is important by considering that the knowledge revealed can be misused, for instance with regard to marginalized groups. This is what Thorne refers to as *moral defensibility*. The research and knowledge produced should be both necessary and relevant to the discipline in question (56).

4.1.2 Participants

Qualitative research involves a number of sampling procedures such as the *theoretical*, *purposive* and *convenience* samples, among others.

In study I, we chose a theoretical sample of persons we deemed most eligible to provide information about and insights into the question at hand. Theoretical sampling is based on the idea of maximum variation and is a strategy developed from grounded theory, in which one deliberately seeks out specific cases based on initial hunches or developing patterns. In ID, where the aim is to uncover clinically relevant knowledge and not formal theorizing as in grounded theory, one does not require the same open theoretical sampling, although the principle of reserving some of the sampling criteria until one is underway in the data collection still applies (56, p 92). We wanted to explore the experiences of persons who had been genetically tested before they were 16 years old, but at the same time we wanted them to be old enough to have reflected on the testing and possibility of having the disease. Considering this rationale, we chose to include persons between the age of 16 and 21 years. This meant that only a limited number of participants met the inclusion criteria. Of the 28 persons eligible, 12 gave their consent but only 10 were able to participate in the interview.

In study II, we chose a convenience sample in connection with a biennial patient seminar arranged by NAPOS. The rationale was that we could recruit participants from the entire country and that that we expected that attendees at the seminar who were interested in participating in our study would provide important information about their experiences with PCT. Convenience sampling is a sample based on “pure convenience” and can be a good source of insight for the applied qualitative researcher, especially when there is little prior knowledge of the phenomenon at hand. However, it is also an approach that requires careful reflection on and attention to how the specific context can make the sample different from the general population of these patients (56, p 89-90).

Considering that we believed that participants at the seminar might provide the information needed to answer the research question, one could argue that this sampling had an element of purposive sampling. In purposive sampling, one tries to identify in

advance the important conditions or groupings that may contribute to the findings' relevance for the intended audience. Based on ethnography, an important concept of purposive sampling is the "key informant". Although this might be difficult to identify in a clinical setting, the ideal informants in an ID might be people who are articulate and who can reflect on the experiences one wishes to explore (56, p 90-91).

The invitations to participate in the focus groups were mailed along with the invitations to the patient seminar. This meant that persons *not* attending the seminar had the opportunity to participate in the focus groups, and we planned to organize additional focus groups if we did not obtain enough information during the patient seminar. However, no one who did not attend the seminar provided consent to participate in the focus groups. Considering the rich material provided by the three focus groups, we did not consider it necessary to arrange additional focus groups.

4.1.3 Individual interviews

In study I, the data were collected in individual qualitative interviews of 10 young persons who had been predictively tested for AIP as minors (<16 years of age). Qualitative interviews are generally referred to as *structured*, with a structured questionnaire, *semi-structured*, with an interview guide and open-ended questions, or *in-depth*, in which a few issues are covered in great detail and the questions are based on what the interviewee says. We used a semi-structured approach and an interview guide with main topics and open-ended sub-questions, but with the opportunity to diverge by pursuing responses or new topics of interest.

The qualitative research interview is a special meeting between people. It is important to recognize that clinical and qualitative research interviewing is quite different in both nature and purpose (58). For clinicians in the health field, interviewing is a familiar activity; however, the skills learned through clinical interviewing are not necessarily appropriate for qualitative research interviews (56, p 78). From the clinician's point of view, the purpose of an interview is to find answers to questions so that proper management of the patient's condition can be established. As such, open-ended questions are less useful because the clinician must seek conclusions, usually within a

limited amount of time. By contrast, in the qualitative research context, the aim is to discover the participant's own meanings and to avoid making or imposing assumptions (58). This means that new ideas or themes that were not anticipated can strengthen the study and provide the kind of data that are unique to qualitative research.

Because human communication is so intertwined with the context and social setting, and is a dynamic process that affects both the interviewer and the interviewee, it is important to be aware of how the double role of being both a (genetic) counsellor and a researcher might affect the participants. When performing qualitative research, it is important to consider how one is viewed by the participants, and this is especially important when the researcher is a health-care worker. Although there is no therapeutic intention, there is a potential for insight and reflection by the participants. By asking "tell me more about that" or "can you elucidate or clarify", interviewees can be challenged to contemplate their experiences and, consequently, to discover new connections and meanings and to develop new insights into their experiences. In this sense, just by interviewing participants about their experiences, the experience itself changes and takes on new aspects to consider. Research interviews are an active process, and non-directiveness and being aware of potential leading questions are essential (58). To be able to produce relevant and clinically important results with potential applications, it is vital that the data collection is performed with reflexivity and humility so that the interviews do not simply reflect the researcher's own personality, passion or expected findings (56, p 129).

All interviews were performed by the first author. Five interviews were performed at each participant's home and five were performed at a hospital close to each participant's home, as chosen by each participant. The participants came from different parts of Norway, and all but one interview required the interviewer to travel some distance. All interviews were performed on separate dates, except for two that were performed on the same day because they were in the same city, to which the researcher was required to travel.

Each interview started with an introduction to the interviewer and a presentation of what to expect from the following session. It was noted that there were no right or

wrong answers and that it was the participant's own experience that was of interest. The right of the participant to withdraw consent to participation at any time before publication was mentioned explicitly. The participants were told that the interviewer would strive to achieve full anonymity but, with qualitative findings and presentation of quotes, this could not be guaranteed. Permission was asked for the interviewer to contact the participants by telephone for clarification in cases of uncertainty about the meanings or statements, although this was not considered necessary. All interviews were audiotaped and field notes were taken. In one of the interviews, the tape recorder malfunctioned, and an additional 20-minute session was required during which the participant was asked to repeat some of the most striking and interesting information.

4.1.4 Focus groups

Focus group studies are designed to provide distinctive types of data based on the interactions between and discussion among the participants, and in this way to capitalize on the different experiences of the participants (58). Although originally developed for use in communication studies of mass media, marketing and advertising, it has become popular in a number of fields, including health sciences (59). We found focus groups appropriate for studying PCT because of the long, perhaps lifelong, periods of remission and we expected that some of the participants would have few experiences with PCT. Hence, we anticipated that communication between participants could help to elucidate the different aspects of their experiences with PCT.

When determining the number of focus groups needed, it is often considered a rule of thumb that three to five groups can provide "saturation"; that is, that one can anticipate that adding more groups will not generate new understandings or insights (60). There are several factors to consider when determining the number of participants in a group. Larger groups will typically require greater participation by the moderator, which is generally undesirable and demands skills of the moderator, but can be advantageous if the topic is something that the participants have little involvement with. An appropriate number of participants is generally regarded to be between six and 10 participants, depending on the topic and research question. Sustaining the discussion might be difficult with fewer than six but difficult to manage with more than 10 (59,

60). We recruited 21 participants and found that three groups of seven participants each was optimal. In our experience, the size of the groups was appropriate because it allowed a good pace and discussion among the participants, who seemed to participate enthusiastically; although some were more verbal than others, all participants could voice their opinions.

Some homogeneity of the group composition is generally advantageous for enhancing interaction and making the participants feel comfortable enough to discuss the topic at hand (60). When planning the composition of the groups, we tried to achieve a somewhat equal combination of women and men, and we set as inclusion criteria that all participants would have some experience with PCT symptoms during the past 5 years. Because of last-minute changes by some participants, the two first groups had a similar number of men and women whereas the third group had five women and two men. The groups had similar discussions, although there were some differences in group dynamics, which meant that some topics received more attention in some groups than in others.

The first group can be informally called the “chronic group”. This group had a comprehensive discussion of the topic of the health complaints that can be attributed to PCT. Some of the participants had chronic health complaints, such as tiredness and fatigue, brought this aspect into the discussion more than the two other groups. The second group can be referred to as the “blood-values group”. They were more interested in ferritin level and when to start phlebotomy than were the other groups. The third group can be labelled “the horror stories group” because they discussed the most dramatic depictions of PCT. However, it must be emphasized that the groups did not differ to the extent that labelling them as different groups is justifiable; that is, the informal labelling presented here is included only to show that the group dynamics can differ and how one person in one group can shift the focus and direction of the discussion and the interplay between the participants.

Moderator involvement refers to the degree to which the moderator manages the group dynamics by controlling the discussion (60). In our focus groups, we used a semi-structured interview guide (see Appendix 1). Free discussions among the participants

were encouraged. Moderator involvement was limited to specific situations such as moving to a new topic at the end of each discussion, when discussion strayed from the research question, or when some participants were not contributing to the extent that they wished. If interesting points came up and a more thorough elucidation of that topic was wanted, the moderator used the field notes and waited for an appropriate moment to follow up on the statement. However, because of the limited time and number of participants, the moderator sometimes need to take a more active role in a focus group interview than in an individual interview. Two co-moderators (one in each group) aided in the management of the three focus groups. Both had experience in qualitative research and were knowledgeable about porphyria. Their main tasks were to help in any unexpected situations, for instance if somebody knocked on the door during the focus group interview and asked a question. Otherwise, they were asked to take notes on the participants' statements, which was helpful in identifying the speaker in the later transcriptions. In hindsight, this may not have been necessary because the participants came from different parts of Norway and had distinct dialects and, although the discussions became lively, the participants were good at waiting "their turn" for speaking.

4.1.5 Analysis

In qualitative literature, the words "theme" and "categories" are sometimes used interchangeably. The following definitions are used in this presentation of the analytical steps used in papers I and II. A *category* or *code group* is a "collection of similar data sorted into the same place, and this arrangement enables the researcher to identify and describe the characteristics of the category". A *theme* is "a meaningful 'essence' that runs through the data" (61). This implies that, when describing the analytic process, the categories are used as a working step towards developing the final themes presented in the articles.

ID allows the researcher to use the analytic approaches that are appropriate for answering the research question at hand. Instead of committing to a certain philosophical or theoretical position, a pragmatic and eclectic approach, which is based firmly on reflective decisions, is considered to be more appropriate and better

suites to aid the researcher's creative processes to achieve relevant and fruitful results. This implies that ID does not provide any rigid step-by-step "recipe" for producing sound research results but instead refers to recognized and well-established procedures that the inexperienced (or experienced) researcher might use. No such step-by-step instructions should be followed blindly or uncritically because this could result in technique overshadowing creativity in the process and introduce the risk of ending up with empty and meaningless results (56, p 153).

When it comes to analytic approaches, ID allows for a variation of techniques and traditions, as long as the use is based on a logical, systematic and transparent process relevant to the research question at hand. This means that deviance from the standard procedure is not necessarily wrong, but rather what Sandelowski (Sandelowsky in foreword 56) calls *strategic non-compliance*. It is the researcher and not strict devotion to the analytical rules that should drive the interpretation. Creativity and intuition are therefore important, and a too-rigorous coding process can cause the loss of important insights. It is therefore recommended that, as a point of exit, the analysis takes a wide focus and is sceptical of the immediate impressions by taking care not to start a too detailed coding process too early. This will help to prevent premature coding threatening the process by blinding the researcher (56, p 145-147). All ideas and frameworks that are brought into the study must be carefully examined and noted so that they do not influence the researcher in ways that may not be intended. This might be harder to do in studies related to disciplinary knowledge compared with those based on formal and explicit theories (56, p 99).

The analysis presented in paper I is described in a short and general way, and a more thorough description is presented here. This analysis was based mainly on an ID approach; however, given that the first author had prior experience with STC, this influence should be considered. After eight of the 10 interviews were completed and transcribed verbatim, the total text was read as a whole, and as the last two interviews were completed, they were incorporated into this holistic reading. The text was then transferred into QSR N6 Software (QSR NUD*IST. Qualitative Research and & Solutions Pty Ltd., 1997). The reading identified nine categories: 1) disease in the

family; 2) own disease; 3) predictive testing; 4) information; 5) seriousness; 6) psychosocial aspects; 7) positive aspects; 8) negative aspects; and 9) GC. These categories were identified in the text based on the research question but also mirrored the interview guide to some extent. The categories were deliberately created as open to avoid the premature closing of categories.

Using these categories, each informant's interview was then coded. Text that did not provide meaning related to the research question was removed. At this step, quotes that seemed to stand out were collected in a separate document. In the next step, summaries of each category were decontextualized so that they were no longer based on individual interviews, which allowed for cross-case combinations. Using these summaries, an iterative process was started in an attempt to present the meanings identified in the previous categories. This process was lengthy and, after several rounds of going back to the text as a whole and looking at the decontextualized text, four themes emerged. At this stage some choices were made about which results would be prioritized and presented under each theme, and whether the results would be relevant to the intended audience. As a final analytic step, the total text was read as a whole, and all of the interviews were listened to again, with the completed themes in mind, to ensure that meaning was not lost or added in the analytic process.

4.1.6 Analysis paper II: Systematic text condensation

The analysis in paper II was influenced and inspired by STC (62) but not followed strictly. STC was initially developed as a strategy for guiding novices in qualitative analysis. It is easy to share and aids transparency in the analytic process (62), which was one of the main motivations for using this approach in paper II. STC is a strategy for qualitative analysis elaborated from Giorgi's psychological phenomenological analysis four-step procedure. STC is an explorative approach whose aim is not to cover the full range of experiences but rather to present possible and vital experiences of a phenomenon on a descriptive and conceptual level. A decision trail was used to aid both reflexivity and transparency in this process. However, as Malterud says, the analytic process can never be fully articulated (62).

STC follows four steps.

Step 1: Obtaining a total impression and overview of the data.

At this point, one tries to stay atheoretical and to avoid preconceptions. In the analysis of paper II, this was done by reading the transcripts from all of the interviews as a whole while keeping an open mind and avoiding systematizing the results. In STC, as in ID, stepwise analysis is recommended, and the reading of transcripts should start before all the data are gathered. In STC, one of the reasons for this is to keep the amount of data manageable. Because all three focus groups were held on two consecutive days, this was not feasible and the total data material was read as a whole, although there was some informal analysis immediately after each focus group. At this stage, four *preliminary* themes were identified as a basis for further analysis: 1) large variations in symptom experience; 2) taking control; 3) treatment; 4) prevention of symptoms.

Step 2: Identifying and sorting meaning units.

At this stage, the data are organized systematically by going through the text and coding the *meaning units*. A meaning unit is a text bit containing some meaning relating to the research question. The meaning units are sorted into categories. Both STC and ID recommend a very flexible process and that rigid coding should be avoided (56, 62). In paper II, this was done by first sorting the identified meaning units under the four preliminary themes identified in step 1, which now functioned as categories. This process involves decontextualizing data by removing them from their original context. This was performed across cases, following the natural sequence of the focus group communication by manually cutting sections out of the transcripts using the word processing copy–paste function and inserting them into new documents.

Step 3: Condensing from code to meaning

In STC, the empirical data have now been reduced to, in our case, four code groups. Each code group was then analysed internally by sorting meaning units into

subgroups. In STC, an artificial quotation is produced based on the condensed subgroup; however, this was not done in our analysis. Instead, we synthesized the meaning units that were collected across cases into “coherent” statements belonging to each individual participant in the focus groups. In paper II, this is called “longitudinal coding at an individual level” for every subcategory. This was done to see more clearly each individual’s “narratives” and provided a step towards understanding the material in depth. This was done both for the entire empirical material and on the subcategory level, in addition to the initial cross-case analysis.

Step 4: Synthesizing from condensation to descriptions and concepts

This final step in the analytic process is to re-conceptualize and present the descriptions and concepts that can form credible stories to elucidate the research question. In this process, the researcher takes on the role of re-narrator. In this research, this was (as always) a lengthy and iterative process, which involved making sure that meanings were presented conscientiously while recognizing that this is a “multivocal synthesis” that is not expected to represent every participant’s exact meanings (62). This step results in a condensed and more abstract presentation of the meanings in each main theme. Identifying headings for the themes and sub-themes is considered an important part of the analysis and is expected to express a highlighted perception of what the study adds. As a final step, the total text was re-read several times while systematically searching for data that challenged the results.

4.2 Study III

Paper III is based on a cross-sectional questionnaire mailed to all persons older than 18 years and registered with AIP or PCT at NAPOS. In this paper, only data from the PCT population was used.

4.2.1 Study population

Of the persons registered with PCT at NAPOS, 40 were excluded. Thirty-four of these were because they had sPCT but there was no contact or analysis of samples performed during the preceding 10 years. Three were registered with an unknown address and three had an unclear diagnosis or subclinical PCT. Of 484 included

persons, 272 returned the questionnaire (56%). One hundred and seventy responses were returned after the primary dispatch (May), and 80 and 22 were returned after the first (June) and second reminder (October), respectively

Twenty-five persons did not participate for the following reasons. Two were deceased, nine were returned marked with “address unknown”, nine returned their consent form stating they did not want to participate, two returned the questionnaire unanswered, one could not participate because of health issues, and two contacted NAPOS with questions regarding their diagnosis, and were consequently excluded because of subclinical PCT. The total of 186 non-responders included 82 women and 104 men. Of these, 15 were registered as having latent PCT and 171 as having active PCT. Their age ranged between 20 and 95 years: 43 were younger than 50 years and 143 were older than 50 years. After exclusion of nine participants who had returned the questionnaire but had not answered the question about disease activity, a total of 263 participants were included in the final analyses. This resulted in a total response rate of 54%, although the number of respondents varies in the statistical analyses because of missing items on some scales.

4.2.2 Patient-reported outcomes

A PRO can be defined as “*a measurement of any aspect of a patient’s health status that comes directly from the patient, without interpretation of the patient’s responses by a physician or anyone else*” (63, p 8). In paper III, self-reported health complaints, illness perception and porphyria-specific distress were analysed in addition to various data about demographics and self-reported disease activity. A presentation of the three standardized and validated measurement instruments used in paper III follows. The instruments and demographic questions are presented in Appendix 2.

4.2.4 The Brief Illness Perception Questionnaire

The BIPQ is defined as a “*nine-item scale designed to rapidly assess the cognitive and emotional representations of illness*” (40). The original Illness Perception Questionnaire (IPQ) assesses the five cognitive illness representations adapted from the CSM of Leventhal et al (64). A revised version of the questionnaire (IPQ-R) elaborated the model further by splitting the control component to personal and

treatment control and adding the assessment of emotional representations of illness, which is an important aspect of the CSM. Finally, a new dimension to assess the extent to which the illness representations provide a coherent understanding of the illness was incorporated (65).

In this study, we used the BIPQ Norwegian version (66), which is a shorter version of the 80-item IPQ-R. Because we used a battery of instruments in the full questionnaire, the shorter BIPQ was deemed more suitable. The BIPQ has satisfactory validity and reliability and provides a rapid assessment of illness perception, which could be particularly useful in large-scale studies (40). Five items measure cognitive illness representations (consequences, timeline, personal control, treatment control and identity), two items assess emotional representations (concern and emotions), and one item assesses illness comprehensibility (coherence). In the present study the instrument was made porphyria specific; for example, the word “illness” on the general BIPQ version was changed to “porphyria” (see Appendix 2).

Responses to the first eight items are measured on a continuous 10-point scale. The ninth item comprises an open question about the causal explanation of the disease. This last item was not used in our study (paper III). According to the literature, a total score can be computed, and higher scores indicate a higher perceived threat by the condition (40). In the present study, the internal consistency (i.e., the degree of interrelatedness among the items (67)) of the total scale was checked by calculating Cronbach’s alpha and was found to be adequate (Cronbach’s alpha = 0.67)(63, 68, 69).

4.2.3 The Subjective Health Complaints Inventory

In the present study, self-reported subjective health complaints (SHCs) were measured using the Subjective Health Complaints Inventory. An SHC has been defined as a measure of “...*the occurrence and severity of somatic and psychological complaints. It records ailments based on objective diseases, but is particularly sensitive to health complaints with minimal or no clinical findings*” (70). Others have defined SHCs as “*all health complaints experienced by a person*” (71).

The aim of the SHC is not to arrive at new diagnoses or disease classifications, but may be a useful tool to follow the well-being, or lack of such, in individuals or specific groups of individuals. The SHC “*seem to be a fast, inexpensive, simple and reliable way to assess SHCs as they occur in the normal working population, without diagnoses, hypotheses or attributions*” (72). The Subjective Health Complaints Inventory measures both the frequency and severity of self-reported health complaints during the past 30 days on a 0–3 Likert scale without mapping the diagnosis or symptom attributions. The instrument is a 29-item scoring system that is categorized into five subscales: musculoskeletal complaints (headache, neck pain, upper back pain, lower back pain, arm pain, shoulder pain, migraine and leg pain); pseudoneurology (palpitation, heat flushes, sleep problems, tiredness, dizziness, anxiety and sadness/depression); gastrointestinal (gas discomfort, stomach discomfort, diarrhoea, constipation, gastritis/ulcer, heartburn and stomach pain); allergy (allergies, breathing difficulties, eczema and asthma); and influenza (cold/flu and coughing) (72, 73). The instrument has shown satisfactory reliability and validity (72). In the present study (paper III), only the mean total severity scores was assessed.

4.2.5 The Impact of Events Scale

The IES is defined as “*a broadly applicable measure of subjective distress relating to any life event*” (41). In the original instrument, IES was found to have satisfactory reliability as shown by adequate test–retest results. Sensitivity was tested by calculating the expected and relevant differences in self-reported responses to life events of varying magnitude and by detecting changes observed by experienced observers (41). A review of the psychometric properties of the scale concluded that the instrument is a useful measure of stress reactions after a range of life events, and that the two-factor structure has satisfactory reliability and validity and can be used clinically to discriminate between mild and severe distress (52). A later review concluded that “*the IES performs very well as a self-report instrument for subjective psychological distress related to a specific stressor*”(50). In paper III, we chose to use the term “psychological distress” when referring to the measured responses of intrusion and avoidance, and this term is used throughout the present thesis.

Although the IES was not developed to assess post-traumatic stress disorder (PTSD), the instrument is used widely as a measure of PTSD. This has led to criticism of its content validity because it does not contain items covering hyperarousal, a diagnostic criterion for PTSD. As a result, a revised version of the IES has been proposed (IES-R) (49), which aims specifically to assess and diagnose PTSD.

In paper III, the instrument was made porphyria specific by adding the word “porphyria” to all 15 questions; for example, item 1 was changed from “I had waves of strong feelings about *it*” to “I had waves of strong feelings about *porphyria*” (see appendix 2). In the original development of the instrument, the anchoring to a specific context was done by entering the life event at the top of the form (41).

4.2.6 Statistical analyses

One-way Welch analysis of variance (ANOVA) was performed to determine whether scores on the BIPQ, SHC total score, and IES intrusion and avoidance differed between the three PCT subgroups (Table 2, paper III). There were some outliers, as assessed by boxplots, and the data were not normally distributed for each group, as assessed by the Shapiro–Wilks test. There was heterogeneity of variances, except for three BIPQ items (treatment control, coherence and overall BIPQ), as assessed by Levene’s test of the homogeneity of variances. A one-way Welch ANOVA was consequently used to identify differences in scores between the three PCT subgroups because this is considered an appropriate test when there is heterogeneity of variances (69).

In the multiple linear regression analysis, those scoring 0 on the IES subscales were removed from the analysis, and the remaining participants were included. The analysis of the subscale intrusion included a total of 51 participants who reported active symptoms and a score >0 and 155 who reported remission or latent disease and a score >0. For the avoidance subscale, the corresponding numbers were 50 and 139, respectively. Because of non-normality, the variables were log transformed in the multiple linear regression analysis (Table III, paper III) and the logistic regression analysis. The variables were back transformed to their original units in the results presented (Table III, paper III). We also performed control tests to determine whether

other psychosocial factors such as cohabitation or employment status (working/not working) were significant predictors of porphyria-related distress. However, entering these factors into the multiple linear regression models did not change which independent variables (IVs) came out as significant.

Scoring of the PROs and the handling of missing data were done according to the scoring manual for the BIPQ (40, 74), IES (41) and SHC (72).

ETHICAL CONSIDERATIONS

The three empirical papers and the present thesis comply with the Declaration of Helsinki. All the three studies were approved by the Norwegian Regional Ethics Committee; the reference numbers are: paper III: 2010/149; paper II: 2012/1078 and paper I: 2008/9943-ØYSV. In paper I, the guidelines at the time of the study also required permissions from the Norwegian Social Science Data Service, and the necessary approval was gained (reference number 19838/2/GRH).

For all participants in both the qualitative and quantitative studies, informed written consent was required for participation.

For participants younger than 18 years of age (paper I), written consent was obtained both from the participants and their legal guardian.

The objective of interpretive descriptive research is to present knowledge that may have practice implications. This means that one must defend why the knowledge to be generated is necessary because of the potential risk that such knowledge can be misused, for example, in regards to marginalized groups. This is what Thorne refers to as the *moral defensibility* of the research performed (56). When performing predictive genetic testing of minors for a disease for which there are no guaranteed actions that will improve prognosis, it seems evident that an investigation of the effects such testing might have is easily defended. In the case of paper I, however, both the results and the research process itself needed to be assessed. Discussing life situations with young participants is very personal and may be a new situation for many participants. There might have been some problematic aspects that emerged that did not have anything to do with porphyria but gave rise to the realization that the situation could be

ethically challenging. Some participants opened up during the interview, but there was no opportunity to follow up on their personal stories. On the other hand, this may not necessarily only be negative. As mentioned earlier, the aim of a qualitative interview is not therapeutic, but having the opportunity to reflect on one's own situation can be beneficial and thus may have a positive and therapeutic effect. However, one cannot ignore that the interview itself may have altered the young participants' perception of the disease—for better or worse.

Qualitative studies have some problematic issues such as the potential for identification of participants because their pseudonyms are attached to the quotes presented in the text and tables. This problem was contemplated, but we found it important to contextualize the quotes and to provide some background information, and consequently we judged this to be acceptable. The problem of anonymity was an extra challenge for the focus groups, as in any group situation, and this was addressed explicitly in each group. All the focus group members were requested not to share any of the information they had learned outside of the group, which in other situations may have been difficult because they were participating in a patient seminar and expected to share their experiences.

In the cross-sectional questionnaire study, participants were asked to return their written consent to participate together with the finished questionnaire. In a few cases, the questionnaire was returned without the consent. After discussions with representatives of the Regional Ethics Committee, we decided to consider the fully answered questionnaires as consent to participate and consequently chose to include them in the study.

The recruitment of participants for the study in paper III may have had ethical implications because some of the people who were sent the questionnaire may not have known or considered themselves to have PCT. This was also an argument for not including persons registered with sPCT at NAPOS who had not had biochemical tests for >10 years. This was the feedback from two persons who contacted NAPOS with questions regarding the diagnosis. One had been predictively tested many years ago and did not know that he or she was a mutation carrier. The second person asked if he

or she had the disease, and the person in question proved to be diagnosed subclinically while being tested for another type of porphyria.

SYNOPSIS OF RESULTS

6.1 Paper I: Psychosocial aspects of predictive genetic testing for acute intermittent porphyria in Norwegian minors

AIP was experienced as a vague condition, and participants and their relatives attributed a variety of symptoms to the disease. Early genetic testing and diagnosis was considered important and its perceived advantage was that the patient could take precautions by modifying lifestyle, but finding motivation for such modification was difficult. AIP posed few psychosocial challenges to the participants but although AIP was a small part of the participants' identity, the risk of manifest disease was a cause of concern for some. This can be ethically challenging and underlines the importance of appropriate counselling. The participants were content with their present level of knowledge, but they expected this to change if their situation in life changed. However, they felt they could obtain relevant information when needed.

6.2 Paper II: A skin disease, a blood disease or something in between? An exploratory focus group study of patients' experiences with porphyria cutanea tarda

Participants' symptoms varied from fragile skin to what they described as a desperate situation comprising huge blisters, skin falling off and feeling as if in a "horror movie". For some, itching was a considerable problem. PCT was perceived as being a blood rather than a skin disease, and this made participants contemplate whether other health issues were caused by PCT and if there were more to this disease than the specialists knew.

Although most participants had not experienced relapses, they regarded PCT as a chronic disease that required controls and prophylactic phlebotomy for the rest of their lives. There were reports of frequent controls, blood tests and prophylactic phlebotomy. Treatment with phlebotomy was not without problems, but it caused rapid improvement and made the situation less dramatic.

6.3 Paper III: Illness perception and psychological distress in persons with PCT

PCT is a disease that is accompanied by photosensitivity, and little is known about the patient's perspective of this condition. Two hundred and sixty-three participants answered a cross-sectional questionnaire. One trend in their responses was that persons reporting activity of PCT symptoms also reported a greater perceived illness threat, more health complaints and greater psychological distress compared with those in remission or the latent phase. However, there was no association between self-reported PCT activity and higher scores on psychological distress. Perceived illness threat and total health complaints were associated with greater psychological distress. PCT was perceived as a chronic condition with strong personal and treatment control. This has implications for the clinical follow-up of PCT patients in both the active and remission phases.

DISCUSSION

This chapter is divided into a discussion of the most important empirical findings, which is followed by a discussion of methodological considerations.

7.1 Discussion of the results and empirical findings

The discussion of the most important findings is based on the specific aims formulated in the papers and the overall objective of this thesis. This section is divided into discussions of relevance for AIP and PCT combined, which is followed by a discussion of the results for AIP and PCT separately.

7.1.1 Papers I–III: AIP and PCT

AIP and PCT present with completely different symptomology and challenges and, for many clinicians, the choice to combine the two conditions in the same thesis might not be obvious. However, this is logical for the genetic counsellor working exclusively with porphyrias because of the focus on the two most common forms for porphyria, which have received little attention in terms of the patients' subjective experiences.

Results from all three papers in this thesis indicate that separating symptoms of AIP and PCT from other health complaints can be difficult. This was reported by the young

participants in study I, but was also evident in the comments made by their relatives. This was also evidenced in the data in papers II and III but was more unexpected because the symptoms of PCT are skin related and were not expected to be confused with other health complaints, except perhaps those associated with other dermatological symptoms. That patients with a confirmed diagnosis attribute various health complaints to their diagnosed condition is perhaps not surprising, but is it problematic?

In paper I, some of the young participants worried that they would not be able to work full time if they developed active disease, a finding that shows that how the condition is perceived has important implications for the patients. In paper II participants reported inappropriate and frequent follow-up, blood tests and prophylactic phlebotomy. The results of paper III, in which psychological distress related to porphyria was associated with illness perception and total burden of health complaints but not with symptom activity, indicates that attributing general health complaints to PCT can be distress causing. This means that there is potential for overtreatment, medicalization and psychological distress related to attributing any health complaints to their condition. The theories of Horowitz and Leventhal were both developed partly with the aim of improving patient compliance with preventive measures and treatment of disease. To the genetic counsellor dealing with the risk of disease as much as disease itself, the point of departure is also that of avoiding medicalization of persons at risk for developing symptomatic disease. Medicalization can be understood as the increasing number of human aspects of life that are understood in medical terms (75). A recent Norwegian study showed that genetic counsellors and geneticists who provide GC in fact view it as a defence against medicalization (76). In this sense, one could claim that, as surely as clinicians and counsellors must understand porphyria in light of the biopsychosocial understanding of disease, it is also necessary to have a clearer definition of what constitutes AIP and PCT symptoms. Genetic counselling is a communication process aiming at helping individuals and families understand medical facts and diagnosis, and the probable course and what management is available, including understanding options for dealing with risk of recurrence in a sensible way (39). This perspective favours using the biomedical approach to defining an AIP attack

and the symptoms of PCT because patients risk further medicalization and overtreatment in interpreting any health complaint as a sign of AIP or PCT. This is something that should be debated and discussed continuously. In the latest guidelines for the follow-up of PCT patients, NAPOS advises that too-frequent controls for patients in remission might contribute to the medicalization of this patient group and is warned against.

At a time when the risk of various diseases is gaining increasing attention, the possibility of predictive genetic testing means that persons may have to relate to diseases they do not yet have—and are likely to never develop. The CSM is a theoretical framework developed by psychologists to describe how individuals perceive and construct risk in relation to illness. This model recognizes that individual risk perception is not necessarily based on rational and objective risk estimates but is instead influenced by personal and others' experience with illness, for example that of family members (77). This is illustrated in paper II by stories of family members who found it problematic to have children if one was a carrier of a pathogenic UROD mutation. There were also considerable discussions in the focus groups about whether they would want at-risk relatives to have predictive genetic testing. This underlines the ethical aspects and emphasizes the need for appropriate counselling about genetic testing. So how can we use these results in GC and predictive testing for AIP or PCT? Risk communication can be defined as “*the open two-way exchange of information and opinion about risk, leading to better understanding and better (clinical) decisions*” (Ahl et al 1993, pp 1047 in 77). Research has shown that individuals have a tendency to dichotomize risk—that is, they have either a higher risk or average risk. Simply offering people predictive genetic testing without proper counselling or the possibility of later updates and further counselling can be of little practical value and possibly damaging and distressing. Also in regards to Horowitz' stress-response theory, a dose-by-dose strategy is suggested for people to deal with genetic test results (78). Although one would regard this intuitively as less important in low-penetrant conditions with good prognosis such as PCT, results from paper II and III indicates that the opposite may be true for some persons. A review article about the patient perception of clinical genetics found evidence that there is a tendency to overestimate

risk and that, although there is little evidence of the effect of this perception, a high risk estimation can affect health adversely and lead to inappropriate preventive measures (77). This is an argument of the need for health-care providers to understand patients from a biopsychosocial perspective while also maintaining a biomedical view of the disease itself. When possible, clear answers should be provided about what is caused by porphyria and, importantly, what is not. The BPM also acknowledges that a more biomedical approach is sensible for cases of exacerbation of chronic disease (42).

7.1.2 Paper I: AIP

In the case of predictive genetic testing of minors, information about risk was considered advantageous and beneficial, even when it did not include any explicit changes in plans for the future. That AIP was a small part of the participants' lives and identity was a finding in itself. Participants did not change their lifestyles *because of* AIP or *in fear of* developing active AIP. One should consider these findings in the context of the Norwegian health-care system. Norway is classified as a so-called "welfare state"; because of its strong petroleum-based economy, it is characterized by large public expenditure on public health-care services and extensive social securities (76). That three of the participants were clear about their expectations of active AIP as invariably resulting in impairment of their ability to work and that they might not be able to continue their chosen careers may have been discussed differently if these were young adults in countries where they could not expect to be cared for by the welfare system if unable to work. One would expect that the risk of not being able to work would affect plans for the future in some form and that AIP affects career and family planning has been reported by others (20).

How this is handled depends on the social context as well as on personality and the way risk and the threat presented by AIP is perceived. The findings of paper I fit with the concept that illness perception and coping with illness is a process, as presented in the CSM of illness perception. This is illustrated by the finding that the participants perceived that their current knowledge about AIP was sufficient but that they expected this to change if their situation in life changed. It is unclear why active AIP was

perceived as incompatible with the ability to work, which raised the question about whether this perception is a realistic and accurate view of the possible future consequences. The literature defines recurrent AIP attacks as four or more attacks per year (10). Only 3–5% of persons with manifest AIP fall into this category, which means that most persons with AIP will be able to keep a job, even if they develop manifest disease. By contrast, a study from Sweden showed that one-fifth of the subjects with AIP reported receiving disability pension, but the authors warned that these figures might not be appropriate in the present because it was easier to obtain approval for the disability pension in previous years (22).

There is evidence to suggest that how relatives experience a particular disease influences personal risk perception, coping with, and adjustment to, that disease (77). That the young participants who described a fear of developing manifest AIP had relatives with poor health and that their health problems seemed to be attributed exclusively to AIP might explain their expectations that active AIP has very serious consequences in terms of living a normal life. It has been estimated that around 20 % of those receiving bad news in regards to genetic testing will develop symptoms of stress response syndrome, although these numbers refer to genetic testing for serious disease (78). What constitutes “serious” disease is however subject to discussion, and illness perception and individual perception of risk are also factors here, but AIP can be potentially life-threatening. This also supports the concept mentioned above that a clear definition of what health problems can, and cannot, be caused by AIP is important to both the person experiencing symptoms and their at-risk relatives who opt to have predictive testing to learn about their potential risk of developing AIP.

The finding that genetic testing and carrier status did not have a large psychosocial impact on the participants may not necessarily extend to other persons or participants. This illustrates what Thorne says is *probable truth* in qualitative research. Researchers must remain humble in view of what can be known about a phenomenon (56). However, this does not change the experiences reported by participants in this study. Without claiming that these experiences are the same for all persons with an AIP

mutation, they do provide suggestions for possible ways of handling the challenges of AIP.

It was clear that, also for the participant who were anxious about the development of manifest AIP, knowing their risk of AIP did not change their plans for the future or cause them to take precautions. The results of paper I showing that the psychosocial impact of predictive genetic testing was quite small are consistent with a recent systematic review article that concluded that there was little evidence of harmful psychological consequences of genetic testing and providing such information to children. However, there is a lack of data on the subject, and clinical caution is still warranted (79).

7.1.3 Papers II and III: PCT

The present research shows that PCT is not always unproblematic and that it can have implications because of both the severe symptoms and the patients' perception of the illness. For instance, compared with melanoma patients, persons with active PCT scored higher on consequences, timeline and identity, and higher or equal on the emotional response item on the BIPQ (80). The biomedical view of PCT is that it is a disease with good prognosis that is easily managed and treated, but at the same time there is also a focus on potential late complications such as diabetes, cirrhosis and liver cancer (81, 82). This could explain the association between illness perception and psychological distress. Some PCT patients worry about late complications of PCT and whether or not they take the necessary precautions. However, although there was a significant association between illness perception and psychological distress, the direction of this association is uncertain and the design of the study did not allow for conclusions about causality.

Whether PCT is a distress-causing life event is debatable. Paper II showed that PCT may have a large psychosocial impact on some patients and a smaller impact on others. We therefore wanted to investigate the levels of distress reported by the participants and to identify those factors associated with higher levels of porphyria-related distress. We found that 20% scored 0 on the Intrusion subscale and 27% scored 0 on the Avoidance subscale of the IES. This was not surprising, as we expected many

participants to report PCT as not a distress-causing condition. Perhaps further analyses of those reporting no psychological distress could have provided important information, but we did do a logistic regression analysis to identify the variables associated with scoring > 0 on the IES and this confirmed that illness perception and total subjective health complaints were significantly associated with a score > 0 . Another aspect that could have yielded interesting information was to identify the participants who reached a clinically significant level of distress. By using cut-off values, the individuals whose scores on the IES suggested a cause for clinical concern could be identified. Various cut-off values have been suggested (49, 83, 84), but they do not seem to be used much and it is unclear whether these are useful in clinical settings. How to identify PCT patients with clinically significant levels of psychological distress must therefore probably rely on the clinicians expertise and experience, but a study from 2004 has shown that dermatologists recognize depression and anxiety disorders in only 33% of outpatients (85) and that psychiatric disorders frequently go undetected in dermatology clinical practice (23, 86).

In study III, illness perception and higher scores for SHCs were significantly associated with higher distress scores. One could debate whether the emotional representations of PCT measured by BIPQ are closely related to the construct of porphyria-related distress and that this can partly explain the significant association between the BIPQ and IES. The literature claims that elements of fear, anger and *distress* are incorporated into the emotional representation of illness (40), although claims that they are representations of avoidant and intrusive thoughts are speculative. This was also one of the arguments for using the *total* illness threat measured as a variable in the multiple linear regression models. The total sum includes measures of both emotional and cognitive representations of illness and is a measure of how threatening the illness in question is perceived (40).

That those reporting higher perceived threat by PCT would report more psychological distress was expected. However, it was surprising that reporting more health complaints was associated with greater distress. There is little reason to suspect that persons with PCT should report higher or lower prevalence or severity of SHCs than

the population at large, except that PCT usually presents at a mature age and is associated with liver disease and certain lifestyle factors, such as alcohol and smoking (87), factors that are known to affect health. In paper II, the participants did discuss their suspicion that PCT caused health complaints other than skin manifestations, and there was a tendency to attribute a variety of health complaints to PCT. SHCs occur in more than 75% of the Norwegian population when assessed over a 1-month period (88), and it has been suggested that SHCs are relatively stable in the population but that factors such as illness perception and workload may affect the reported prevalence and severity of SHCs (89). This raises the question about whether the observation that the total burden of health complaints is associated with porphyria-related distress is connected to the experience of PCT as a systemic condition. That is, the more health complaints a patient reports and experiences, the greater the distress because the patient assumes and perceives these SHCs as directly related or somehow connected to PCT. According to the CSM, the perceived cause of disease can be split into internal and external causes (46). Whether PCT is caused by internal or external factors is an interesting question. In Norway, about 50% of PCT cases are associated with a mutation in the UROD gene and can be classified as fPCT (16). However, because of the low penetrance of 10% and the fact that PCT also occurs in a sporadic and non-inheritable way, it is perhaps not biomedically correct to denote PCT as condition caused exclusively by internal or external factors. Although sunlight is a necessary and obligatory factor for developing *symptoms* of PCT, sunlight does not in itself *cause* the excess hepatic production of porphyrins. This refers back to the philosophical question of what illness *is*. According to the BPS model, the difference between being well and sick is not merely the result of biological factors but will always be influenced by culture, social, psychological and/or environmental aspects (42).

The qualitative focus group study showed that PCT is perceived as something more than an uncomplicated skin disease. We found this interesting and felt that it indicates the need to assess the perception of PCT by persons living with this condition in the active, remission and latent phases. The results reported in paper II showed that PCT was perceived as a chronic condition requiring follow-up, controls and prophylactic treatment, and that some patients found it necessary to attend very frequent controls.

PCT was suspected to cause a range of symptoms and health complaints. The results reported in paper III confirmed that PCT is perceived as a chronic and lifelong disease despite its good prognosis and likelihood of full remission. But why do patients in remission, who no longer need treatment, report psychological distress? Is it the uncertainty of new relapses? In view of the results showing that the total health complaints were associated with porphyria-related distress and the results in paper II showing that some PCT patients have a tendency to attribute just about any health complaint to PCT, a possible explanation is that health complaints other than skin symptoms are considered to be caused by PCT and this then contributes to patients reporting greater psychological distress. An alternative explanation is that the possibility of confusing other health complaints with PCT symptoms results in a “false” self-reported classification of the participant’s current status into active, remission or a latent phase of PCT.

The participants in paper III reported having a high understanding of PCT, but does this give an accurate picture? According to the CSM, individuals’ beliefs about their condition will be influenced by personal experience and information from health professionals, media and other people, and might not be accurate in the biomedical sense (47). PCT is frequently associated with other diseases (alcoholism, hepatitis and others), but we did not collect data about these diseases, which can modify illness perception and health complaints. On the other hand, both the BIPQ and IES were porphyria specific as used in this research, and the answers provided here may pertain only to PCT. However, the findings included in papers II and III suggest that it can be difficult to separate PCT from other conditions and other health complaints. This is important to keep in mind when interpreting the results. Associated diseases and lifestyle factors are highly relevant and should be considered when treating and counselling this patient group.

Although itching in PCT patients was a symptom reported by 24 % of participants in a previous study (82), this is a symptom that is rarely mentioned in regards to PCT and it came as a surprise that itching was perceived as the most problematic symptom for some participants in study II. However, one cannot draw any conclusion as to whether

it is the accumulated porphyrin level in the skin that causes the itching or even whether PCT patients experience more itching than the normal population, although we can conclude that itching is experienced as a considerable problem for some patients and that it is very likely to cause problems such as delayed skin healing, additional skin ruptures and possibly skin infections in patients with clinical PCT. To investigate this further, the NPR introduced this variable in their questionnaire. Recent results from the NPR (unpublished data) show that itching was one of the most frequent symptoms reported by PCT patients experiencing clinical relapse. Itching is also associated with reduced QoL (90) and should not be underestimated. During clinical consultations, itching should therefore be identified and addressed appropriately.

Participants in the focus group study noted that phlebotomy treatment caused rapid improvement and contributed to making the diagnosis less dramatic. The results of paper III confirmed that PCT was perceived as a condition with high personal and treatment control.

The time since the diagnosis and symptom activity may be associated with psychological distress related to porphyria. A meta-analysis of 66 studies that used the IES to measure the psychological impact of specific life events found that only a small proportion of scores could be attributable to age, gender or cultural differences, whereas the type of event and time elapsed since the event were strong predictors of stress levels (50). That we did not use the time since the last experience of symptoms or diagnosis as an IV in the multiple linear regression analysis could be considered a weakness in the design. By contrast, symptom activity was not significantly associated with distress, which would be an expected association if the time since diagnosis was a relevant factor.

A significant gender difference in clinical presentation of PCT was reported by Munoz- Santos et al (82). They found that women had more facial hypertrichosis, pruritus and involvement of skin areas other than hands and face. Gender differences in the perception and experience of symptoms such as hypertrichosis were discussed but were rejected by the focus groups. Paper III also concluded that gender was not significantly associated with porphyria-related distress.

7.2 Methodological considerations

When considering the methodological aspects, the two qualitative papers (papers I and II) can be evaluated in view of the criteria and considerations appropriate for qualitative studies using an ID approach. In this section, the methodological aspects of papers I and II are evaluated and discussed together. Paper III and the quantitative approach used are discussed separately and in the context of the criteria appropriate for this approach. A short discussion of mixing methods follows.

7.2.1 Credibility in the qualitative studies (Papers I and II)

Quality in qualitative health research is a complex and ongoing topic of discussion. However, according to ID, there are four main criteria for judging the quality of the qualitative research process: *epistemological integrity*, *representative credibility*, *analytic logic* and *interpretive authority* (56, p 101, 223-226). In this thesis, these four key criteria were used as a point of exit for the methodological discussions about papers I and II.

Epistemological integrity refers to the coherence that is necessary between stated epistemological assumptions and the chosen research design; i.e., the research question and the interpretation of data and analytical strategies must be consistent with the epistemological standpoint of ID. According to ID, “the truth” will always be complex, contextual, constructed and ultimately subjective (54). This implies that one can never know the absolute truth but can still value knowledge as the probable truth, which is the best we have so far (56). Our research question focused on exploring the experiences of individuals who had been predictively tested for AIP as minors and the experiences of persons with PCT, and as such aimed at producing knowledge that was relevant for practice with potential applications to the counselling of porphyria patients. This is consistent with the stated aim that, ideally, the results of an ID should have practice implications (56) without assuming that the knowledge revealed is true for all AIP and PCT patients. If anything, the results presented show that the participants’ experiences varied and that the individual patients’ perceptions and experiences should be taken into consideration in clinical consultations. That the analytic strategies chosen for interpreting the data sources must be consistent with the

epistemological assumptions in ID means that the use of STC as an analytical inspiration must be in agreement with the fundamental principles of ID. For instance, both ID and STC claim that data collection and analysis should be performed simultaneously so that a constant comparative approach can be achieved. Although simultaneous data collection and formal data analysis were not conducted in either paper I or II, there was a conscious effort to follow up the findings in successive interviews and focus groups. In this sense, we argue that a degree of informal analysis was performed and that the fundamental principles of constant comparative method were met.

To achieve *representative credibility*, the sampling procedures must be in agreement with the results claimed to have been found (56, p 224). When recruiting participants to the study described in paper I, we chose a sampling strategy to explore the experiences of persons who had been predictively tested as minors, but at the same time we wanted them to be old enough to have reflected on the experience. Using this rationale, we chose to include persons between the ages of 16 and 21 years. This can be viewed as an arbitrary choice of age and, although our intent was that this sample could provide the information of interest, we cannot know whether participants younger than 16 years or older than 21 years would have provided different but valuable information. For this reason, we also kept the option open to expand the inclusion criteria if necessary.

One of the results of the study was that AIP was a small part of the participants' identity. In hindsight, it is possible that a larger number of participants could have revealed other experiences. That AIP was not a large part of the participants' lives also meant that the interviews did not provide the very rich information one may have wished for. On the other hand, this could also be viewed as a finding in itself, which is our conclusion based on the fact that this was an impression given in all 10 interviews. In ID, what is considered an appropriate sample size will always be debatable and there is no objective justification for a specific number. Relying on "saturation" is problematic because health research can never claim to have obtained sufficient data to cover all possible relevant understandings of the clinical phenomena in question (56, p

97-98). Also in STC, the concept of “saturation” is deemed impossible to achieve and is not a goal for data collection (62). The term “information power” has been proposed as a more suitable guidance for judging sample size in qualitative studies (91).

When considering the sampling procedures in study II, the approach of recruiting only participants from a patient seminar requires careful reflection in terms of how the specific context may have provided a sample that is different from the more general population of PCT patients. It is not unlikely that the participants at the seminar were especially interested, preoccupied or perhaps “threatened” by their PCT diagnosis, whereas others with a different illness perception may not have been represented. In this perspective, some form of methodological triangulation is valuable and can help find what Thorne refers to as “substantive completeness” (56, p 224). One way of doing this was to design study III to challenge several aspects of the findings of study II. However, this does not mean that the findings from each study cannot stand alone or provide important knowledge for clinical practice.

Analytic logic may be understood in terms of the claim of transparency in the research process and a need for explicit reasoning from the fore-structure through to interpretations and claimed results. Thorne (2008, p 225) suggests the use of an audit trail, which is a description of the pathway of decision making throughout the research process, so that another researcher can follow this. There is seldom allowed sufficient room for this in the traditional limitations of a research article and is therefore the analytical steps taken are presented more explicitly in the material and methods sections of this thesis. By referring to analytical approaches such as the use of STC, the process of transparency can be aided in the limited space that is usually available in published articles with strict word limits. Analytical decisions were discussed with co-authors (supervisors) to aid the reflexive process, thus making the analytic logic more transparent.

The analytic process in qualitative research is always influenced by the researcher’s point of view and contains an element of interpretation; at the same time, there needs to be assurance that the researcher’s interpretations are trustworthy. This is what Thorne calls *interpretive authority*. Sufficient information must be provided about the

data that form the basis of the results and interpretations, and the background and intentions of the researcher (56, p 225). The researcher consequently needs to be overt about the background and perspective upon which the interpretations are based. The researcher's background and pre-understanding should be presented. In papers I and II, this was possible to only a limited degree, but providing a personal preface to this thesis has hopefully provided an important backdrop for the reader to judge more easily the credibility of the results. This is even more important when the researcher, as is the case in this thesis, is working closely with the study population.

Ideally, one should not interview one's own patients because the participant may wish to please the clinician, or in this case, the genetic counsellor, and try to give answers he or she thinks the interviewer wants to hear (58). This might have been especially relevant in this research because the participants were young, had relatively little experience with AIP, and AIP was only a small part of their identity. That the participants wanted to provide "the right" answers was an impression formed during the interview process, although it is difficult to differentiate between whether this was because of the participants' young age or their wish to seem well informed regarding AIP (or both). During the interviews a conscious effort was made to not let the participants feel that they were "tested" in any way. There is a possible power imbalance in that the researcher was both the person performing the research interviews and the person the participants would contact if in need of counselling about AIP. For instance, in paper I, one participant had received GC from the interviewer before the interview.

It is also important to provide sufficient contextual information about the participants, the interview situation and the topics of the interviews. We aimed to provide this through the presentations of the participants and the themes of the interview guide in the articles. This gave rise to a potential problem in protecting the participants' anonymity because their pseudonyms and personal information could be connected to the quotes presented. This was discussed, but the need to contextualize the quotes and provide background information was deemed important in terms of the research credibility and for making sense of the results.

7.2.2 Validity and reliability in the quantitative study (paper III)

In the following discussion of the PRO instruments used in the present study, the COSMIN definitions of measurement properties were used as point of exit. COSMIN stands for COsensus-based Standards for the selection of health Measurement INstruments, and provides the standard criteria developed for evaluating measurement properties (67). The quality of a measurement instrument is based on three criteria: *validity, reliability and responsiveness* (92). Responsiveness is the ability of an instrument to detect change over time in the construct being measured (63). Because we used a cross-sectional design (paper III) not intended to assess change over time, responsiveness is not discussed in further detail.

Reliability refers to “*the degree to which the measurement instrument is free from measurement error*” (63, p 96) and to what extent scores for un-changed patients are the same for repeated measures (92). This quality domain contains three measurement properties: internal consistency, reliability and measurement error (92). The instruments used in paper III were all found to have satisfactory reliability (40, 52, 72), and only internal consistency in relation to the use of a total sum score on the BIPQ will be discussed further.

Internal consistency is defined as the degree of interrelatedness among items on a scale (67), and is a measure of to what degree the items measure the same construct. It does not, however, say anything about what this construct *is* (63). The BIPQ is intended mainly as a single-item measure but can also be used to assess how the total threat of an illness is perceived, provided that the internal consistency is considered appropriate for the sample in question (40).

We chose to use Cronbach’s alpha to assess the internal consistency. The acceptable value frequently used for this coefficient is between 0.70 and 0.90 (63), while others refer to a cut off of at least 0.60 but preferably 0.70 or higher (93). One might argue that a Cronbach’s alpha of 0.67 is low in relation to the choice of using the BIPQ as a total score in the multiple linear regression analysis. There is also some controversy about the use of Cronbach’s alpha as a measure of internal consistency in assessing PRO. Some researchers contend that this is not a very reliable measure (68), whereas

others argue that Cronbach's alpha is a valid measure of internal consistency (63). One of the criticisms of Cronbach's alpha as a measure of internal consistency is that the coefficient value is highly dependent on the number of items and a low number of items will usually give a lower value (63). Because Cronbach's alpha is the best-known parameter for assessing internal consistency, we chose to use the BIPQ total score in the multiple linear regression analysis.

Validity refers to the degree the instrument measures the construct it says it measures. There are three properties of this: content validity, construct validity and criterion validity (92).

Content validity refers to whether the instrument's items reflect the construct the instrument is supposed to measure. There are several aspects to be considered when evaluating content validity, such as whether the instrument is comprehensive and relevant (92). It is worth considering whether relevance was a problem with our use of the IES because we observed a floor effect. About 25% of the respondents scored 0 on this measurement, and this could be interpreted to mean that the instrument was not relevant for this population. On the other hand, Horowitz and colleagues (41), and later authors (49, 50, 52) have concluded that the IES is an effective measure of subjective psychological distress relating to any life event, and as such, should be relevant for *any* population if one does not have the appropriate knowledge on how the "event", in this case PCT, impacts those inflicted. Paper II provided strong indications that for some, PCT seemed to have a large psychosocial impact. Because we expected that PCT would cause little or no distress for many (the floor effect), it is not surprising that a large proportion scored a total of 0 on the IES. The floor effect is not uncommon when using an existing instrument on new populations but is more problematic in longitudinal studies in which it may affect the responsiveness of the instrument (63, p 233).

Content validity also involves face validity, or whether the instrument appears to reflect the construct being measured. What is acceptable face validity is not subjective to set standards but is based on subjective evaluation. Comprehensiveness and relevance can be evaluated by experts and the patient population it is intended for (92).

The total questionnaire was therefore piloted on a group of “experts” who were persons working at NAPOS who had extensive experience with both porphyria and the research process. The feedback we received was that the questionnaire was generally comprehensible and easy to answer; the main negative comment was that the total questionnaire was long and took 20–45 minutes to answer. This was an element to consider since only three instruments are used in the present thesis. That said, the total data material has also resulted in two master theses (94, 95) and will hopefully also result in the publication of an article on illness perception among people with AIP.

There was no pilot study applied to the patients and this was a criticism made by one of the two porphyria patient organizations in Norway, which mentioned this in their annual membership magazine and encouraged patients uncomfortable with the questionnaire to not reply or to withdraw previous returned questionnaires (96). In retrospect, we do regret this, but because we did not use any instruments that were made specifically for the present studies, there were limited opportunities to alter the wording. Before the study began, both the overall aim of the study and the recruitment procedures were discussed with representatives of the same patient organization and they did not have any remarks about the forthcoming study. It can be debated that this might have affected both the representativeness and generalizability of the study by reducing the total number of respondents or by causing a selection bias, in addition to compromising the content validity by not testing the questionnaire on actual patients. However, we did not receive any complaints or desire to withdraw from the study and do not have the impression that these factors affected recruitment. On the other hand, this might be viewed as problematic from an ethical perspective, and we regret that some of the representatives from the patient organization did not experience sufficient user involvement.

Construct validity refers to the degree to which a measurement instrument really measures the construct it is intended to measure (63, p 169). Both the IES and the BIPQ have strong theoretical foundations and have been used throughout the research literature (40, 41, 47, 49, 50, 64, 97). The SHC Inventory was used in this study to survey the degree of self-reported health complaints the participants reported. The

authors refers to the 29 items comprising the questionnaire as “*commonly reported subjective health complaints*” (72) and “*a wide range of subjective health complaints*”(88) without further explaining how the 29 items were chosen. This might pose a problem in regards to the five domains measured by the instrument because there seems to be a lack of information on how these were developed. An essential feature of the inventory is however the avoidance of attempting to attribute complaints to diagnoses or theoretical speculations into psychological or psychosomatic factors (72), and as such using the total sum score of SHC might be less problematic. The PCT sample was not matched against the Norwegian population, and we could not say anything substantial about whether persons with PCT have more health complaints than the average population.

Criterion validity is important in regards to the study’s external validity. The term criterion validity is defined as “*the degree to which the scores of a measurement instrument are an adequate reflection of a gold standard*” (67). This is understood in terms of measures of objective standards, such as measurement of height and weight. One aspect that might contain an *element* of criterion validity in paper III is the categorization of the participants’ condition into latent, remission and active PCT using self-report. As mentioned in paper III, it is possible that the patients confused other health complaints with PCT symptoms, and this may have affected the classification into latent, remission and active PCT. One possibility could have been to collect a urine specimen together with the questionnaires, for analysis of porphyrin excretion levels. This could have provided important information regarding biochemical status, although there are individual variations in the level of porphyrin excretion that leads to the development of symptoms. Such urinalyses could therefore also have proved difficult to interpret in regards to clinical status and the classification of participants. Another aspect of the categorization into active, remission and latent phases being based on self-report is that those in the latent PCT group are assumed to have been predictively tested for a known UROD mutation in their family, but this cannot be guaranteed.

In future, inclusion of objective measures may help prevent the possibility of “false” self-classification. The use of instruments specific to dermatology should also be considered. In the present thesis, our aim was not to investigate QoL. However, there is a shortage of research on QoL in people with PCT, and instruments such as the Skindex or the Dermatology Life Questionnaire Index (DLQI) could be relevant measures, preferably in combination with a generic QoL instrument such as the World Health Organization QoL instrument (WHOQOL) (98). On the other hand we used instruments specific to the condition; that is, both the IES and the BIPQ were made porphyria specific.

Another important aspect in regards to external validity is representativeness. *Selection bias* should always be considered because it can affect the generalizability of results. The fact that we excluded those with no known UROD mutation and no available samples for control of their PCT during the past 10 years could be considered problematic in this regard. Although this did not comprise a large number of persons (n = 34), it may have created a selection bias. The mailing of the questionnaires in May, June and October may have affected the results because this is the “high season” for PCT symptoms. This should be considered, and might have yielded a larger proportion of persons with active PCT in our sample. We did not include any analysis of the 186 non-responders, but they comprised about the same number of women (n = 82) and men (n = 104), and most were older than 50 years (n = 143).

Another potential problem in regards to generalizability was the response rate. However, we argue that a response rate above 50% is generally considered satisfactory and average response rate in studies utilizing data from individuals is estimated to 52.7% (99).

When discussing validity and reliability in quantitative research, one must consider both the instrument properties and the suitability of the chosen design and analytical approach. Because about 25% of the participants scored 0 on the IES, many participants were eliminated from the multiple linear regression analysis. The rule of thumb for sample size is 15 participants per independent variable (IV) or $n > 50$ plus an additional eight cases per IV. More cases are needed if the data are skewed (100).

Because we included a total of five IVs, we would need a minimum of ≥ 90 plus additional cases for skewed data. We believe that our sample size fulfils these rules because we had a total of 263 cases eligible for analyses, minus those scoring 0 on the IES subscales, which yielded a total of 185 subjects for the analysis of intrusion and 168 for avoidance in the multiple linear regression analysis (Table III, paper III). Although the number of eligible participants with active PCT was low, we used the dichotomized variable active/not active PCT as an IV in the regression analysis, and the total number of cases was satisfactory. Thus, we do not believe that this represents a problem.

7.2.3 Mixing methods

Whether the scientific approach in this thesis should be called a “triangulation of methods”, “mixed-method” or “multiple-method” research design will vary between individual researchers. When planning the design of the present thesis, several senior researchers warned against mixing methods; not because one or the other paradigmatic approach was considered “wrong”, but simply that mixing the two was considered unfeasible or that it would not be possible to attain the necessary skills and competence to manage both appropriately. A dispute between researchers taking a quantitative purist stance on social science and those advocating a qualitative purist view has resulted in what has been termed a “paradigmatic war” and the “incompatibility thesis”, which claim that qualitative and quantitative methods cannot and should not be mixed (101). The philosophy of using mixed research is an attempt to take multiple viewpoints and perspectives, and a pragmatic approach to knowledge (102), which was also the viewpoint of the present thesis. Also, Thorne noted that ID is especially suited for a “mixed standpoint” (56, p 224).

It is also believed that learning and teaching epistemological and methodological pluralism provide a better understanding of the methodological possibilities available and thus promote collaboration, which is necessary in an increasingly more complex and interdisciplinary research reality (101). This is especially important in the world of the porphyrias (and other conditions), where the social sciences meet a strong positivist culture of research. The viewpoint in this thesis is that mixing paradigms can

be an advantage and is in agreement with Johnson and Onwuegbuzie that mixed methods constitute “ a research paradigm whose time has come” (101). Taking a “mixed position” has allowed for a broader understanding of the challenges met by persons with AIP and PCT, and has provided empirical findings that complement and elaborate each other.

On the other hand, the question of being able to attain, in a restricted time period, the necessary competency to manage appropriate and high-quality research is a valid one. Hopefully, this is feasible, and may be especially relevant in light of qualitative approaches such as ID, which emphasize the educational and applicable background in the health sciences by explicitly drawing on an eclectic and pragmatic approach to knowledge (56).

When defining what constitutes a mixed-methods design, one of the many issues debated is the stage at which the mixing occurs. Although there is general agreement that the mixing can occur at all stages of the research process (102), others are clear that the use of the term “mixed methods” demands the inclusion of an additional and supplemental analytical strategy that contains a component that cannot stand alone; that is, the mixing of methods must be within one study and published as a complete project (53). We used separate and individual empirical parts that can stand alone while also complement and build upon each other to answer the overall aim. Thus, we opted to take the safe stance by defining this thesis as a multiple-method research approach, in which multiple methods are defined as “*two or more complete projects attached to an overall inductive aim. The research questions for each study are separate, but complementary to the overall aim*” (53).

CONCLUSIONS AND IMPLICATIONS FOR PRACTICE

Predictive testing for AIP entailed few psychosocial consequences, but the results indicate the potential for increased patient anxiety even without necessarily generating lifestyle changes. The ethical implications and clinical caution need to be considered when predictive genetic testing is performed on minors. Recent clinical research advocates caution, although there is little evidence of psychological harm to minors who undergo genetic testing (79). Appropriate counselling and informed consent are

advisable and are mandatory in Norway; this is a judicially sound decision that is supported by the results of this thesis and other studies, in addition to international ethical guidelines (32, 33).

At their worst, PCT symptoms can be dramatic. Itching must be taken seriously. Participants had a perception of PCT as a systemic condition and a tendency to attribute a range of health problems to the condition. This could lead to improved compliance with treatment and regular follow-ups and controls, but also medicalization and overtreatment. This finding suggests a need for information and reassurance in clinical consultations. During the clinical consultation with these patients, it is important to discuss the patient's perceptions of the illness and to consider the total burden of health complaints and psychological distress. Patients with a high perceived illness threat and multiple health complaints might be especially vulnerable to psychological distress related to PCT, and clinicians should be attentive to the totality of each patient's situation.

FUTURE PERSPECTIVES

This thesis has shed some light on the experiences and challenges faced by persons with AIP and PCT. Further research is warranted. According to paper I, it is reasonable to question whether psychological distress about AIP is more closely associated with perceptions about the illness than with AIP symptom activity. Data have already been collected for a follow-up study to describe the perceptions of illness and psychological distress in AIP patients, and to identify the factors associated with distress in this group. Further investigations of the health-related challenges and QoL in adults with AIP experience are also of interest, and qualitative and explorative studies are recommended. The patients themselves have recommended the need for further research into the experiences of people living with porphyria (4).

As far as we are aware of, no large-scale QoL studies of PCT patients are performed, and the use of dermatology-specific instruments such as Skindex or DLQI, combined with a generic QoL measurement such as the WHOQOL-Brief (98) could yield interesting information. Such studies should also take into account the time since diagnosis and symptoms. A longitudinal study that used dermatology-specific

instruments with a high degree of responsiveness will be suitable for detecting changes over time (63) and could be distributed to newly diagnosed patients and followed up throughout treatment and long-term remission. This could be helpful in identifying the vulnerable periods of time for this patient group. Also register-based research (NPR) will be important in order to investigate QoL in PCT patients. Qualitative research that focuses on patients in remission could provide a better understanding of why PCT patients experience the condition as something requiring frequent follow-up and prophylactic treatment, and whether this is problematic.

NAPOS offers predictive genetic testing and counselling, and an evaluation of the benefits and effectiveness of these would provide important information. The results of the present thesis indicate that clear and concise information about AIP and PCT for patients is lacking. A clearer definition of what constitutes an AIP attack is needed. New register-based research, both national and international (NPR and EPR), will hopefully aid in this process and provide information about the psychosocial implications of AIP and PCT.

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A skin disease, a blood disease or something in between? An exploratory focus group study of patients' experiences with porphyria cutanea tarda*

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Background Porphyria cutanea tarda (PCT) is characterized by fragile skin with blistering on sun-exposed areas. Symptoms typically develop in late adulthood and can be triggered by iron overload, alcohol intake, oestrogens and various liver diseases. Treatment consists of phlebotomy to reduce iron, or increasing urinary porphyrin excretion by administering chlorochin. To optimize patient care, health personnel need to understand the subjective experiences of PCT.

Objectives To explore the experiences of persons with PCT with regard to symptoms, treatment, follow-up and prevention of the disease.

Methods Interpretive description was used as a qualitative approach. Twenty-one participants attended three focus groups. All participants had experienced PCT symptoms during the last 5 years.

Results Participants' experiences varied from trivializing symptoms and fragile skin to what was described as a desperate situation, with huge blisters, skin falling off and feeling as if one was in a 'horror movie'. For some, itching was very troublesome, preventing sleep and delaying skin healing. In managing PCT a shift in focus from skin to blood was described. PCT was perceived as a chronic and systemic disease causing a range of health problems. Strategies for preventing symptoms ranged from doing nothing to frequent controls and check-ups.

Conclusions Participants had a systemic perception of PCT, and a tendency to attribute a range of health problems to the condition. This study adds insight into the experiences patients have with PCT.

What's already known about this topic?

- Photodermatoses can have a profound impact on quality of life, but little is known of the subjective experiences of porphyria cutanea tarda (PCT).

What does this study add?

- Participants' symptoms varied from fragile skin to what was described as a desperate situation.
- Participants had a systemic perception of PCT and a tendency to attribute a range of health problems to the condition.
- Itching was reported to be a severe problem for some participants.

Porphyria cutanea tarda (PCT) is a rare disease characterized by fragile skin and blistering on sun-exposed areas. Increased urinary porphyrin excretion causes red- or dark-coloured urine.

Symptoms typically develop in late adulthood and can be triggered by hepatic iron overload, alcohol intake, oestrogens, hepatitis C and various liver stressors, in combination

with exposure to light. The prevalence of symptomatic disease is estimated to be 1 in 10 000.^{1,2} The condition exists in both a familial and sporadic subtype. Compared with 25% of cases worldwide, about 50% of cases of PCT in Norway are hereditary because of two founder mutations.^{3,4} Penetrance is very low, and only an estimated 10% of mutation carriers develop symptoms throughout life. Treatment consists of avoidance of precipitating factors, phlebotomy to reduce iron or increasing urinary porphyrin excretion by administering chloroquine.⁴

It might take 6–15 months before complete clinical and biochemical remission is reached,^{5,6} but the prognosis is good, and many patients experience lifelong remission. To detect relapse, urinary porphyrin concentration, iron and liver functions should be assessed annually.^{4,7}

The principal aim of the Norwegian Porphyria Centre is to optimize the diagnosis, treatment and follow-up of patients with porphyria. Although the clinical benefits of mutation screening are controversial,⁴ distinguishing between sporadic and familial cases appears to be important to many patients and their relatives,³ and NAPOS therefore offers, in hereditary cases, predictive genetic testing and counselling to at-risk adult family members.

Photodermatoses can have a high psychological impact.⁸ Jong *et al.*⁹ investigated quality of life (QoL) in patients with a range of photodermatoses, including PCT. They concluded that, overall, photodermatoses had a major impact on QoL, but that PCT had a lower impact on QoL than did other cutaneous porphyrias. Very little knowledge of the psychosocial impact of PCT is available and more information on the subjective experiences is therefore needed to secure optimal treatment, follow-up and counselling of this group. The aim of the present study was therefore to explore the experiences persons with PCT have regarding symptoms, treatment, follow-up and prevention of the disease.

Methods

This study was based on interpretive description, which is a well-documented qualitative approach with emphasis on clinical practice and exploration of health-related issues.^{10–12} Focus groups with interactive discussions were deemed appropriate.¹³ The study complied with the principles of the Declaration of Helsinki and was approved by the Norwegian regional ethics committee (2012/1078).

Recruitment

A convenience sample was recruited in connection with a biennial patient seminar arranged by NAPOS in 2012.¹² Information regarding the focus groups was included with invitations to the seminar. Experience with symptoms during the last 5 years was set as the inclusion criterion. Forty-six people with PCT participated at the seminar and 23 provided written consent to participate in the focus

groups. Two were excluded because of clinical remission exceeding 5 years.

Data production and participants

The patient seminar consisted of joint sessions and lectures on symptoms and treatment, in addition to conversation groups for patients to share their experiences. Three focus groups with seven participants were held over two consecutive days at the seminar.¹⁴ In light of the rich information provided, the sample size was deemed satisfactory.¹² The interviews lasted approximately 90 min. The participants included 11 women and 10 men, aged 31–77 years. Three participants reported having haemochromatosis (Table 1). The interviews were moderated by the first author (J.A.), who is experienced in counselling patients with porphyria. One co-moderator participated in the first two groups while a second participated in the third group. The interviews were semistructured and focused on three main themes with sub-questions. The main themes of the interview guide were: (i) experience with symptoms; (ii) treatment; and (iii) future expectations. Emerging themes that were not addressed by the interview guide were followed up in consecutive interviews.

Analysis

Analysis was performed in accordance with interpretive descriptive guidelines and was also influenced by systematic text condensation.^{11,12,15} Analysis was primarily performed by the first author (J.A.), with discussions and guidance from the other authors (E.G., S.S. and M.R.). Audio recordings of the interviews were transcribed verbatim and initially read as a whole. In the first step, focus was on reflections and main impressions and four preliminary themes were identified: (i) large variations in symptom experience; (ii) taking control; (iii) treatment; and (iv) prevention of symptoms. In step two, coding and text condensation were performed based on these themes, while special attention was given to avoidance of premature closure of coding.¹² Coding was first conducted cross-case, followed by longitudinal coding at an individual level.¹⁵ In step three, coding was elaborated with subgroups and further text condensation. Step four was an iterative process where focus shifted from the decontextualized codes and the transcripts as a whole; based on this, a synthesis of the coded material was presented as three main themes with sub-themes. For validation, the full transcripts were re-read several times and systematically searched for data that challenged the results.

Results

The results are presented as three main themes with sub-sections. Quotes are used to elucidate and elaborate the experiences of the participants. Participants are anonymized.

Table 1 Participant characteristics

Sex	Age (years)	Year of elevated urinary porphyrin levels	Type of PCT	HFE status
Group 1				
Nick	61	2001, 2009	Sporadic	Normal
Frank	59	2009	Sporadic	Heterozygous H63D
John	56	2005, 2008	Familial	Normal
Linda	60	2008	Sporadic	Normal
Michelle	62	1998, 2009	Sporadic	Normal
Nora	34	2012	Sporadic	Homozygous C282Y
Alice	52	2010	Familial	Normal
Group 2				
Peter	67	2006	Familial	Normal
Jack	56	2004, 2008	Familial	Normal ^a
Simon	57	2010	Familial	Normal
David	68	2005	Sporadic	Normal
Andrea	62	2006	Sporadic	Heterozygous C282Y ^a
Lucy	66	2010	Sporadic	Normal
Julie	58	2008	Sporadic	Heterozygous H63D
Group 3				
Tony	77	2001, 2009	Unknown	Unknown
Martin	51	2009	Familial	Heterozygous C282Y ^a
Sandra	64	2011	Familial	Normal
Lilly	58	2009	Familial	Normal
Monika	55	2009	Familial	Heterozygous C282Y
Rachel	56	2010	Familial	Heterozygous C282Y
Veronica	31	2009	Familial	Normal

PCT, porphyria cutanea tarda; HFE, haemochromatosis gene. ^aParticipants reported having haemochromatosis.

Theme 1: large variations in participants' experiences of skin symptoms – from trivializing to nightmare descriptions

Trivializing symptoms

Participants' skin symptoms typically presented as small blisters or very fragile skin, and simple things like putting hands into a pocket could cause skin trauma. Slow-healing sores were suspected by participants to have been caused by burning or cutting themselves without noticing, or from allergic reactions to chemicals or similar incidents. Discoloured urine was explained by drinking too little. This tendency to trivialize PCT symptoms as being caused by 'normal things' resulted in participants waiting to seek medical expertise, which contributed to a delayed diagnosis. Several persons explained that other people's comments about their skin made them realize they needed to see a doctor. When they finally did, diagnosis was often missed, especially if they were not referred to a dermatologist. Veronica explained:

I haven't had those really large, fluid-filled blisters. But I had very small blisters and really fragile skin. I've had to be very careful not to bump into things when it was at its worst, because it didn't take much, just barely scraping with a fingernail. And it never healed; it just itched. And also the part with the coloured urine,

because that started long before the symptoms on my hands did.

Itching – an underestimated problem?

It became evident that itching was a problem, with some considering itching to be the worst aspect of PCT. Itching was attributed to skin healing and seen as a sign of rising porphyrin levels. Participants would itch both when experiencing symptoms and when in remission. The itching was predominant at night, and would typically start after going to bed. It was debatable whether this was because of the warmth of the bed, or because it was more noticeable at this time. The itching disrupted or prevented sleep, and already fragile skin was easily ruptured, resulting in bleeding, further delaying skin healing and increasing the probability of infection. Some slept with gloves on to prevent inadvertently hurting themselves. Nick said:

It itches so much [several nods in agreement], so that's what I feel is the biggest problem. And then you lie awake at night and you scratch and it bleeds. Because of this, it never heals because it is scratched too often. ... It is there all the time, but it is at night that I scratch because I cannot help myself. So yes, that is when I notice it the most. It itches all the time, but that is when you might hurt yourself.

Skin symptoms at their worst: 'living in a horror movie'

At its worst, PCT was painful, causing large fluid-filled blisters that would rupture, run and cause fragile skin to fall off. Fluids from blisters would squirt when shaking hands with others, and one explained that she drained her blisters with hypodermic needles. Bandaging was time-consuming and, when removed, skin would be ripped off. Participants would wear hats and cotton gloves to protect their skin and hide their symptoms from others, which would result in comments that they were 'snobs'. One participant had to empty blister fluids from his gloves while working. Everyday situations such as putting on shoes could cause the skin to peel off and sometimes these areas would become infected. When the PCT symptoms were at their worst, the situation was experienced as dramatic and described as 'being in a horror movie'. Lilly said:

I was just desperate! And my grandchildren? At that point, I didn't know if I could touch them or give them a hug or what, you know? It just kept running! It was burning! . . . So, it was a desperate situation, also because you don't know what it is. I was thinking, "Oh my god! Am I going to lose the skin on my entire body?" You know? Can no one help me?

Theme 2: a skin disease, a blood disease or something in between?

A shift in focus from skin to blood

After their diagnosis was established, participants described a shift in focus. One participant explained that she was surprised when she understood that PCT was not a simple skin disease. At first, PCT presented as skin symptoms, and diagnosis was based on patients seeking medical care for this. However, after diagnosis was established, the focus shifted from the skin to the blood. The use of phlebotomy as a treatment for PCT emphasized this. Blood samples, blood values and phlebotomy introduced a technical aspect, and many participants displayed a keen interest. They brought copies of their blood work to the focus groups and compared and discussed who had the highest ferritin levels and at what level they preferred to undergo prophylactic phlebotomy. Nora said:

Yes, and it's like I can feel something crawling in my skin. And after I learned about this, I just feel the porphyrins flying around.

Suspecting porphyria cutanea tarda caused more health problems than skin symptoms

Many participants suspected PCT caused health problems that were not limited to the skin. They felt that porphyrins were in their blood, and that genes and enzymes were involved,

which made them comment that things in the body were connected. A variety of symptoms caused by PCT were proposed and the participants showed a growing need to find legitimate reasons for other health complaints. Maria explained:

Perhaps it is a bit more complicated than what is believed? That there are actually more symptoms? That more things are connected to it? Because this is something that happens inside the body; that's what I think, that there might be.

Their suspicion was explained by the fact that the symptom in question arose at the same time as their skin symptoms appeared, and that other explanations had not been detected. Participants learned that they had similar health problems after speaking with other patients, which confirmed their suspicions. Fatigue was explicitly discussed as being related to PCT, but known acute porphyria symptoms, such as stomach pains and muscle aches, were also attributed to PCT, both by participants and sometimes by local health personnel. Participants questioned why these symptoms were not recognized by medical experts as being related to PCT and pointed to the need for further research. However, the focus on what could be attributed to PCT was so evident in the groups that some participants commented that surely not everything could be caused by the disease.

Theme 3: managing porphyria cutanea tarda – strategies for prevention, treatment and controls

Preventive strategies: frequent controls, taking calculated risks or doing nothing?

PCT was perceived as a chronic condition that patients needed to manage for the remainder of their lives. For some, this meant frequent controls and a vigilant lifestyle, with a focus on eating habits, avoiding the sun and generally being careful. For others, prevention involved taking blood samples and having control intervals. Control intervals varied greatly, from having ferritin levels never checked to having them checked every 2 weeks, every month and twice a year. The merits of this were debated by participants, and the more 'experienced' patients with PCT were asked for advice as to how often they should be tested, which test should be done and who should perform them. A few participants said they did nothing to prevent PCT. As Lilly said, 'I have a disease, but I'm not ill'. Most took calculated risks and would enjoy alcohol, sun and good food, but in moderation. They said they knew they risked skin symptoms, but it was worth it. However, the suspicion that PCT caused other problems was more worrying. Lilly said:

I think about it. But I choose to do it. And I think, like, if I'm traveling to sunny places, if I happen to get a blister, well that's just. . . I have a blister, blood samples and bloodletting. But what I might think about

sometimes is, what does it do to other things in the body? Right? I'm thinking cirrhosis. Kidney failure? I mean, what if I defy this and perhaps avoid getting a blister. But perhaps I got it because I didn't take the precautions I should. And I just used bloodletting as a way to exceed my limitations. Do you understand what I'm saying? Because I don't want that, but this is something you don't know a lot about yet. Right? What it does to other organs? Because if it's just a rash that can be treated with draining blood? Well, then we can just do whatever we want, can't we?

Phlebotomy: simple and effective, but also demanding and exhausting

Phlebotomy was viewed as very effective and provided rapid relief from skin symptoms. Participants described the process of letting blood as uncomplicated and easy, but, when they were asked for further details, aspects that were more problematic emerged. There were discussions as to whether participants could lose important components of the blood that their bodies needed. Some explained they would not drive a car or ride a bicycle the same day, or they needed to take the day off because they would get very tired. Several had stories of fainting and of 'going too low in blood values', some to the point that hospitalization was considered. Andrea dreaded having phlebotomies:

Ah, I just felt that I was sweating and I was just about to faint. So now when I am to let blood, it never used to bother me, but now! Uh! Will they hit the spot or not? So I start sweating already then. Because when the needle is inside, and they start looking for the vein. No. I'm finished. I dread it! Really!

Disagreement over the genetic testing of family members

Participants agreed that genetic testing was a choice that every individual needed to make for themselves and that whatever choice was made should be respected. There was disagreement as to whether they would recommend testing of healthy family members. For some, knowledge of genetic status was very useful; for others, it was a cause of unnecessary worry. Several pointed out that knowledge of PCT could be acquired without genetic testing. Moreover, participants who did not worry much about their own PCT were anxious about whether their children and grandchildren had inherited the predisposing gene. Exactly how genes were involved and how this would affect their health seemed to be unclear and contributed to making PCT more serious, as the following quote from Julia illustrates:

I've told both my sisters, they know I have this. But they weren't interested in testing themselves and one of my sisters, she has two grandchildren, she didn't even want them to know that I have this. This was in regards

to not wanting it to ruin their chances of having children. It was their choice.

Discussion

This was a qualitative study and the transferability of results must be viewed in relation to context and the sociocultural setting.¹⁶ PCT is associated with haemochromatosis,¹⁷ hepatitis and certain lifestyle factors, such as the intake of alcohol, which should be considered when interpreting the results. In the present study, all participants claimed to have normal or restricted alcohol consumption, and hepatitis and alcohol as predisposing factors therefore probably do not influence the results or their interpretations. However, the psychosocial stigma connected to hepatitis and alcohol abuse might have prevented persons from volunteering to participate in the focus group or limited their willingness to share this with the group, a common problem in research based on voluntary participation. The interviews were held in association with a patient seminar, which might have heightened the participants' awareness of PCT and thus affected their reflections. This might have contributed to richer information, which is desirable in qualitative studies. We argue that participants' awareness does not compromise the validity of the study, but rather reflects that human experiences cannot be reduced or separated from their context.

The results showed a large variation in experiences, from trivializing symptoms to very dramatic symptoms with a great psychosocial impact on those afflicted. This is interesting in view of the findings of Jong *et al.*,⁹ where PCT had a lower impact on QoL, measured by the Dermatology Life Questionnaire Index, (DLQI), than other cutaneous porphyrias. That the DLQI did not capture this variation in experiences is, perhaps, not surprising. Health-related quality of life measures are important for the assessment of disease severity, especially in nonlife-threatening diseases such as skin diseases.¹⁸ However, they are especially aimed at generalization through a focus on central tendencies, and condition-specific instruments such as the DLQI are designed to be responsive to change.¹⁹ Both these aspects can be problematic considering that there were only 12 people with PCT included in the study of Jong *et al.*,⁹ and they were likely in clinical remission.⁹ However, the qualitative design of the present study was aimed directly at exploring health issues and providing substantive and rich descriptions of the participants' experiences with PCT. We argue that focus groups based on interactive discussions might be especially suited for capturing and elaborating the diversity of experiences of participants in clinical remission.

Some participants with PCT mentioned itching to be a troublesome symptom. Although pruritus is not well documented in PCT, it has been reported previously.²⁰ Itching is common in many skin conditions and is likely to delay skin healing, and is associated with reduced QoL, depression and sleep disturbances.^{21–24} Consequently, this unsuspected finding warrants further investigation. To obtain more information on

this topic, the Norwegian Porphyria Registry has introduced this as a variable in the questionnaire sent to patients.

Based on the experiences of the participants in this study, venesection was an acceptable first choice in treatment; however, some problematic aspects were introduced and, as low-dose chloroquine is widely used,⁴ this might be preferable for some patients. Our findings suggest that too vigilant a strategy in the prevention of symptoms might lead to medicalization rather than benefitting the patient. To the best of our knowledge, there seems to be a lack of data regarding biochemical and clinical relapse frequency. However, an annual assessment of urinary porphyrin concentration and iron metabolism is suggested in the detection of relapses.⁴ Although PCT has been associated with changes in glucose metabolism,²⁵ and an increased risk of liver cancer,²⁶ the mechanisms are unclear and do not warrant the frequent check-ups (every 2 weeks or every month) reported by some participants.^{27–29}

PCT is generally defined as a skin disease but, aetiologically, it is also a hepatic and metabolic disorder.^{5,30} Because the symptoms are of a cutaneous nature, one would expect that the patients experienced PCT as a skin condition. However, participants in this study described a shift in focus from skin to blood and began to perceive PCT as a chronic and systemic disease. The tendency to attribute health problems to PCT was striking. We are all 'naïve psychologists' seeking to explain why events occur and to attribute causal explanations.³¹ According to the common sense model (CSM) of illness,^{32,33} there are five components of illness representations that help people make sense of their symptoms: the identity or the label given to the condition; the perceived cause of the condition; the predictive understanding of how long the condition will last; the individual's beliefs about the consequences of the condition; and whether the condition can be cured or controlled.³⁴ In this case, the identity of the condition is 'porphyria'. Porphyrias are a group of diseases, and separating PCT from other porphyrias can be difficult for both patients and healthcare providers. Patients with PCT may perceive the disease as being chronic and systemic because porphyrins, enzymes, blood and genes are involved, and treatment consists of bloodletting. This perception can, in turn, explain why participants in this study attributed a number of their health problems to PCT. The CSM uses the perception of the condition to guide which further actions are taken.³⁴ Lilly stated that medical experts do not fully understand the possible long-term complications that this patient group might expect, and therefore phlebotomies cannot be an 'easy fix' if symptoms arise. As Lilly commented, 'if it's just a rash that can be treated with draining blood, well, then we can just do whatever we want to, can't we?' The genetic component of PCT also seemed intriguing to the participants. A worry that a PCT mutation might prevent anyone from having children, as was the case in the family of one participant, emphasizes that the perceived cause of the condition and the understanding of its consequences should not be underestimated. When addressing the issue of symptoms, consequences and controllability of PCT in clinical consultation, it is therefore important to

recognize that the patient's illness representation can influence perception of risk and how they express and act upon this information.

The results show that, at their worst, PCT symptoms can be experienced as dramatic, and that a shift in focus from skin to blood after establishing the diagnosis led to the perception of PCT as a chronic, systemic disease that may cause a range of unknown health problems. This suggests there is a need for information and reassurance in clinical consultations, and as long as patients are in biochemical remission and follow control guidelines,⁴ there is little reason for them to expect health problems related to PCT. The effects of itching in PCT should not be underestimated and was reported to be a severe problem for some participants. It is important that physicians and healthcare personnel, as well as specialist centres that give advice on PCT, are aware of the differences in how the patients experience their disease, and that many of them experience it as much more than a skin disease, so that patient care and disease management can be optimized.

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CLINICAL REPORT

Illness Perception and Psychological Distress in Persons with Porphyria Cutanea Tarda

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Porphyria cutanea tarda (PCT) requires long-term treatment and follow-up, although many patients experience life-long remission. The aim of this cross-sectional postal survey was to describe and investigate the association between illness perception, health complaints, self-reported symptoms and distress in persons with PCT. The participants perceived PCT as a chronic condition with high levels of personal and treatment control. Persons who reported active symptoms scored higher on perceived illness threat, total health complaints and psychological distress compared with those in remission or latent phases. However, a higher perception of illness threat and the total burden of health complaints were more closely associated with psychological distress than were perceived PCT symptoms activity. This has implications for clinical consultation; dermatologists should be attentive to symptoms activity, but also recognize that patients in remission with a high perceived illness threat and multiple health complaints might be especially vulnerable to psychological distress with regards to PCT. Key words: porphyria cutanea tarda; illness perception; psychological distress; subjective health complaints; psychosocial.

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Porphyria cutanea tarda (PCT) is the most common form of the porphyrias, a group of rare and mainly inherited metabolic diseases caused by reduced enzyme activity in the haem synthetic pathway (1). The prevalence is estimated at 1 in 10,000 (2), and approximately 50% of cases in Norway are hereditary, with a 10% penetrance (3). PCT symptoms usually present in late adulthood as skin fragility, blistering, milia, hypertrichosis and increased pigmentation on sun-exposed areas, and can be triggered by iron overload, hepatic conditions, oestrogens and high alcohol intake. Treatment includes avoidance of precipitating factors, phlebotomy and/or administration of chloroquine (1, 4). Complete clinical remission can take up to 6–12 months (5, 6), but the prognosis is

good, and lifelong remission is common. Guidelines suggest that urinary porphyrin concentration, iron and liver function should be assessed annually in order to detect relapses (1, 4). Patients in biochemical remission have normal tolerance for sunlight.

Very little is known about the subjective experiences of PCT and, to our knowledge, only 2 previous research reports have focused on the psychosocial aspects of PCT. Jong et al. (7) found that PCT had less impact on quality of life (QoL) than did other cutaneous porphyrias and photodermatoses in general. However, only 12 persons with PCT participated in the study, and the results should therefore be interpreted with caution. In contrast, a previous qualitative study found that PCT symptoms at their worst could be very dramatic and have a large psychosocial impact. The participants had a perception of the condition as systemic and chronic, and had a tendency to attribute a range of health problems to PCT. There were also reports of over-treatment, and frequent controls for patients in long-term remission (8). PCT patients are a heterogeneous group, comprising persons with active symptoms, those in remission and asymptomatic mutation carriers (latent PCT), and they require various degrees of treatment and long-term follow-up. To optimize patient care it is, therefore, important to expand our understanding of how PCT is perceived and experienced by the patients themselves.

The aims of the present study were: (i) to describe and compare illness perception, self-reported health complaints and psychological distress in persons with various activity of PCT; and (ii) to examine the associations between illness perception, self-reported health complaints, PCT symptoms, and psychological distress.

PATIENTS AND METHODS

Design

A cross-sectional survey comprising a battery of self-evaluative questionnaires was posted to all persons older than 18 years with PCT registered at the Norwegian Porphyria Centre (NAPOS). The study was approved by the Norwegian Regional Ethics Committee (2010/1140) and complies with the Declaration of Helsinki.

Sample and recruitment

NAPOS conducts nationwide diagnostics based on biochemical and DNA analysis in addition to predictive genetic testing. Almost

all persons with a known porphyria diagnosis in Norway are registered at NAPOS. Participants were recruited by NAPOS in May 2010. Follow-up reminders were sent to non-responders in June and October the same year. Diagnosis was based on analysis of urinary and faecal porphyrins in addition to plasma fluorescence scanning and uroporphyrinogen decarboxylase (UROD) DNA analysis according to established criteria (9). "Sporadic" PCT patients, for whom porphyria analysis had not been performed in the past 10 years, were excluded from the study, based on the assumption that they had not experienced any PCT symptoms in the past 10 years.

Participants were categorized as having active PCT (porphyria symptoms in the day or week of the survey), PCT in remission (previous symptoms, but not at present) or latent PCT (mutation carriers who had never experienced PCT symptoms). Categorization was based on self-reports and was assessed by the following question in the questionnaire: "Have you had any porphyria-related complaints/symptoms?" followed by the answer categories: 1, never; 2, previously; and 3, have today/this week.

Measures

Socio-demographic characteristics. The socio-demographic variables included sex, age, work status, educational level, cohabitation status and having children.

Patient-reported outcome measures

Illness perception. The Brief Illness Perception Questionnaire (BIPQ) (10, 11) assesses the illness representations as adapted from the common sense model of Leventhal et al. (12) and has satisfactory validity and reliability. The questionnaire comprises 8 items measuring different dimensions of illness perception: consequences, timeline, personal control, treatment control, identity concern, emotions and coherence (illness comprehensibility). Identity refers to the symptoms a person views as part of the disease. Responses are measured on a 0–10-point scale. An overall score was computed by summing across the 8 items. Higher scores reflect a higher perceived threat associated with the condition (13).

Self-reported health complaints. The Subjective Health Complaints (SHC) inventory measures self-reported health complaints during the past 30 days on a 0–3 point Likert scale and without mapping the diagnosis or symptom attributions. The instrument is a 29-item scoring system that is categorized into 5 factors: musculoskeletal, pseudoneurology, gastrointestinal, allergy, and influenza complaints (14, 15). The instrument has satisfactory reliability and validity (15). In the present study, only the mean total sum score was assessed.

Porphyria-related psychological distress. The Impact of Events Scale (IES) measures psychological distress defined as the degree of impact of a specific event experienced at present, in this instance, porphyria. The responses are measured on 2 subscales: intrusion and avoidance. Intrusion is characterized by unbidden thoughts and strong waves of feelings, and avoidance includes denial of the meanings and consequences of the event. The scale comprises 15 items: 7 on intrusion and 8 on avoidance. The responses are assessed on a 0–5-point Likert scale. The psychometric properties have been found to be satisfactory (16, 17).

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics Version 22.0 (Armonk, NY, USA). Most analyses were based on the 3 subgroups: active, remission and latent PCT. If more than 50% of the items were missing, the sum scores were not calculated for the IES subscales and the SHC inventory total (15). When calculating the overall score on the BIPQ, items 3, 4 and 7 were reversed according to the manual. If any items were missing on the BIPQ, the overall score was not calculated (13).

Differences in socio-demographic variables were investigated using Pearson's χ^2 test for independence for categorical variables. Separate 1-way Welch analysis of variance (ANOVA) was used to determine whether the scores on the BIPQ, SHC and IES subscales differed between the 3 PCT subgroups. There were some outliers and non-normality. As a sensitivity test we used a Kruskal–Wallis non-parametric test, which identified the same significant outcome measures as the ANOVA.

To investigate the associations between illness perceptions, self-reported health complaints and porphyria-related psychological distress, 2 separate multiple linear regression analyses were conducted. The IES subscales intrusion and avoidance were the dependent variables and age, sex, SHC inventory total score, BIPQ total score and perceived PCT symptoms were entered as the predictors in the models. PCT symptoms were dichotomized into present symptoms (active PCT) or not present symptoms (remission and latent PCT). Twenty and 27% of the participants scored a total of 0 on the intrusion and avoidance subscales, respectively, thus creating a "floor effect". To meet the assumption of normality, those participants scoring a total of 0 on the IES subscales were removed from the multiple linear regression analysis. This resulted in a total of 185 (IES intrusion subscale) and 168 (IES avoidance subscale) for the regression analysis. Those scoring 0 on the subscales were distributed as follows: intrusion: active symptoms, $n=6$, not active symptoms, $n=51$; avoidance: active symptoms, $n=7$, not active symptoms, $n=61$. The assumptions of linearity, independence of errors, homoscedasticity and extreme outliers were met. Violation of the assumption of normality of residuals was addressed through logarithmic transformation of the outcome measure variables.

To investigate the likelihood of scoring 0 or >0 on the IES subscales, logistic regression analyses were performed, using the same predictors and dependent variables as were specified in the multiple linear regression analyses.

RESULTS

A total of 484 persons registered with PCT were sent a postal questionnaire, and 272 were returned (56%). Nine participants were excluded from further analysis because of a missing response to the question categorizing participants into having active PCT, PCT in remission or latent PCT. A total of 263 (54%) questionnaires were eligible for further analysis.

Socio-demographic characteristics

Of the 263 respondents, 57 reported having present active PCT, 172 had PCT in remission and 34 reported latent PCT. For the total sample, the mean age was 59 years (range 25–88 years). Significant socio-demographic differences were found between the groups with regards to sex, age, and occupational and educational status. The active PCT group had more men than women, and the latent group had considerably more women. The mean age was >10 years younger in the latent PCT group than in the remission and active groups. For occupational status, 70% of the latent group reported being employed compared with 33% of the active group. Higher percentages of the active and remission groups than the latent group claimed disability benefits or were retired (Table 1).

Table I. Socio-demographic characteristics of the sample

	Porphyria cutanea tarda; n (%) or mean (range)				p-value
	Total n=259–263	Active n=57 (22)	In remission n=172 (65)	Latent n=34 (13)	
Sex					
Male	121 (47)	34 (60)	78 (46)	9 (27)	
Female	141 (53)	23 (40)	93 (54)	25 (73)	0.01*
Age, years	59 (25–88)	61 (29–87)	60 (25–88)	49 (31–87)	<0.01*
Occupational status					
Working	117 (44)	19 (33)	74 (43)	24 (70)	
Retired	77 (30)	18 (32)	56 (33)	3 (9)	
Disability pension	54 (20)	14 (25)	36 (21)	4 (12)	
Other	15 (6)	6 (10)	6 (3)	3 (9)	<0.01*
Educational status					
Secondary school	58 (23)	10 (18)	45 (27)	3 (8)	
High school	117 (45)	32 (56)	71 (42)	14 (41)	
College/university	84 (32)	15 (26)	52 (31)	17 (50)	0.03*
Cohabitation					
Living alone	66 (25)	16 (29)	43 (25)	7 (21)	
Cohabitant	196 (75)	40 (71)	129 (75)	27 (79)	0.70
Children					
Yes	232 (89)	54 (96)	146 (85)	32 (94)	
No	30 (11)	2 (4)	26 (15)	2 (6)	0.51

*p-value <0.05. For categorical variables, p-values were calculated with χ^2 test for independence or Fisher's exact test when expected cell frequencies were <5. p-value calculated with one-way analysis of variance (ANOVA) for continuous variables (age). Tukey's *post-hoc* test showed that there were no significant differences between active and remission groups, but between latent and both remission and active sub-groups.

Patient-reported outcome measures

The total sample scored >8 on the timeline item on the BIPQ, indicating a high belief in the condition being chronic. The active PCT group had significantly higher perceived illness threat compared with the other PCT subgroups. They also had considerably higher mean scores on the identity item, meaning that they believed more symptoms were caused by PCT compared with remission and latent PCT. The total sample had a relatively high perception of coherence and personal control.

On the treatment control item, the total sample scored even higher; although the remission group scored highest.

The active PCT group had a significantly higher mean score on total intensity and frequency of subjective health complaints compared with the remission and latent PCT subgroups. The active PCT group had a higher mean value on reported psychological distress (intrusion and avoidance) than the remission subgroup, which had a higher mean score than the latent group (Table II).

Associations between illness perception, health complaints, self-reported porphyria cutanea tarda symptoms and psychological distress

When investigating the associations between illness perception, health complaints, self-reported PCT symptoms and psychological distress, we found that illness perception and total score on subjective health complaints were significantly associated with a higher score on the intrusive scale and that the total model explained 30% of the variance. The same predictors were also significantly associated with the avoidance score and explained 20% of the variance. The

self-reported presence of PCT symptoms were not significantly associated with psychological distress related to porphyria (Table III). This means that although participants reporting active PCT scored higher on perceived illness threat, total health complaints and porphyria-related psychological distress, PCT symptoms activity was not significantly associated with psychological distress.

We used the same predictors to investigate the probability of scoring >0 on the IES avoidance and

Table II. Scores on the Brief Illness Perception Questionnaire, Subjective Health Complaints Inventory and Impact of Events Scale (IES)

Patient-reported outcome measures	All participants Mean (95% CI)	Active PCT Mean (95% CI)	PCT in remission Mean (95% CI)	Latent PCT Mean (95% CI)	p-value	Cronbach's α
<i>Brief Illness Perception Questionnaire (0–10)</i>	(n=235–261)	(n=51–57)	(n=156–170)	(n=28–34)		
Consequences	3.2 (2.9–3.5)	4.9 (4.1–5.7)	2.9 (2.5–3.3)	1.6 (1.0–2.2)	<0.01*	
Timeline	8.1 (7.7–8.5)	8.8 (8.2–9.4)	8.0 (7.5–8.4)	7.3 (5.8–8.8)	0.05*	
Personal control	5.8 (5.5–6.2)	5.4 (4.7–6.2)	6.2 (5.7–6.6)	4.9 (3.4–6.3)	0.9	
Treatment control	7.5 (7.1–7.8)	7.6 (6.9–8.4)	7.7 (7.2–8.1)	6.1 (5.2–7.1)	0.02*	
Identity	2.9 (2.6–3.3)	5.8 (5.2–6.5)	2.6 (2.2–2.9)	0.2 (0.0–0.3)	<0.01*	
Concern	3.4 (3.0–3.7)	4.8 (4.0–5.6)	3.2 (2.8–3.6)	1.9 (1.2–2.7)	<0.01*	
Coherence	5.6 (5.2–6.0)	5.9 (5.2–6.6)	5.7 (5.2–6.1)	4.7 (3.7–5.7)	0.12	
Emotional response	2.9 (2.5–3.2)	4.4 (3.6–5.3)	2.7 (2.3–3.0)	1.3 (0.7–1.9)	<0.01*	
Overall score	31.5 (29.9–33.2)	39.6 (35.8–43.4)	29.7 (27.9–31.5)	27.2 (23.3–31.1)	<0.01*	0.67
<i>Subjective health complaints</i>	(n=255)	(n=56)	(n=166)	(n=33)		
Total sum score	15.1 (13.6–16.7)	20.5 (16.7–24.2)	14.1 (12.4–15.8)	10.7 (7.7–13.7)	<0.1*	0.88
<i>Impact of Events Scale</i>	(n=258)	(n=57)	(n=169)	(n=32)		
Intrusion (0–35)	7.0 (6.0–7.9)	11.7 (9.1–14.3)	6.1 (5.1–7.1)	3.0 (1.6–4.4)	<0.01*	0.93
Avoidance (0–40)	7.2 (6.2–8.1)	12.1 (9.5–14.7)	6.1 (5.1–7.1)	4.3 (2.2–6.4)	<0.01*	0.85
<i>Score above 0 on IES</i>	(n=206/189)	(n=51/50)	(n=136/120)	(n=19)		
Intrusion	8.7 (7.7–9.7)	13.1 (10.5–15.8)	7.6 (6.5–8.6)	5.1 (3.1–7.0)	<0.01*	
Avoidance	9.8 (8.7–10.9)	13.8 (11.1–16.4)	8.6 (7.5–9.7)	7.3 (4.4–10.1)	<0.01*	

p-values for differences between means calculated using the Welch analysis of variance (ANOVA). *p-value ≤0.05. PCT: porphyria cutanea tarda.

Table III. Multiple linear regression analysis with Impact of Events Score (IES) as the outcome measure

Variable	Intrusion (n = 185)			Avoidance (n = 168)		
	B	95% CI	p-value	B	95% CI	p-value
Constant	2.25	1.14–4.57	0.02	2.37	1.12–5.01	0.02
Age	0.99	0.98–1.00	0.11	1.00	0.99–1.01	0.87
Sex	1.09	0.86–1.34	0.44	1.13	0.86–1.47	0.38
SHC total	1.02	1.01–1.03	<0.01*	1.02	1.01–1.04	<0.01*
BIPQ total	1.03	1.01–1.04	<0.01*	1.01	1.00–1.32	0.04*
PCT symptoms	1.24	0.92–1.68	0.15	1.31	0.94–1.81	0.11
Adjusted R ²			0.30			0.20

* $p \leq 0.05$. The total model was significant ($p < 0.001$). Analysis was performed on log-transformed outcome variables. The estimates and confidence intervals (CI) presented in the table were back-transformed to the original units of measure. Participants scoring 0 on the IES subscales (Intrusion $n = 57$ and Avoidance $n = 68$) were removed from the regression analysis. SHC: Subjective Health Complaints; BIPQ: Brief Illness Perception Questionnaire.

intrusion scales. Logistic regression analysis produced a significant model that confirmed that a higher score on total illness perception and more self-reported health complaints were significantly associated with scoring > 0 on porphyria-related psychological distress.

DISCUSSION

The current study found a trend towards higher perceived illness threat, more self-reported health complaints and more porphyria-related psychological distress in participants reporting active PCT compared with those reporting latent PCT or PCT in remission. However, the regression analysis did not support an association between PCT symptoms and higher scores on porphyria-related distress. By contrast, perceived illness threat and total health complaints were associated with greater porphyria-related distress.

The finding that perceived illness threat, and not reported symptoms activity, was associated with porphyria-related distress suggests that, although PCT symptoms can be dramatic, PCT in remission can also be challenging for patients. Exactly what it is that makes some patients view PCT as a threatening disease cannot be answered by the present study. In view of the results showing that total health complaints are associated with PCT-distress, and that our previous study (8) showed that PCT patients can find it difficult to separate PCT from other conditions, a possible explanation might be that health complaints other than skin symptoms are also thought to be caused by PCT, and this is contributing to patients reporting higher psychological distress. Others have shown that the perception of disease is associated with psychological distress and QoL in dermatological disorders (18–20), and despite the diverse aetiology, photodermatitis (21) can have a major impact on QoL (7), psychological well-being and lifestyle (22), which suggests that the management of photosensitivity disorders requires a biopsychosocial approach (18, 23)

and that further studies are warranted investigating how PCT in both active and remission phases impacts QoL.

In agreement with the findings of our previous study using focus groups (8), we found an overall high belief in the condition being chronic. This can be viewed as positive, in that it might increase compliance with the guidelines for control and preventive measures. Annual assessment of urinary porphyrin excretion, iron metabolism and liver function are recommended (1). On the other hand, many patients with PCT are expected to experience life-long remission, and a high degree of perceived chronicity and illness threat can entail an ethically challenging situation with a potential for medicalization of this group. Our previous study found evidence of over-treatment; for example, frequent blood samples (every 2 weeks and every month) in patients in remission (8).

Participants with active PCT scored significantly higher on total self-reported health complaints compared with the remission and latent PCT groups. Various hepatic conditions, haemochromatosis and lifestyle factors, such as high alcohol intake and smoking, are associated with active PCT (1, 4, 24) and might contribute to explaining this finding in patients reporting active PCT. The finding that PCT is associated with other diseases may also have impacted on illness perception. Although data about this (i.e. alcoholism, hepatitis, etc.) was not investigated in the present study, the illness perception measurement (BIPQ) was porphyria specific and is expected to reflect the perception of PCT independent of other conditions.

The socio-demographic differences between the PCT groups might also explain some of the observed differences. Although there were more men than women in the active PCT group, women are generally known to report more substantial health complaints (25). An alternative explanation is that attribution of health complaints to PCT could have resulted in a “false” self-reported classification of PCT activity, which is consistent with the findings of our earlier study in which participants reported experiencing PCT as a systemic disease suspected to cause a range of health complaints (8). The active PCT group also scored significantly higher on the identity item, indicating that this group attributed more symptoms to PCT.

Whether or not PCT is a distress-causing life-event, is debatable. Previous findings have, however, shown that PCT could certainly have a large negative psychosocial impact for some (8). In the present study, we did not use individual cut-off values to differentiate between distress and no distress, but rather tried to identify the factors associated with higher distress scores. Individual scores > 9 on the IES subscales have been used as an indication of distress of a moderate character (26). Others have suggested a total sum score of ≥ 40 as signifying a stressful event (27). Although these cut-off values are intended for assessment on an individual level, it is interesting to note that, as a group, those reporting active

PCT had a mean score on the intrusion and avoidance subscales in the “moderate distress” category.

A positive finding was that the total PCT sample reported relatively high scores on coherence (understanding of the condition) and personal control. A high belief in treatment control was also reported, and the remission group reported the greatest belief in treatment, which indicates that they experienced their treatment as adequate and effective, which fits well with previous findings (8). Compared with the personal control scores in those with contact dermatitis (mean 3.5) (19), the PCT patients had a greater belief in their own control of the condition.

The classification of participants into active PCT, PCT in remission, and latent PCT was based on self-reported information. Although this study was aimed specifically at exploring the subjective experiences of the participants and their own interpretation of their situation with regards to PCT, a dermatology-specific instrument and objective evaluation of symptoms could have strengthened the study. A response rate of 54% is somewhat low and can be viewed as a limitation in terms of representability.

In the present study, PCT was perceived as a chronic condition with a high degree of treatment control. Although persons reporting active PCT had more health complaints and perceived PCT as more threatening compared with those reporting latent PCT or PCT in remission, psychological distress was more closely associated with a higher perception of illness threat and the total burden of health complaints than were perceived PCT symptoms. This has implications for clinical consultations with this patient group. It seems evident that PCT patients need clear and concise information and guidance with regards to what health complaints are caused by PCT.

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APPENDIX I

INTERVJUGUIDE FOKUS 105 min = 1 time 45 min.

A. "Kaffepause" (10 min) Ønske velkommen til fokusgruppeintervju (10 min)

- Presentere moderator og co moderator, og informere om rollene
- Si noe om "spilleregler" for fokusgruppeintervjuet, vi ønsker å lære av deltakerne, forteller personlige historier, interaksjon. Ingen rette og gale erfaringer
- Oppfordre til taushetsplikt deltakerne imellom, vår taushetsplikt som forskere og helsepersonell.
- Gi mulighet til å trekke seg fra intervjuet og studien
- Informere om at gruppesamtalen er en enkeltstående hendelse. Ta kontakt ved behov.
- Introduksjonsrunde: Navn, hvor er de fra? Ca diagnoseår og behandling?

B. "Tre tema for intervju" (70 min)

1. "Å være syk"

Hva har gjort størst inntrykk? Hva husker de best?

Påvirker PCT:

- Selvbilde?
- Jobbsituasjon?
- Den øvrige helsen?

Hvordan reagerer andre?

Hvilke begrensinger kan PCT medføre?

2. Behandling

Tanker rundt hva som forverrer og utløser symptomer?

Tiltak i hverdagen?

Blodtapping? Annen behandling?

Helsepersonell og helsevesenets oppfølging?

3. Fremtiden

Gentest?

Andre i familien?

Hva forventer dere av symptomer i tiden fremover?

Tanker om livssituasjon fremover?

Forebygging og egeninnsats?

C. Oppsummering og innspill (10 min)

Co moderator gir en oppsummering av inntrykk fra gruppen

Gruppen gir tilbakemelding

D. Avslutning (5 min)

Avrunde, takke for oppmøte

APPENDIX II

Spørreskjema i forhold til helserelaterte utfordringer ved porphyria cutanea tarda (PCT)

INFORMASJON OM DEG

1. Kjønn: Mann Kvinne
2. Alder: _____ år
3. Bosted:
- Østlandet Sørlandet Vestlandet
- Midt-Norge Nord-Norge
4. Bosituasjon: Bor alene Bor med ektefelle/ samboer / partner Annet bofellesskap (eks barn, søsken, foreldre, andre)
5. Har du barn? Nei Ja
6. Utdanning:
- Grunnskole
- 3-årig videregående skole / yrkesskole el. l
- Fullført høyskole / universitet
7. Betrakter du deg hovedsakelig som:
- Yrkesaktiv Hjemmearbeidende med omsorg / husarbeid
- Alderspensjonist Skoleelev/student
- Arbeidsledig Trygdet/arbeidsufør
- Annet
8. Har du hatt porfyrirelaterte plager/symptomer? Aldri hatt Hatt tidligere Har i dag / siste uke

Brief Illness Perception Scale (BIPQ)

Vennligst sett en ring rundt det tallet som best samsvarer med din mening om de følgende spørsmålene.

1. Hvor mye påvirker porfyri livet ditt?

0 1 2 3 4 5 6 7 8 9 10
Ingen Voldsom
Påvirkning påvirkning

2. Hvor lenge tror du at porfyrien din vil vare?

0 1 2 3 4 5 6 7 8 9 10
Svært kort tid For alltid

3. Hvor mye kontroll føler du at du har over porfyrien din?

0 1 2 3 4 5 6 7 8 9 10
Absolutt ingen Svært stor
kontroll kontroll

4. Hvor mye mener du at behandlingen kan hjelpe mot porfyri?

0 1 2 3 4 5 6 7 8 9 10
Ikke i det Svært
hele tatt hjelpsom

5. Hvor mye opplever du symptomer fra porfyri?

0 1 2 3 4 5 6 7 8 9 10
Ingen symptomer Mange
i det hele tatt alvorlige
sympto

6. Hvor bekymret er du angående porfyri?

0 1 2 3 4 5 6 7 8 9 10
Ikke bekymret Svært
i det hele tatt bekymret

7. Hvor godt føler du at du forstår porfyri?

0 1 2 3 4 5 6 7 8 9 10
Forstår ikke i det Forstår
hele tatt svært godt

8. Hvor mye påvirker porfyri deg følelsesmessig? (dvs gjør den deg sint, redd, urolig eller deprimeret?)

0 1 2 3 4 5 6 7 8 9 10
Ikke påvirket i det Svært
hele tatt følelsesmessig
påvirket

9. Vennligst skriv ned i rekkefølge de tre viktigste faktorene som du tror forårsaket porfyrien din.

De aller viktigste årsaker for meg:

1. _____
2. _____
3. _____

Impact of Events Scale (IES)

Sett ring rundt det svaralternativet som passer best

	<i>I høy grad</i>	<i>Ganske mye</i>	<i>Middels</i>	<i>Noe</i>	<i>Litt</i>	<i>Aldri</i>
1. Jeg har hatt perioder med sterke følelser omkring porfyri.....	1	2	3	4	5	6
2. Ting jeg har sett og hørt minnet meg plutselig om porfyri.....	1	2	3	4	5	6
3. Tanker om porfyri har trengt seg på også når jeg ikke har villet.....	1	2	3	4	5	6
4. Bilder av porfyri har plutselig dukket opp i tankene mine.....	1	2	3	4	5	6
5. Enhver påminnelse har gjenoppplivet følelser knyttet til porfyri.....	1	2	3	4	5	6
6. Jeg har hatt vanskelig for å sove på grunn av tanker og bilder om porfyri.....	1	2	3	4	5	6
7. Jeg har vonde drømmer om porfyri.....	1	2	3	4	5	6
8. Jeg vet mange uforløste følelser er der, men jeg har skjøvet dem bort.....	1	2	3	4	5	6
9. Jeg har ikke tillatt meg å bli følelsesmessig berørt når jeg tenker på porfyri eller blir minnet om den.....	1	2	3	4	5	6
10. Jeg har ønsket å bli kvitt minner om porfyri.....	1	2	3	4	5	6
11. Jeg har forsøkt å la være å snakke om porfyri.....	1	2	3	4	5	6
12. Jeg har opplevd det uvirkelig, som porfyri ikke har hendt eller ikke var virkelig.....	1	2	3	4	5	6
13. Jeg har holdt meg unna ting eller situasjoner som kan minne meg om porfyri.....	1	2	3	4	5	6
14. Mine følelser om porfyri er nærmest lammende.....	1	2	3	4	5	6
15. Jeg har ikke tillatt meg selv å ha tanker om porfyri.....	1	2	3	4	5	6

Subjective health complaints inventory (SHC)

Helseproblemer siste 30 dogn

NB! Det er viktig at du fyller ut både *hvor plaget* du har vært, og *omtrent antall dager* du har vært plaget siste tretti dogn.

Nedenfor nevnes noen alminnelige helseproblemer (sett ring rundt tallet som passer)	Ikke plaget	Litt plaget	Endel plaget	Alvorlig plaget	Antall dager plagene varte (omtrent)
1. Forkjølelse, influensa	0	1	2	3
2. Hoste, bronkitt.....	0	1	2	3
3. Astma	0	1	2	3
4. Hodepine	0	1	2	3
5. Nakkesmerter	0	1	2	3
6. Smerter øverst i ryggen	0	1	2	3
7. Smerter i korsrygg.....	0	1	2	3
8. Smerter i armer.....	0	1	2	3
9. Smerter i skuldre	0	1	2	3
10. Migrene	0	1	2	3
11. Hjertebank, ekstraslag	0	1	2	3
12. Brystsmerter	0	1	2	3
13. Pustevansker.....	0	1	2	3
14. Smerter i føttene ved anstrengelser.....	0	1	2	3
15. Sure oppstøt, «halsbrann»	0	1	2	3
16. Sug eller svie i magen	0	1	2	3
17. Magekatarr, magesår	0	1	2	3
18. Mageknip.....	0	1	2	3
19. «Luftplager»	0	1	2	3
20. Løs avføring, diaré	0	1	2	3
21. Forstoppelse	0	1	2	3
22. Eksem.....	0	1	2	3
23. Allergi	0	1	2	3
24. Hetetokter.....	0	1	2	3
25. Søvnproblemer	0	1	2	3
26. Tretthet	0	1	2	3
27. Svimmelhet	0	1	2	3
28. Angst	0	1	2	3
29. Nedtrykt, depresjon	0	1	2	3

APPENDIX III

Search strategy

Initial searches were performed on Medline and Web of Science, and repeated regularly by the author to find research related to the psychosocial and subjective experiences with AIP and PCT.

A systematic search was conducted with the assistance of a trained librarian on January 7, 2016. The search was performed on the following electronic sources: Medline, Embase, PsychINFO and Cinahl.

7. Jan. 2016

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to Present>

Search Strategy:

- 1 psychology.fs. (834100)
- 2 exp Porphyrias/ (8946)
- 3 porphyria*.ti,ab. (7552)
- 4 2 or 3 (10087)
- 5 "Quality of Life"/ (136057)
- 6 ("Quality of life" or QoL or HrQoL or HRQL).ti,ab. (181246)
- 7 exp Adaptation, Psychological/ (108750)
- 8 Social Adjustment/ (22028)
- 9 (coping or cope or distress).ti,ab. (135246)
- 10 ((adapt* or adjustment* or responsiveness or sensitivity) adj3 (social or psycholog* or behavio*)).ti,ab. (20194)
- 11 (sense of coherence or SOC).ti,ab. (10507)
- 12 Illness Behavior/ (715)
- 13 ((sick* or illness) adj5 (behavio* or perception or role)).ti,ab. (6991)
- 14 psychology.fs. (834100)
- 15 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 (1139293)
- 16 4 and 15 (121)

7. Jan. 2016

Database: (Ovid) Embase <1974 to 2016 January 06>

Search Strategy:

- 1 exp porphyria/ (11633)
- 2 porphyria*.ti,ab. (8483)
- 3 1 or 2 (12369)
- 4 exp "quality of life"/ (323612)
- 5 ("Quality of life" or QoL or HrQoL or HRQL).ti,ab. (269590)
- 6 exp coping behavior/ (43492)
- 7 exp social adaptation/ (94968)
- 8 (coping or cope or distress).ti,ab. (175327)

- 9 ((adapt* or adjustment* or responsiveness or sensitivity) adj3 (social or psycholog* or behavior*)),ti,ab. (24299)
- 10 (sense of coherence or SOC),ti,ab. (13211)
- 11 illness behavior/ (3364)
- 12 ((sick* or illness) adj5 (behavior* or perception or role)),ti,ab. (8900)
- 13 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (668402)
- 14 3 and 13 (144)

7. Jan. 2016

Database: Ovid PsyclNFO <1806 to December Week 5 2015>

Search Strategy:

-
- 1 porphyria/ (78)
 - 2 porphyria*.ti,ab. (133)
 - 3 1 or 2 (140)

7. Jan. 2016 Cinahl (Ebsco)

- | | | |
|----|--------------------------------|-----|
| S1 | (MH "Porphyrias+") | 188 |
| S2 | TI porphyria* OR AB porphyria* | 127 |
| S3 | S1 OR S2 | 211 |