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ORIGINAL ARTICLE

Acute porphyrias: a German monocentric study of the biochemical, molecular genetic, and clinical data of 62 families

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Abstract

In Germany, analyses of clinical and laboratory features of patients with acute porphyrias are only available for hereditary coproporphyria (HCP) but not with other acute porphyrias, acute intermittent porphyria (AIP) and variegate porphyria (VP). The aim of the study was to analyze a large cohort of patients with particular focus upon quality of life aspects. Sixty-two individuals from separate families with acute porphyrias (57 AIP, 5 VP) were included into an observational study collecting biochemical, genetic, and clinical data. A questionnaire was designed to complete anamnestic information and to assess the influence on quality of life. Most frequent signs and symptoms or laboratory abnormalities were abdominal colicky pain, red coloration of urine, and hyponatremia. Depression or anxiety was reported by 61% or 52% individuals, respectively. Fatigue was mentioned as the most quality of life-limiting symptom. In 59/61 patients, mutations could be identified. 44% (20/45) had to be admitted to an intensive care unit. Heme arginate was used in 64% (29/45) of patients for treatment of acute attacks at least once and in 33% for long-term treatment with high frequency of administration. Serum creatinine values increased in 47% (7/17) of the patients with recurrent attacks. Our analysis confirms a substantial influence of the diseases on the quality of life on patients. Percentages of urine discoloration and intensive care unit admissions were much higher than in other reports. Long-term treatment with heme arginate requires careful monitoring of iron status and renal values.

Keywords Acute porphyria · Quality of life · Recurrent attacks · Mutation analysis

Introduction

The porphyrias are rare inborn errors of metabolism which occur in the pathway of heme biosynthesis [1]. Among the acute porphyrias which AIP and VP are the most frequent, HCP occurs much less often.

In Germany, only one detailed analysis of patients has been published two decades ago, in this case with HCP [2]. Worldwide, reports are available from experts from various countries such as the US [3], France [4], Argentina [5], Spain [6], Sweden [7], Switzerland [8], South Africa [9], Italy [10], Finland [11], China [12], or India [13].

Rarely, however, all relevant aspects (clinical data, biochemical and genetic data, and quality of life reports) have been included in the same report.

Here, we describe our effort to provide as many aspects as possible (ethnic, biochemical, genetics, therapy, influence upon quality of life) in a cohort of 62 individuals treated at one porphyria center in Germany.

Methods

In 62 patients with confirmed AIP or VP in a prospective approach, disease characteristics such as signs and symptoms at diagnosis and during the course of disease were collected. Informed consent was given by the patients. Included were symptomatic patients with biochemical and molecular genetic proof of acute porphyria and asymptomatic gene carriers in whose family a member had been diagnosed with acute porphyria. Forty-five of the 62 had developed symptoms during

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their life so far. The other 17 were asymptomatic carriers in whose family the diagnosis of acute porphyria with genetic confirmation had been made.

Biochemical criterion for the presence for AIP or VP was the increase of 5-aminolevulinic acid (5-ALA)/creatinine to values higher than 2.83 μmol/mol creatinine or 0.9 μmol/mol creatinine for porphobilinogen (PBG), respectively, with a decrease of PBG deaminase in red blood cells (13.3–24.7 nmol/l/sec or 70% to 130%) to less than 70%. The porphyrin precursors were determined as described [14]; PBG deaminase was measured as described [15]. Nearly all biochemical analyses were performed in the EPNET porphyria laboratory in Karlsruhe.

Mutation analyses could be performed on 59 gene carriers. Nearly all determinations were carried out in the Dortmund laboratory which has proven experience with this analysis for a long time [16].

Clinical, biochemical, familial, and genetic data were collected in our local database.

For development of a porphyria-oriented quality of life questionnaire, the QLQ-C30 EORTC questionnaire and a hematological questionnaire developed by our group [17] were consulted, and then a novel questionnaire addressing aspects important for porphyria patients was developed. This questionnaire consists of 9 questions: the first part focusses on the characteristics of the porphyric attacks including number of attacks, signs, and symptoms during but also between attacks and treatment of symptoms. The second part concentrates on the impairments in different aspects of daily life such as mobility, self-sufficiency, professional career, spare time, complications during medical procedures like surgery, and family planning. After informed consent, the patients were asked to put symptoms in a ranking scale that reflects their experienced influence on their quality of life. In the third part, the patients could estimate the severity of their overall impairment by their illness and of the impairment of mood on scales ranging from 0 to 10. They could also give expression to their subjectively experienced effectiveness of the treatment they received and the influence of side effects on their quality of life.

The patients were furthermore given the opportunity to add aspects that seemed important to them and had not been addressed in the questionnaire.

Results

Patients' characteristics

In 57 (92%) individuals, AIP was diagnosed, in 5 (8%) VP. Of the total of 62 patients, 52 (84%) were females. Three were of Turkish origin, one of Greek, one was Hungarian, one from India, one from Sudan, and two from South Africa, the remainder of German origin. Average age when the initial diagnosis of porphyria was made was 31.8 years in women and 34.8 years in men. Patients were documented between 18 and 218 months.

Signs and symptoms

Abdominal colicky pain and red coloration of urine were present in all AIP patients suffering from an acute attack and then—in descending order—nausea, back pain, vomiting, and various other signs and symptoms (Fig. 1).

Attack frequency varied from once in a lifetime to monthly recurring attacks (Fig. 2).

Symptoms between attacks that required symptomatic therapy, for example, pain medication, antiemetics, or antidepressive treatment, but were not treated with heme arginate were mild colicky pain, nausea, obstipation, vomiting, persisting back pain, weakness, anxiety, and depression.

Two AIP patients had concomitant familial Mediterranean fever (FMF) which made differential diagnosis of abdominal pain difficult in some instants [18].

Three of the five VP patients developed symptoms. One of them (VP1) reported photosensitivity of the skin and eyes, itching, depression, and paranoia. Another one (VP3) had episodes of abdominal pain and skin symptoms. A third one (VP4) had 4 acute attacks with abdominal pain, nausea, obstipation, tachycardia, seizures, back pain, and red coloration of urine. Between acute attacks, abdominal pain and back pain continued to occur.

Biochemical analyses

Urine samples for PBG- and 5-ALA determinations were always collected when patients with known acute porphyrias presented in the clinic with signs of acute attacks. Heme arginate therapy, however, was given solely based on clinical judgment. In most of these patients, PBG and/or 5-ALA levels were between 22 and 45 μmol/mol creatinine and were elevated when compared to determinations occasionally obtained during symptom-free intervals.

In some patients, attacks occurred in spite of only mildly elevated precursor levels like in one female patient who showed symptoms of an acute attack and required treatment with heme arginate: her PBG/creatinine ratio was 7.24 μmol/mol (ref: < 0.88), while her 5-ALA/creatinine ratio was 1.80 μmol/mol (ref: < 2.59).

On the other hand, when we collected urine in some of the asymptomatic gene carriers, we observed elevated PBG- and 5-ALA levels in the urine although the individuals did not report symptoms. When we measured both precursors in such a secretor daily for a whole week, we found fluctuations from

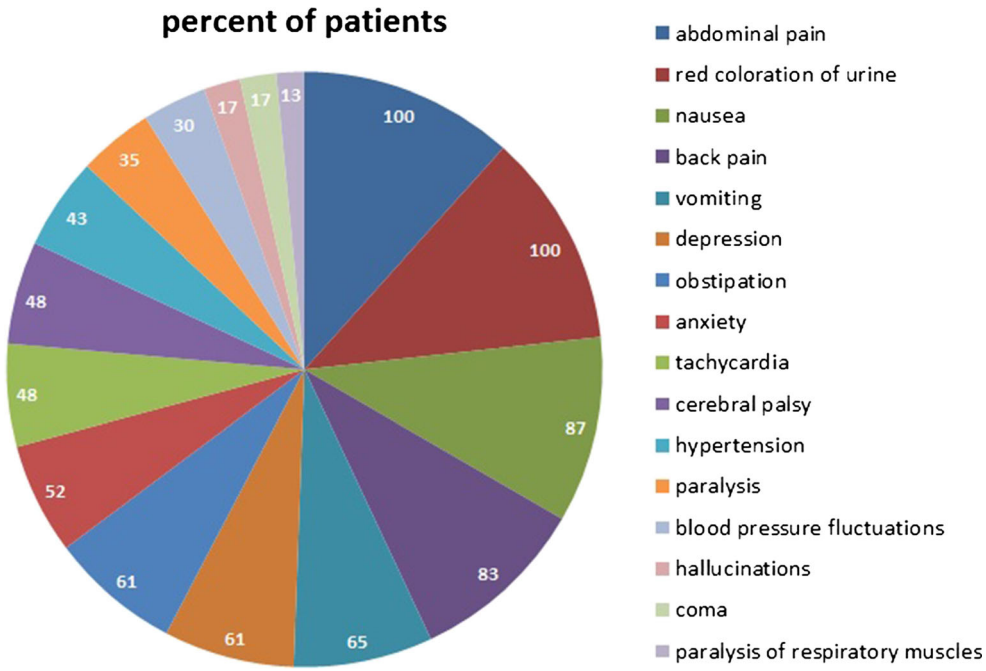

Fig. 1 Signs and symptoms in AIP patients

day to day for 5-ALA between 8.48 and 40.82 and for PBG between 4.5 and 19.11 μmol/mol creatinine.

PBG deaminase activity was determined in 49 of 57 AIP patients: median value was 52% or 9.8 nmol/l/sec. Of the 49 patients, 46 had the typical variant; in 3 patients, the atypical variant was present.

Mutation analyses

In 59 of 62 patients, mutation analysis was performed [16, 19]. In five patients with biochemically confirmed AIP, no mutation could be identified.

In our cohort, mutations leading to the atypical non-erythroid form of AIP were detected in a total of 5/54 or 9,2% of patients and target the exon1-intron1 splice site (two patients with c.33+2T>C, three patients with cC.33G>T). Both mutations result in the activation of an intron 1 derived cryptic splice site and are expected to encode a truncated premature protein. The mutation c.331G>A (pGly111Arg) was most frequently observed (9/54 or 16,7% of analyzed AIP patients). Other mutations occurred much less frequently (Fig.3), but three additional mutations were each identified twice (3,7% each): c.445C>T (p.Arg149*), c.500G>A (p.Arg167Gln) and c.575G>A (p.Gly192Asp).

In 53,7 % (29/54) of the patients, a private mutation was found.

The most frequent type of mutation was missense mutations (46,3 %), followed by splicing defects (24 %), nonsense mutations (9,3 %)/(9,3%), insertion/deletion/duplications with consecutive frameshifts (9,3%) and one codon deletion that leads to the missing of one amino acid without causing a frameshift (1,8%). In 5 patients (9,3%) the mutations remained cryptic.

Mutation analysis of the five VP patients revealed the mutation c.175 C > T in two patients, 1082insC also in two patients, and the mutation c.763C > T in one individual.

Comparing the enzymatic activities of AIP patients with the most common mutation in our cohort, i.e., c.331G > A (p.Gly111Arg), to the enzymatic activities of all patients with other mutations, did not show significant differences between those two groups. We could not find a genotype-phenotype relation between type of mutation and enzymatic activity of PBG deaminase.

Incidence of liver tumors or liver transplantation

In three patients, liver tumors (2 hepatomas and 1 bile duct carcinoma) occurring at the ages of 70, 69, and 77 were diagnosed. Interestingly enough, two of the patients with liver tumors were sister and brother, which may indicate that additional genetic factors contribute to the development of liver tumors in porphyria patients. Molecular analysis of the tumors of these patients was presented elsewhere [20].

In two female patients, liver transplantations were carried out: both suffered from severe recurrent attacks in spite of the use of heme arginate. In the first, the transplantation was carried out without any serious complications. Follow-up examinations for a period up to 15 months after transplantation showed normalized biochemical results. No transplantation-associated complications could be observed. As expected, no further porphyric attacks occurred. The second patient received a double liver and kidney transplant. 18 months after

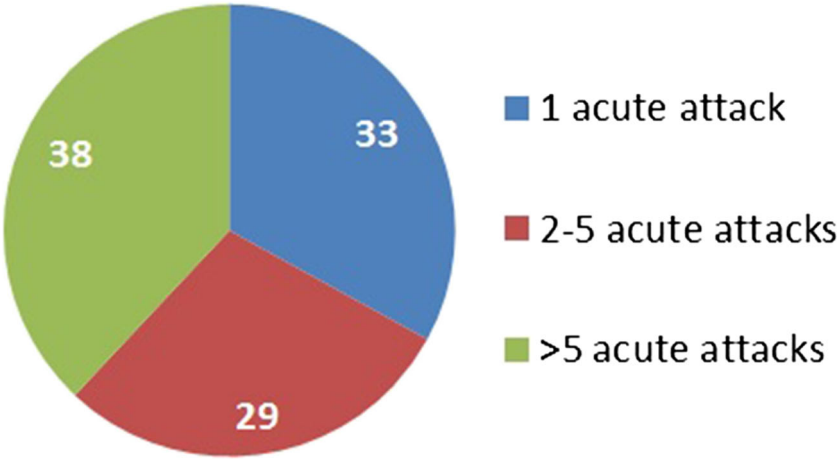

Fig. 2 Frequency (%) of attacks in their life (current status of observation)

transplantation, she became pregnant and had a premature baby. At the time of writing, mother and child are well-off.

Treatment

Of the symptomatic AIP patients, 44.4 % had to be admitted at least once to intensive or intermediate care units. 64.4% of symptomatic patients (based on clinical judgment in recurring attacks) received treatment with heme arginate (Normosang®) at least once.

Comparing the creatinine values of patients who received treatment with heme to those who did not receive heme showed that in the heme group 40% had elevated creatinine values (ranging from 1.18 to 2.85 mg/dl), while in the non heme group only 25% had slightly elevated creatinine values (ranging from 1.15 to 1.43 mg/dl). The average creatinine value of the heme group was 1.16 mg/dl, and the average of the non-heme group was 1.01 mg/dl.

Since heme preparations contain iron (22 mg iron in 250 mg heme = 88 mg per 4 day treatment), ferritin values were regularly checked in patients who were on continuous treatment with this substance: since menstruations cause a monthly loss of 2.5 to 40 mg iron, only in some patients heme treatment led to a continuous iron accumulation reflected by

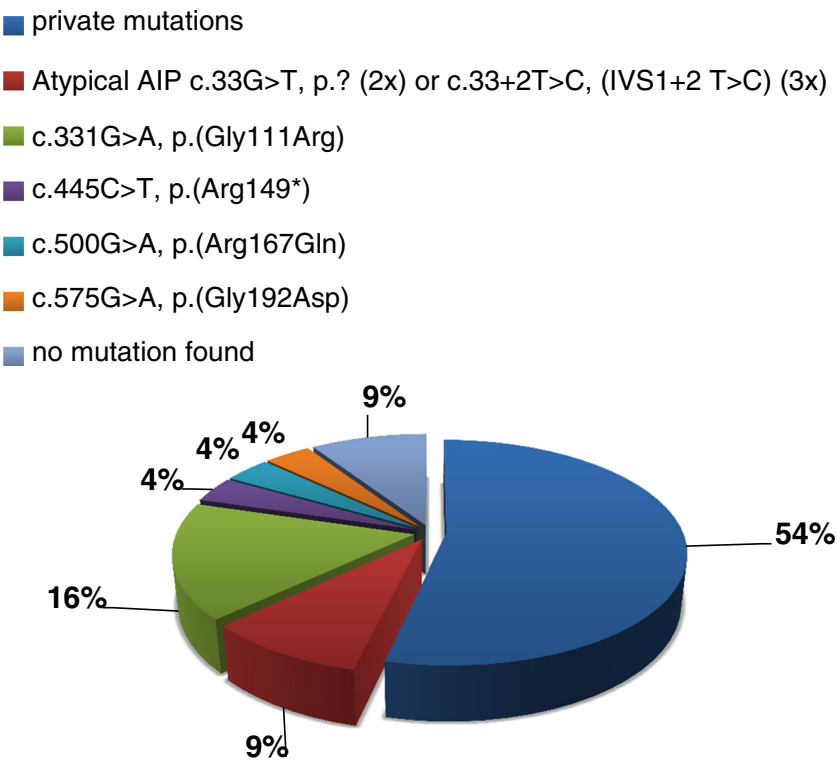

Fig. 3 Frequency of mutations in AIP patients/gene carriers (%)

increasing ferritin values. Ferritin determinations in acute porphyrias are of limited value since ferritin is an acute-phase protein which can be released from a metabolically disturbed liver. Hence we see also fluctuations of the ferritin levels in porphyria patients without any heme arginate treatment. Only in one female patient who obtained heme arginate for more than 10 years we observed ferritin levels up to 2000 ng/ml which made liver transplantation necessary (see below). The only reliable noninvasive method for measuring iron accumulation in the liver is T2*MRI. We have no data with this method so far, however.

Prophylactic treatment

Fourteen females and one male (33% of all symptomatic AIP patients) received heme arginate over a period of at least 1 year on a regular basis.

Pregnancies

Fifteen of 21 female AIP patients who answered the questionnaire with regard to pregnancy reported a total of 32 pregnancies: 23 healthy children were born, 4 were still under pregnancy, and 5 reported abortions (4 spontaneous, 1 induced). Four acute attacks during pregnancy were reported; in one of these cases, an abortion was induced due to severe symptoms. In this case, the pathological examination of the placenta showed changes compatible with a perfusion disorder.

One patient became pregnant after a double transplant (see above).

Mortality

One female patient who had developed a hepatoma after more than 20 years without AIP symptoms died after surgery with curative intention.

Another patient (22 years old) died during the first manifestation of AIP due to a very severe form of the disease with electrolyte imbalance, optic and acoustic hallucinations, tetraparesis, diaphragm paresis with consecutive need of intubation, and necessity of a transient pacemaker because of recurrent asystolies.

Another patient who died at the age of 63 had suffered from severe neurological complications (tetraparesis) during her first attack at the age of 46 and was wheelchair-bound because of residual neurological symptoms; she had recurrent attacks and developed a chronic renal insufficiency as complication of the disease. The cause of her death was unknown.

Hence, a total of 3 patients (5%) died during the time of observation. All of them were symptomatic AIP gene carriers.

Results of the questionnaire

Quality of life

Nineteen of 23 (83%) patients who answered the questionnaire stated an impairment of their mobility by neurological symptoms, fatigue, abdominal pain, back pain, tachycardia, or mental problems.

Nineteen of 23 (83%) patients reported difficulties in self-sufficiency: 4 of them, who had severe residual neurological symptoms, even stated permanently impaired self-sufficiency.

Eleven of 23 (48%) patients stated interferences of the disease with their careers: 5 reported about disease-related problems with their employer, and 6 (26%) even lost their job. Two patients had to retire early; one was incapacitated because of health problems. Three hairstylists reported about problems with the ingredients of hair dyes they had to work with. According to them, these chemicals triggered acute attacks.

One male patient became a freelancer because he did not feel able to work full time anymore.

More than 70% of patients stated limitations regarding their spare time activities. Especially traveling long distances was difficult or even impossible due to paralyses, fear of acute attacks, and need for medical care, fatigue, or weakness. Four patients described coping strategies like regular meals to avoid low blood sugar, avoidance of excessive exhaustion, and long recovery phases after acute attacks.

Three patients reported acute attacks after surgical interventions, one after local anesthesia as part of a dental treatment.

Two patients had problems with their pain management after surgical interventions. They did not receive sufficient pain medication because of a lack of knowledge of their physicians about treatment options for porphyria patients.

When patients were asked to assess the degree of the impairment of their general quality of life on the scale (from 0 to 10), they chose an average of 5 with a range of 0 to 8. Except from one patient, all expressed that they had at least a slightly decreased general quality of life because of their disease.

Regarding the influence of porphyria on mood and mental health, all patients expressed at least some degree of impairment. They stated an average of 4.8 on the scale.

The efficacy of the treatment patients received (including therapy with IV heme, glucose, pain medication, and other symptomatic medication) showed a wide range: one patient stated that he did not benefit from treatment at all. Overall, however, patients tended to express relatively good effectiveness (average of 6.7). Four of 20 (20%) patients stated a very good efficacy of the therapy received (10 on the scale).

Assessing the impairment of quality of life by adverse effects of treatment for porphyria patients chose an average of 2.3 on the scale. Overall they expressed a good tolerability of the therapies they received.

Among the symptoms having the largest negative impact on their quality of life, chronic fatigue was reported to be the most impairing symptom followed by colicky pain and disease-related mental problems. Patients with severe residual neurological symptoms named them as most impairing symptoms.

Discussion

This report of 62 patients from separate families is the only cohort of acute porphyria patients such as AIP and VP reported from Germany so far. Not surprisingly female patients and those with AIP represented the largest groups. The female preponderance has been explained with the potential impact of female sexual hormones on the clinical expression. However, there are many more genes differently expressed between females and males who could contribute to the sex-specific phenotype of porphyrias [21]. As known from previous studies, age of onset is around 30 years.

Among our patients, we have at least two cohorts of patients: the one in whom the diagnosis first was made mainly on intensive care units (with hyponatremia, neurology, elevated precursor levels, enzyme assays, etc.) and the second with known porphyria who shows up in the clinic regularly or maybe once every year or 2 years with suddenly occurring symptoms; the latter patient is "experienced" in knowing what the characteristics of an acute attack are. Always they are dominated by abdominal and/or back pain. When we agree with the patient, heme arginate treatment is given. We take urine samples but cannot wait for the results (usually 2 days).

We also measure CRP at patient presentation. In our hands, acute attacks are normally not associated with CRP increase (unless an intestinal infection has triggered the attack). The coexisting FMF is a real problem, but we measure CRP and serum amyloid A (SAA, elevated during FMF attack) upon presentation in the clinic. On rare occasions, we gave heme arginate but upon receipt of the lab values had to conclude that this had been an FMF and not a porphyria attack.

With regard to signs and symptoms, we observed much higher values for urine discoloration (100%) and hyponatremia (51%) when compared to other reports (for instance, 33% in Ref. [13]). In our experience, the triad of abdominal pain, hyponatremia, and urine discoloration should raise the suspicion of the presence of porphyria trait. The high rate of final porphyria diagnosis in intensive/intermediate care units demonstrates the delay of the correct diagnosis (until the patient got really sick) and should also alert physicians in the emergency room to consider these disorders in their differential diagnosis.

As reported by others, we found increasing signs of renal impairment [22, 23], i.e., serum creatinine values of one patient rose from 1.3 to 2.3 mg/dl during the course of the disease (between 1999 and 2014).

Porphyria is no contraindication for pregnancy in view of the successful pregnancies reported by our patient cohort. This confirms reports by some [24] but contradicts others [25]. According to the latter authors, women with porphyria should be monitored closely during pregnancy because of a higher risk for adverse pregnancy outcomes. They also report excess risk for small gestational age and low birth weight in subgroups of their cohort. We have no data on birth weight and gestational age. The use of heme arginate during pregnancy in one of our patients was free of complications.

The high percentage of patients who suffered from repetitive attacks (33.3%) or were on preventive heme treatment emphasizes the special needs this subgroup deserves. These patients due to their symptoms often have to deal not only pain management on a daily basis but are also often the ones who have to face major impairments in daily life such as impaired mobility and ability to care for themselves and difficulties in their professional life with consequences for their careers.

When we compare our findings with a recently published patient perspective study [26], our cohort cited fatigue as the most impairing symptom, whereas their patients ranked pain over all other symptoms as the "most bothersome" symptom, followed by nausea, abdominal pain specifically, memory loss, and constipation. This could be due to the fact that their cohort consisted only of patients with a high frequency of acute attacks and therefore be associated with a higher symptom burden.

Consistent with our results, they also observed that many symptoms that occur during an acute attack are also present between acute attacks as chronic manifestations of the disease.

Over the years, an increasing number of studies have addressed the issue of quality of life of patients with acute porphyrias and underscored the requirement for better therapies ([27–30] .

Recently, the results of a prospective multinational natural history study of patients with AIP with recurrent attacks (EXPLORE) have been reported in which 112 patients were analyzed for a period of 12 months [31]. Objectives of this study on this subgroup of patients were medical history, medication, signs and symptoms, biomarkers, and quality of life. When we compare the results of the EXPLORE study with our data, we find many matches with our own results (Table 1).

In particular, sex distribution, disease distribution, and most signs and symptoms were similar. Major differences between the two studies were: frequency of genotyping, different results in molecular analysis, chronic symptoms during attacks and above all impairment of quality of life.

The fact that we observed very frequently hyponatremia is due to the fact that this is usually observed upon first diagnosis. With regard to quality of life, we found a more dramatic influence of the symptoms and impairments due to porphyria

on many aspects of life which may be due to our much longer observation period.

For the acute treatment of attacks, heme arginate is the treatment of choice, but there may be disadvantages when it is used for longer periods.

As described above, we observed increased creatinine values in patients who were dependent on frequent administrations of heme arginate because of their symptoms.

Recently, a comprehensive study was carried out in patients on long-term heme arginate treatment showing the initial beneficial effect but turning into detrimental effects upon long-term use [32].

For these patients, treatments with novel approaches are on the horizon using siRNA (Givosiran^{R}) or systemic messenger RNA which may become an alternative or additional option to the present therapy [33, 34].

Table 1. Comparison of EXPLORE and MUNICH-Studies

	EXPLORE	***MUNICH***
Patient cohort		
Number	112	62
Distribution of different entities (%)	AIP = 104 (93%) VP = 5 (4%) HCP = 3 (3%)	AIP = 57 (92%) VP = 5 (8%) HCP = 0
Sex distribution (number/%)	Female = 100 (89%) Male = 12 (11%)	Female = 52 (84%) Male = 10(16%)
Genotypes		
Successful genotyping	56	52
Most frequent mutations in AIP	ARG173TRP & TRP283X	GLY111ARG
Signs, symptoms and laboratory abnormalities during attack	Percentage	Percentage
Abdominal pain	About 90	100
Nausea	> 80	87
Vomiting about	70	65
Obstipation about	70	61
Back Pain	> 70	83
Urine discoloration	> 80	100
Anxiety	> 55	52
Depression	> 40	61
Hyponatremia	*no data*	51
Severe symptoms which required intensive care treatment	*no data*	44
Chronic symptoms between attacks	Percentage	Percentage
Nausea	< 20	< 15
Obstipation	< 10	< 5
Back pain	about 12	about 17
Tachycardia	about 3	13
Weakness	< 15	about 17
Depression	about 7	> 25
Abdominal pain	> 20	About 35
Impairment of quality of life	Percentage	Percentage
most impairing symptom	pain	fatigue
Impairment of Self-sufficiency	4	83
Impairment of Career	no data	22% Problems with employer/ 48% Career problems/ 26% job lost because of disease-related problems
Anxiety/Depression	28	100
Impairment of daily Activities	30	74
Urine Porphyrin-Precursors		
5-ALA/Urine Creatinine (Average of maximal-values of patients)	64,1 μmol/mol Creatinine	13,1 μmol/mol Creatinine
PBG/Urine Creatinine during attack (Average of maximal-values of patients)	57,6 μmol/mol Creatinine	26,9 μmol/mol Creatinine

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.Informed consent

Informed consent was obtained from all individual participants included in the study.

Abbreviations 5-ALA, 5-aminolevulinic acid; PBG, porphobilinogen; siRNA, silencing RNA; AIP, acute intermittent porphyria; HCP, hereditary coproporphyria; VP, variegate porphyria; FMF, familial Mediterranean fever

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