



Greater disease burden of variegate porphyria than hereditary coproporphyria: An Israeli nationwide study of neurocutaneous porphyrias

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ABSTRACT

Hereditary coproporphyria (HCP) and variegate porphyria (VP) are referred to as neurocutaneous porphyrias (NCP). Data concerning their systemic presentation are limited and no direct attempt of comparison of the two has ever been made. Our aim was to describe the type and frequency of systemic manifestations of NCPs in Israeli patients. A cross-sectional survey was conducted. The study population included all patients with NCP diagnosed at the Israeli National Service for Biochemical Diagnoses of Porphyrias (INSP) between 1988 and 2019. Of the 83 patients with NCP who were alive in 2019, 61 (73%) completed the survey, 40 with VP and 21 with HCP. Systemic symptoms were reported by 63% of the VP group and 62% of the HCP group ($p = .96$); corresponding rates of cutaneous symptoms were 58% and 5% ($p < .001$). We found no association between the occurrence of systemic and cutaneous symptoms. Among patients with systemic involvement, abdominal pain was the predominant systemic symptom, found in 64% of the VP group and 69% of the HCP group; Analysis of symptom frequency showed that in 68% of the VP group, systemic symptoms (either abdominal, musculoskeletal or neuropsychiatric) occurred on a daily/weekly basis, whereas the HCP group experienced less than one symptom per week ($p < .001$). This nationwide study depicts a significantly heavier disease burden in VP patients compared to HCP owing to its more frequent neurovisceral and cutaneous manifestations.

1. Introduction

The porphyrias are a group of rare metabolic disorders, either inherited or acquired, caused by a specific abnormality in one of eight enzymes of the heme biosynthetic pathway [1,2]. They may be subdivided by the predominant site of the enzyme defect, into hepatic and erythropoietic forms, or by their clinical manifestations, into acute (neurovisceral) and non-acute (cutaneous) forms [3–5]. Variegate porphyria (VP) and hereditary coproporphyria (HCP) are referred to as mixed or neurocutaneous porphyrias (NCPs) because patients can have both potentially life-threatening acute neurovisceral symptoms and cutaneous symptoms. Both are inherited in an autosomal dominant mode with low penetrance [6,7]. Acute porphyric attacks are characterized by pain, usually abdominal, often accompanied by sympathetic

overactivity (systemic arterial hypertension, tachycardia, sweating) and other neurological manifestations (severe fatigue, anxiety, confusion and seizures) [2,5,8,9]. Most of the current information on the clinical systemic manifestations of acute porphyrias is derived from studies of acute intermittent porphyria (AIP) which is more common than HCP and VP [8,10–13], while data on NCPs are relatively limited [8,14,15].

In a recent study, we described the epidemiology of HCP and VP in Israel [6], with the latter being significantly more prevalent than the former [6,10]. The aim of the present study was to investigate the types and frequency of systemic clinical manifestations of NCPs.

Abbreviations: HCP, hereditary coproporphyria; NCP, neurocutaneous porphyrias; VP, variegate porphyria.

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2. Patients and methods

2.1. Study setting and population

The Israeli National Service for Biochemical Diagnoses of Porphyrrias (INSP), located at Rabin Medical Center, was established in 1988 and gained national status in 2000. It is the only certified porphyria laboratory in Israel, and it conducts all porphyria tests referred from all hospitals and clinics nationwide. The laboratory is affiliated with a dedicated porphyria clinic for the management and follow-up of diagnosed patients.

All diagnoses are based on well-established international criteria [13]: All VP patients had a typical prominent peak on plasma fluorescence emission spectroscopy at 404/624-628 nm and elevated fecal porphyrins, with protoporphyrin IX concentrations greater than those of coproporphyrin. HCP patients had elevated fecal porphyrins, of which the main component was coproporphyrin, while maintaining a ratio of isomer III to isomer I greater than 2. Plasma fluorescence spectroscopy of HCP patients revealed only a slight peak at 404/620 nm. Patient, with either VP or HCP, who were diagnosed during an acute attack had highly elevated urinary levels of 5-aminolevulinic acid (5-ALA) and porphobilinogen (PBG).

While genetic analyses conformation was only available in 10 (25%) VP patients and 7 (33%) HCP patients, an additional 8 (20%) VP patients and 11 (52%) HCP patients had a close family member genetically confirmed, thus adding to a sum of 45% of VP patients and 85% HCP patients with a confirmed family mutation.

The study population included all patients with NCP who were diagnosed at the INSP between 1988 and 2019.

2.2. Survey and data collection

All adult patients in the INSP database with a diagnosis of VP or HCP were contacted by telephone between February 1, 2019 and March 1, 2020 and asked to participate in a cross-sectional survey. Interviews were conducted by a well-trained medical professional using a two-part structured questionnaire developed by the head of the Photodermatosis Service (A.L.) and head of the Porphyria Clinic (Y.E.). The first section covered demographic data (age, sex, ethnicity and parents' country of birth), and the second focused on systemic features of NCP. Individuals were considered to have systemic involvement if they experienced at least one systemic symptom induced by or related to porphyria, either abdominal (abdominal pain, vomiting), musculoskeletal (limb pain, limb numbness, muscle weakness), or neuropsychiatric (anxiety, confusion and seizures). Cutaneous involvement was defined as at least one cutaneous symptom that is exacerbated by sun exposure or during summer, or the combination of as at least two different cutaneous symptoms: skin sensitivity, blistering, crusted lesions, scarring or skin hardening and hypertrichosis (see Appendix A of Supplementary Materials for the full questionnaire).

This study protocol was approved by the Institutional Review Board of Rabin Medical Center (RMC-35-19).

2.3. Statistical analysis

Correlations between categorical variables were calculated using chi-squared test or Fisher's exact test, as appropriate. Differences in means were analyzed using Student's *t*-test (two-tailed). Significance level was set at $p < .05$.

3. Results

3.1. Demographics

Between 1988 and 2019, 97 adult patients were diagnosed with NCP. At the time of data collection, 83 were alive of whom 61 (73%)

Table 1

Demographic features of NCP patients.

Characteristic	HCP	VP
No. patients diagnosed in 1988–2019	31	66
Patients alive in 2019	28	55
Patients completing survey	21	40
Age (yr), mean (SD)	49 (19)	48 (17)
Female sex	10 (48)	22 (55)
Ethnicity		
Sephardi Jewish	18 (86)	28 (70)
Ashkenazi Jewish	3 (14)	7 (18)
Other (Jewish)	0	5 (12)
Family history of porphyria	19 (90)	30 (75)

All data are presented as $n(\%)$, unless otherwise stated.

Abbreviations: NCP: neurocutaneous porphyria; HCP: hereditary coproporphyrin; VP: variegate porphyria.

Note: None of the between-group differences were statistically significant.

Table 2

Clinical characteristics of NCP patients.

Characteristic	No. patients (%)		<i>p</i> value
	HCP (<i>n</i> = 21)	VP (<i>n</i> = 40)	
Overall patients with systemic symptoms ^a	13 (62)	25 (63)	0.96
Systemic symptoms alone	12 (57)	9 (23)	0.007
Overall patients with cutaneous symptoms ^b	1 (5)	23 (58)	<0.001
Cutaneous symptoms alone	0 (0)	7 (18)	0.08
Both systemic and cutaneous symptoms (Mixed)	1 (5)	16 (40)	0.003
No symptoms	8 (38)	8 (20)	0.13
Frequent (≥ 1 per week) symptomatic events ^c	0 (0)	17 (43)	<0.001

All data are presented as $n(\%)$.

Abbreviations: NCP: neurocutaneous porphyria; HCP: hereditary coproporphyrin; VP: variegate porphyria.

^a At least 1 systemic symptom induced or related to porphyria: abdominal (abdominal pain, vomiting) Musculoskeletal (limb pain, limb numbness, muscle weakness); Neuropsychiatric (anxiety, confusion, seizures).

^b At least 1 cutaneous symptom exacerbated by sun exposure or during summer or a combination of at least 2 of the following cutaneous symptoms: skin sensitivity, blistering, crusted lesions, scarring or skin hardening and hypertrichosis.

^c Either abdominal (abdominal pain, vomiting), musculoskeletal (limb pain, limb numbness, muscle weakness) or neuropsychiatric (anxiety, confusion, seizures) symptoms.

completed the survey: 40/55 (73%) with VP and 21/28 (75%) with HCP. The main demographic characteristics of the patients are shown in Table 1. The distributions of sex and age were similar in the VP and HCP groups. All patients were Jewish. The majority of both groups were Sephardi Jews (70% and 86%, respectively, $p = .17$), although the VP

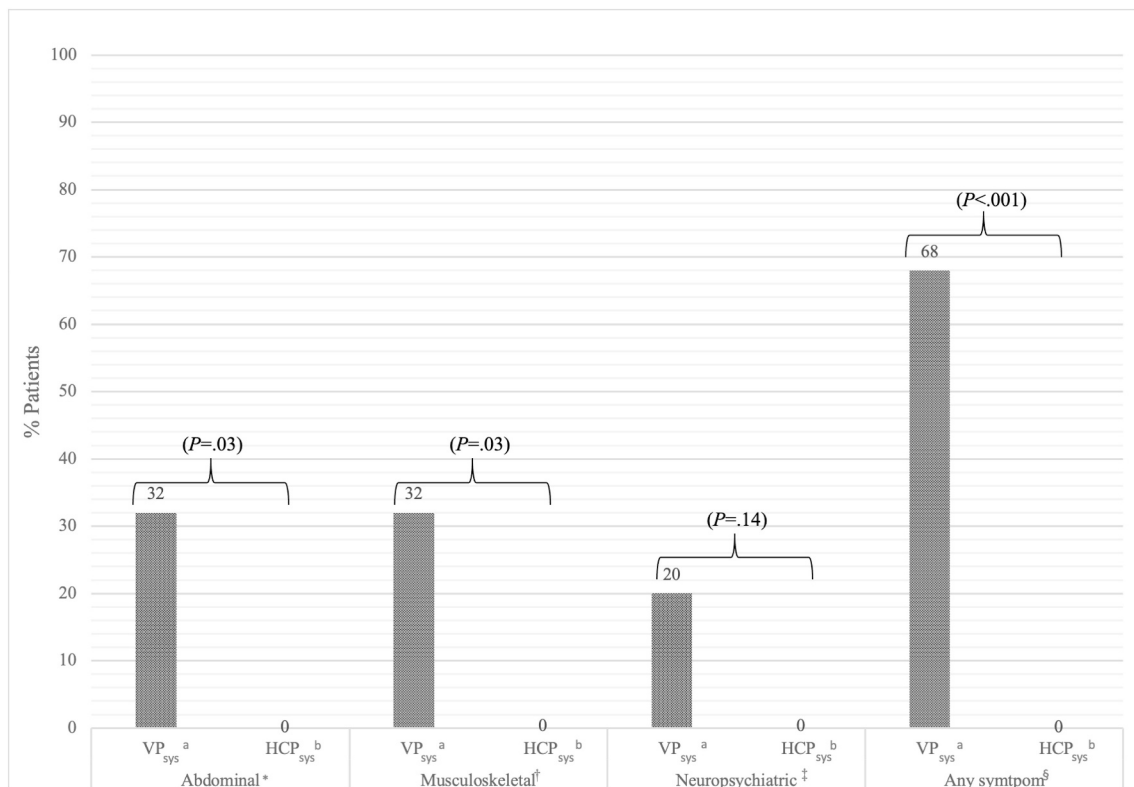
Table 3

Type of systemic symptoms in NCP patients.

Systemic symptom	No. symptomatic patients (%)	
	HCP (<i>n</i> = 13)	VP (<i>n</i> = 25)
Abdominal pain	9 (69)	16 (64)
Vomiting	4 (31)	8 (32)
Limb pain	7 (54)	10 (40)
Limb numbness	5 (38)	8 (32)
Muscle weakness	3 (23)	11 (44)
Anxiety	3 (23)	9 (36)
Confusion	2 (15)	2 (8)
Seizures	1 (8)	2 (8)

Abbreviations: NCP: neurocutaneous porphyria; HCP: hereditary coproporphyrin, VP variegate porphyria.

Note: None of the between-group differences were statistically significant.



Abbreviations: VP, variegate porphyria; HCP, hereditary coproporphyria; Sys, systemic;

^a VP patient group presenting with systemic symptoms.

^b HCP patient group presenting with systemic symptoms.

* Abdominal: abdominal pain, vomiting.

† Musculoskeletal: limb pain, limb numbness, muscle weakness.

‡ Neuropsychiatric: anxiety, confusion, seizures.

§ Any of the aforementioned: gastrointestinal, musculoskeletal, neuropsychiatric symptoms.

Fig. 1. Frequent symptomatic events (≥ 1 per week) among NCP patients with systemic symptoms.

Abbreviations: VP, variegate porphyria; HCP, hereditary coproporphyria; Sys, systemic.

^aVP patient group presenting with systemic symptoms.

^bHCP patient group presenting with systemic symptoms.

* Abdominal: abdominal pain, vomiting.

† Musculoskeletal: limb pain, limb numbness, muscle weakness.

‡ Neuropsychiatric: anxiety, confusion, seizures.

§ Any of the aforementioned: gastrointestinal, musculoskeletal, neuropsychiatric symptoms.

group had a significantly higher percentage of patients of Moroccan origin (65% vs. 24%, $p = .002$). Most patients reported a family history of porphyria (75% vs. 90%, respectively, $p = .19$). None of the patients with VP were South African or of South African descent, and none of those genetically tested carried the protoporphyrogen oxidase (PPOX) R59W mutation which is prevalent among patients with VP in South Africa.

3.2. Clinical manifestations

3.2.1. Systemic symptoms

Similar rates of systemic involvement were observed in the VP and HCP groups (Table 2). Among the patients with systemic involvement (VP_{sys}, HCP_{sys}), abdominal pain was the predominant symptom, found in 64% and 69%, respectively (Table 3). However, in most patients with VP_{sys} (68%), symptoms (either abdominal, musculoskeletal, or

neuropsychiatric) occurred on a daily or weekly basis whereas patients with HCP_{sys} reported less than one symptom per week ($p < .001$; Fig. 1). There were no significant differences between the VP_{sys} and HCP_{sys} groups in rates of hospitalization, either single hospitalization/emergency room visit (56% vs 38%, respectively, $p = .3$) or multiple (3 or more) hospitalizations (32% vs 15%, $p = .44$). No correlation was found between hospitalization (at least once) and the odds of frequent systemic presentation (OR 1.07, 95% CI: 0.18–6.36, $p = .94$).

The VP_{sys} group had a more pronounced trend of frequent use of pain killers (≥ 3 per week), although the difference from the HCP_{sys} group did not reach statistical significance (16% vs. 0%, $p = .28$).

3.2.2. Cutaneous symptoms

Cutaneous involvement was observed in 58% of the VP group and 5% of the HCP group ($p < .001$, Table 2). Coupled systemic and cutaneous presentation was also more prevalent in the VP group (40% vs. 5%, $p =$

Table 4
Potential triggers of systemic symptoms reported by NCP patients.

Precipitating factors	No. symptomatic patients (%)		p value
	HCP (n = 13)	VP (n = 25)	
Alcohol consumption	9 (69)	9 (36)	0.05
Frequency of alcohol consumption ^a			
≥2 doses per day	0	0	
<2 doses per day	9 (69) [*]	9 (36) [†]	
Systemic symptoms ^b during/48 h after drinking	4 (31)	2 (8)	
Smoking	2 (15)	10 (40)	0.16
Smoking frequency			
≥10–20 cigarettes per day	1 (8)	6 (24)	
<10–20 cigarettes per day	1 (8)	4 (16)	
Systemic symptoms ^b during/48 h after smoking	0	3 (12)	
Drug use	3 (23)	10 (40)	0.47
Cannabis	3 (23)	8 (32)	
Other	0	2 (8)	
Systemic symptoms ^b during/48 h after cannabis use	0	4 (16)	
Lessening of systemic symptoms ^b during/48 h after cannabis use	1 (8)	3 (12)	
Systemic symptoms ^b during the luteal phase (females)	3 (50)	6 (38)	0.65

Abbreviations: NCP: neurocutaneous porphyria; HCP_{sys}: hereditary coproporphyrin patient group presenting with systemic symptoms; VP_{sys}: variegate porphyria patient group presenting with systemic symptoms.

^a Where one dose of alcohol = 1 bottle of beer (330 ml) or 1/2 a glass of wine or 2/3 a small glass of hard liquor.

^b Systemic symptoms induced or related to porphyria: abdominal (abdominal pain, vomiting); musculoskeletal (limb pain, limb numbness, muscle weakness); neuropsychiatric (anxiety, confusion, seizures).

^{*} 62%, <1 dose per week.

[†] 32%, <1 dose per week.

.003). There was no association between occurrence of cutaneous symptoms and occurrence of systemic symptoms in either group (VP: OR 2.032, 95% CI: 0.55–7.47, $p = .29$; HCP: OR 2.04, 95% CI: 0.07–56.28, $p = .67$).

3.3. Triggers and management of systemic symptoms

Table 4 outlines specific aggravating factors reported by patients with NCP_{sys}. Most are known to promote the activity of 5-aminolevulinic synthase 1 (ALAS1) via induction of cytochrome P450 [5,12,16].

Alcohol consumption was less common in the VP_{sys} than the HCP_{sys} group (36% vs. 69%, $p = .05$). However, the majority of patients in both groups reported infrequent alcohol consumption of less than 1 dose per week, where dose was defined as 1 bottle (330 ml) of beer or 1/2 a glass of wine or 2/3 a small glass of hard liquor. Most of the patients with VP_{sys} who reported alcohol consumption (78%) also reported frequent systemic symptoms (≥ 1 per week), but the association between these two factors was not statistically significant (OR 2.1, 95% CI: 0.32–13.62, $p = .44$).

A similar trend was also apparent for drug use, with 80% of patients with VP_{sys} reporting drug use also reporting frequent systemic symptoms (OR 2.667, 95% CI: 0.41–17.17, $p = .3$).

In female patients, hormonal menstrual changes were a common trigger of systemic symptoms, especially abdominal pain, in both the VP_{sys} and HCP_{sys} groups (38% vs. 50%, $p = .65$).

A previous hematin infusion for symptoms was solely reported by VP_{sys} patients (12% vs. 0%, $p = .54$), whereas glucose loading was reported in similar proportions by both groups (20% vs. 23%, $p = 1$).

4. Discussion

The present cross-sectional study outlines the systemic features of 61

patients with NCP identified from a nationwide diagnostic porphyria service covering all known patients with porphyria in Israel. This is the first attempt to characterize and compare recurrent subacute and chronic systemic manifestations between VP and HCP in a sufficiently high number of participants in each group. The results showed substantial disparity in symptom frequency and burden of disease between the VP and HCP groups (Fig. 1). Although systemic symptoms were reported by a similar percentage of patients in the two groups, they occurred much more frequently in patients with VP. Taking into account that cutaneous presentation in VP patients is similarly more substantial and affect a much greater portion of patients, these characteristics point to a more considerable disease burden of VP than HCP.

The present study showed that 63% of patients with VP had systemic symptoms and 40% had both systemic and cutaneous symptoms. These rates are close to the 58% and 48%, respectively, reported in an Italian study of 33 patients with VP [17] and the 60% rate of cutaneous involvement found in a study from Argentina [18]. Others, however, reported lower prevalence rates. An earlier study from Western Europe found that only 41% of patients with VP experienced systemic symptoms and 21% had both cutaneous and systemic symptoms [11], similar to values reported in a study from South Africa [19]. Data regarding HCP, however, is even more rare. Our study showed that 62% of patients with HCP experienced systemic symptoms and 5% both systemic and cutaneous manifestations. Mixed presentation rate was close to the 9% reported in both a German study of 53 patients with HCP [20], and a more recent Spanish study [21]. However, both studies reported higher prevalence rates of systemic involvement, 89% and 100% respectively. Variations in systemic and cutaneous manifestations, in both VP and HCP, may be attributed to a range of factors including genetics, comorbidities, climate, and the effort invested in detecting asymptomatic family members.

While cutaneous involvement appears much more prominent in VP than in HCP, thorough research of the literature has yet to suggest a plausible explanation as to why this phenomenon occur. So far, we can only assume that the reason might be attributed to the more hydrophilic molecular nature of HCP's coproporphyrin than VP's protoporphyrin. This may lead to a somewhat better clearance of porphyrins by both urine and stool and thus to some variation in symptom appearance. Further investigation of this clinical presentation is called for.

Studies of acute hepatic porphyria (AHP) described its detrimental effects on employment and ability to work [22], daily functioning and quality of life [15], often exacerbated by frequent repeated hospitalizations and unnecessary surgeries [8]. According to recent literature, over 60% of patients with acute hepatic porphyria experience chronic symptoms and 46% have daily symptoms [15]. However, the bulk of relevant data on the systemic presentation of porphyria is derived mainly from studies of AIP, and more specific research on HCP and VP is warranted [8,15]. Our study revealed that while the prevalence rate of subacute recurrent attacks of systemic symptoms was akin to recent literature in the VP group (43% ≥ 1 per week), HCP had a considerably lower burden of disease.

Smoking and drug abuse as well as use of pain-relieving medications were reported by a higher percentage of patients with symptomatic VP than symptomatic HCP, although our study was underpowered to elicit a statistically significant result. This trend might be attributable to the higher frequency of reported painful manifestations in the VP group and efforts of patients with VP to self-medicate. Studies have shown that initial attempts at pain management in patients with severe illnesses can lead to dependence and increased tolerance, even though aggravation of the disease might ensue over the long term [23,24]. Furthermore, a higher percentage of the VP group had a smoking habit, another possible precipitating factor of NCP [25].

Our study has several limitations. First, patients with only mild symptoms of porphyria may be underdiagnosed, so it is possible that our findings reflect the characteristics of patients with more severe disease. Second, data regarding the disease burden were based on patients' self-

reports which may be influenced by subjective conceptions of symptoms and manifestations. Nevertheless, as the same method of data collection was used in both groups, we believe the findings are accurate. Additionally, we were unable to stratify the patients with systemic symptoms by comorbidities because the data was based on subjective reports and as expected for rare diseases, the number of participants was small.

5. Conclusions

Though both VP and HCP are regarded as acute hepatic porphyrias with mixed presentation, this nationwide study elicits a much heavier disease burden in VP patients compared to HCP patients with more frequent neurovisceral and cutaneous manifestations.

Our study expands the current understanding of the presentation and disease burden of HCP and VP and has implications for improving diagnosis and patient management by generating greater awareness of the disease burden and impact on patients' lives.

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Declaration of Competing Interest

The authors declare they have no conflict of interest.

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