An Analysis of 112 Acute Porphyric Attacks in Cape Town, South Africa

Evidence That Acute Intermittent Porphyria and Variegate Porphyria Differ in Susceptibility and Severity

Richard J. Hift, PhD and Peter N. Meissner, PhD

Abstract: Four forms of porphyria may present clinically with the acute attack, an episodic, severe, and potentially life-threatening manifestation characterized by abdominal and neurologic symptoms. We describe our experience with 112 consecutive attacks observed and treated in 25 patients with the 2 most common forms of acute porphyria in Cape Town, South Africa; 25 attacks in 10 patients with variegate porphyria and 87 attacks in 14 patients with acute intermittent porphyria. The remaining patient experienced more than 100 sequential, severe, and poorly remitting attacks, which are not included in our analysis. In our population, the relative risk of an acute attack in acute intermittent porphyria compared with that in variegate porphyria was 14.3 (confidence intervals, 6.3–32.7). Patients with variegate porphyria were significantly older (median age at first attack, 30 yr) than those with acute intermittent porphyria (median age at first attack, 23.5 yr; $p < 0.0001$), and demonstrated an equal sex ratio, whereas the male:female ratio in acute intermittent porphyria was 2:12 ($p < 0.0001$). There was a significant difference in the incidence of factors precipitating the acute attack. Drug exposure was a frequent precipitant of the acute attack in variegate porphyria, whereas hormonal factors were more important in acute intermittent porphyria ($p < 0.00001$). Patients with acute intermittent porphyria also showed a trend to earlier and more frequent recurrent acute attacks following the initial admission. Mean urine precursor levels, blood pressure, pulse rate, and heme arginate requirement were all significantly higher in patients with acute intermittent porphyria. No significant difference in the frequency of serious complications or in outcome could be shown. We describe our experience with treatment with heme arginate, and provide evidence that heme arginate results in a prompt and statistically significant improvement in symptoms. The incidence of serious complications and mortality in this series was low, confirming a trend to an increasingly good prognosis for patients with acute porphyria who receive expert treatment.

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Abbreviations: AIP = acute intermittent porphyria, ALA = aminolevulinic acid, CT = computed tomography, PBG = porphobilinogen, VP = variegate porphyria.

INTRODUCTION

The porphyrias are a group of metabolic disorders associated with enzyme defects in the heme synthetic pathway and a consequent overproduction of porphyrins, the essential intermediates of this pathway[41]. All are inherited, although porphyria cutanea tarda may be acquired as a result of factors that may reversibly inhibit the enzyme uroporphyrinogen decarboxylase[22,23]. Two of the porphyrias, congenital erythropoietic porphyria and erythropoietic protoporphyria, predominantly affect erythroid heme synthesis. They may be diagnosed by demonstrating characteristic elevations in porphyrin concentrations in erythrocytes. They present clinically with photosensitivity, since porphyrins are photoactive molecules, a property accounting for their characteristic fluorescence under ultraviolet light[39]. Erythropoietic protoporphyria may additionally be associated with liver injury resulting from the hepatic uptake and accumulation of protoporphyrin released from erythrocytes[12].

The remaining porphyrias affect nonerythroid heme synthesis and are described as ''hepatic'' porphyrias. In 3 porphyrias (porphyria cutanea tarda, hereditary coproporphyria, and variegate porphyria [VP]), porphyrins typically accumulate in plasma and skin, resulting in a characteristic photosensitivity. A second clinical presentation, the acute neurovisceral crisis, also known as the acute attack, is seen

From Lennox Eales Porphyria Laboratories, Department of Medicine and South African Medical Research Council, University of Cape Town, Liver Research Center, Cape Town, South Africa.

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Address reprint requests to: Professor RJ Hift, PhD, Department of Medicine, Faculty of Health Sciences, University of Cape Town, Anzio Road, Observatory, South Africa 7925. Fax: 27 21 447 9670; e-mail: rjh@uctgsh1.uct.ac.za.

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in patients with aminolevulinic acid (ALA) dehydratase deficiency porphyria, acute intermittent porphyria (AIP), hereditary coproporphyria, and VP, which are collectively known as ''acute'' porphyrias. The first of these is inherited as an autosomal recessive disorder, whereas the remaining 3 are autosomal dominant traits. For more information on the genotype-phenotype correlation in patients with AIP, see the report by von und zu Fraunberg et al[64] in this same issue. In all 4, the acute attack is associated with elevations of the porphyrin precursors ALA and porphobilinogen (PBG). Elevated concentrations of these precursors may be measured in urine and are used to diagnose the acute attack[21]. Although ALA or PBG may themselves be neurotoxic and therefore responsible for the symptoms of the acute attack, this has never been established with certainty, and others have hypothesized that the acute attack may result indirectly from heme deficiency[42]. In both ALA dehydratase deficiency porphyria and AIP, the enzyme defect occurs proximal to the first porphyrin in the heme synthetic pathway: hence porphyrins (as opposed to their precursors) do not accumulate, and photosensitivity is not a feature.

The acute attack is a potentially fatal condition characterized by severe abdominal pain, autonomic dysfunction, and a motor neuropathy that may progress to quadriparesis[21]. It is associated with hyperinduction of the heme synthetic pathway[41,42]. The cardinal clinical features are an autonomic neuropathy typically presenting as severe abdominal pain, nausea, ileus, hypertension, and tachycardia, which may progress over several days to a motor neuropathy and eventually a profound flaccid quadriparesis[21]. Other features that have been described include confusion, seizures, and psychosis.

The acute attack may be precipitated by a number of factors having in common the potential to induce heme synthesis. This includes exposure to many drugs[43]. Other factors that have been implicated include the menstrual cycle, infection, starvation, and stress[21].

Therapy for the acute attack consists of symptomatic treatment—particularly opiate analgesics—and specific therapy designed to reduce the rate of porphyrin synthesis[29,41,42]. The earliest such treatment was carbohydrate loading[19], which was shown to have a suppressant effect on porphyrin synthesis. Hematin was subsequently introduced into clinical practice[6]. This is a reduced form of heme which is highly effective in inhibiting porphyrin synthesis via a negative-feedback inhibition of the rate-limiting enzyme of the heme synthetic pathway, ALA synthase. In many parts of the world, heme is now administered as heme arginate, which has greater stability and an improved side effect profile[50,58]. The formulation was not yet registered in the United States at the time of this writing.

Both ALA dehydratase deficiency porphyria and hereditary coproporphyria are rare, whereas AIP and VP are more commonly encountered. AIP is associated with a defect in the enzyme porphobilinogen deaminase. It may be diagnosed biochemically by demonstrating elevated urinary concentrations of ALA and PBG in the absence of the characteristic porphyrin elevation typical of the other hepatic porphyrias; by demonstration of a reduced PBG deaminase activity on kinetic assay; or by demonstration of a disease-specific mutation in the PBG deaminase gene[24]. VP is associated with a defect in the enzyme protoporphyrinogen oxidase, the penultimate enzyme in the heme synthetic pathway [29]. It may be diagnosed biochemically by demonstrating a characteristic plasma fluorescence peak at 625 nm; by demonstrating a characteristic pattern of porphyrin accumulation in the stool (principally protoporphyrin and coproporphyrin); or by demonstrating reduced activity in the protoporphyrinogen oxidase enzyme or a disease-specific mutation in the corresponding gene[27]. The prevalence of AIP and VP in Europe is estimated at 1.5 per 100,000 and 0.5 per 100,000, respectively[21]. In South Africa, VP is extraordinarily common, the result of a founder mutation introduced from the Netherlands in 1688, and is estimated to have a prevalence of 3 per 1000 in the white population[14].

Because the porphyrias are uncommon, few centers will accumulate a large experience with the management of the acute attack, and because of the small number of patients with these disorders, we cannot easily design randomized controlled trials of therapy. Indeed, the definitive case series date back to 1980[20,47,49], although 2 more recent papers have reported experience with the acute attack of AIP in Argentina[16] and Chile[45]. In this paper we report our experience with 112 sequential acute attacks in patients admitted to our hospital. Our experience is unusual in that we have treated substantial numbers of attacks associated with both AIP and VP. We have compared the 2 disorders and have identified some important differences. We include details on individual patients who have deviated from the usual course of the acute attack in terms of symptoms, course, or response to therapy. We believe that our experience will assist physicians called upon to treat patients with the acute attack of porphyria.

PATIENTS AND METHODS

All patients admitted to Groote Schuur Hospital, the principal teaching hospital of the University of Cape Town, Cape Town, South Africa, with a diagnosis of the acute attack over a 14-year period were admitted and treated under the direct supervision of 1 of us (RH). A diagnosis of the acute attack was based on the following criteria: proven porphyria, severe abdominal pain in the absence of significant abdominal tenderness, absence of any other cause for the symptoms, and demonstration of elevated urine ALA and PBG concentrations.

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In all cases AIP and VP were confirmed by precursor and porphyrin measurement in urine, stool, and plasma using standard diagnostic criteria[24,27]. The relative frequency of the acute attack was compared with the relative frequency with which new patients with AIP and VP were identified in our diagnostic laboratory, which serves as the reference laboratory for porphyria in South Africa, using the same criteria.

The following details were recorded for every admission: possible precipitating factors, presenting symptoms, physical findings, urine ALA and PBG, and serum sodium, potassium, urea, and creatinine concentrations. Patients were examined twice daily. All complications were documented. Pulse and blood pressure were monitored and recorded. Electrolyte estimations were repeated in patients who failed to improve rapidly or in whom initial values had been abnormal. A record was kept of all drugs administered.

It is frequently difficult to ascribe the acute attack to a specific precipitating event: even when an association is present it may not be causal. For the purposes of this study, we implicated a drug if the acute attack had arisen within 7 days of commencement of exposure to drugs known to be porphyrinogenic. We reported menstrual precipitation only where repeated, stereotypic acute attacks arose during the late luteal phase of the menstrual cycle. We reported an associated infection if the acute attack had arisen within 4 days of the first presentation with infection.

Changes in the severity of symptoms were assessed by 2 methods. First, the total dose of meperidine (pethidine) administered each day was recorded. In the few instances where other opiates such as morphine or fentanyl were administered, the dose was converted to the equivalent dose of meperidine thus: 100 μg fentanyl = 10 mg morphine = 100 mg meperidine. Second, a symptom severity score was applied for each day of the admission, based on a reading of the clinical notes for that particular day. This was made without reference to the meperidine requirements. Pain was scored as follows: 2 = severe pain, 1 = moderately severe pain or pain that had clearly lessened in intensity, 0 = substantially pain free.

Statistical Analysis

All data were entered into a Microsoft Access database. Data were analyzed using Microsoft Access (Microsoft Office XP, Microsoft, Seattle), and statistical comparisons were performed with Statistica (Statistica 6.1, StatSoft Inc, Tulsa) or MedCalc (MedCalc version 7.2.0.0, MedCalc Software, Mariakerke, Belgium) software. Where data were normally distributed (urine ALA and PBG, serum electrolytes, heart rate, and blood pressure), comparisons were made with the Student t-test; otherwise the Mann-Whitney U test was employed. 2×2 tables were analyzed by the Fisher exact test. Sequential data were analyzed by ANOVA, and posthoc analysis was performed with the Tukey honest significant difference. Attack-free survival following the first attack was determined by the Kaplan-Meier method, and differences in attack-free survival between AIP and VP were calculated by Gehan's Wilcoxon test.

RESULTS

Twenty-five patients were admitted and treated for the acute attack during the study period; 15 with AIP (13 women, 2 men) and 10 with VP (5 women, 5 men). During the same period we identified 687 new patients with a diagnosis of VP and 48 with AIP: these are patients referred for testing as consequence of photosensitivity, abdominal pain, or a family history of porphyria. The relative risk for the acute attack for patients with AIP versus VP is therefore 14.3 (confidence interval, 6.3–32.7, $p < 0.00001$). Many of the patients experienced more than 1 attack, and we thus report our experience with 112 attacks. This represents all acute attacks seen by us with the exception of 2 patients who demonstrated a severe course of near-continuous acute attacks without typical periods of remission between attacks. Inclusion of these data would strongly bias our results towards these 2 unusually severe patients. Data relating to the earlier part of the second patient's course, when the attacks were more typical and she was able to return home in periods of remission, have been included.

Our experience is summarized in Table 1. Additional patient information is given in Table 2. Approximately half the patients had repeated attacks. The female:male ratio was significantly higher in AIP than VP ($p < 0.0001$). The median age at the first attack for AIP (23.5 yr) is significantly lower than that for VP (30 yr) ($p < 0.0001$).

Although repeated attacks appeared more common in AIP than VP, there was no significant difference in the proportion of patients experiencing single rather than multiple attacks ($p = 0.70$), nor in the median number of attacks per patient ($p = 0.5$). However, Kaplan-Meier survival analysis shows a tendency for AIP patients to have an earlier relapse than those with VP (Figure 1), although the difference does not reach statistical significance ($p = 0.17$).

Precipitating Factors

Drugs known to be dangerous in porphyria were implicated in 16 of 25 attacks in VP (64%), and in 11 of 87 attacks in AIP (10%). Attacks clearly related to the menstrual cycle were documented in 35 of 69 attacks in women with AIP (51%) and may possibly have contributed to the 30/69 attacks for which no clear cause was evident (43.5%); in contrast, there was not a single episode of menstrually related porphyria in women with VP. AIP is therefore highly significantly associated with menstrual attacks, and drug exposure with VP ($p < 0.00001$).

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TABLE 1. Average Number, Median Number, and Range of Discrete Attacks Classified by Sex and Diagnosis (Data pertaining to the patient with continuous unremitting acute attacks are excluded)

	Variegate Porphyria			Acute Intermittent Porphyria			All
	Male	Female	Total	Male	Female	Total	Total
Patients (n)	5	5	10	2	12	14	24
Age at first attack (yr)	31 (24–36)	30 (27–34)	30 (24–36)	24 (22–27)	23.5 (20–36)	23.5 (20–36)	27 (20–36)
Attacks (n)	18	7	25	14	73	87	112
Patients experiencing single attack (n)	2	4	6	1	6	7	13
Patients experiencing recurrent attacks (n)	3	1	4	1	6	7	11
Median no. of attacks per patient (range)	2 (1–8)	1 (1–3)	1 (1–8)	7 (1–13)	2.5 (1–33)	2.5 (1–33)	1 (1–33)

Uncommon precipitants were pregnancy (1 attack) and infection (2 attacks).

The following drugs were implicated: alcohol and cannabis in combination (9 instances), combined oral contraceptive pill or progesterone (3 instances), erythromycin (1 instance), rifampicin or rifampicin/INH/pyrazinamide combination (2 instances), nonsteroidal antiinflammatory (type unknown, 1 instance), and phenytoin (1 instance). Particularly striking were the drugs of abuse, alcohol and cannabis, which may frequently be taken in combination. Indeed, these were responsible for most of the recurrent attacks in males.

Presenting Symptoms and Signs

The median duration of symptoms before admission for both AIP and VP was 2 days (range, 0–18 d). Clinical features are shown in Table 3. Tachycardia and hypertension were frequently not prominent at initial presentation, but developed as the attack progressed: levels were highest at a mean of 48 hours after admission. Both parameters settled completely with remission of the attack, although 3 patients with AIP, all of whom had repeated episodes, progressed subsequently to chronic hypertension requiring therapy; this was associated in each case with chronic renal impairment.

Unusual Presentations of the Acute Attack

Spontaneous Disappearance of Pain

Two patients, a 27-year-old woman and a 32-year-old man, neither of whom was previously known to have porphyria, were admitted to hospital with abdominal pain. Both were shown to have VP: elevated urine PBG levels confirmed that they were in an acute attack. Neither received heme arginate initially. After approximately 36 hours, the abdominal pain abruptly ceased. This was interpreted as evidence of spontaneous improvement, yet in both cases, disappearance of the pain was followed within approximately 6 hours by the rapid onset of a flaccid quadriparesis. The first patient required a prolonged period of assisted ventilation and prolonged recovery, whereas the second patient was less severely affected.

Presentation with Predominant Psychosis

A 25-year-old woman with a family history of VP presented to her physician with a sudden onset of confusion and abnormal behavior. She had no history of abdominal pain, and no objective neurologic abnormalities, and no cause for the confusion could be found. Electrolytes were normal. A brain computed tomography (CT) scan was unremarkable. Stool and plasma porphyrin analysis confirmed VP. She recovered spontaneously within 7 days. Mental state was entirely normal, although she had evidence of a residual small-fiber neuropathy accompanied by a mild glove-and-stocking sensory loss and hyperesthesia. In this single patient, the acute attack had a predominantly neuropsychiatric presentation, but our experience suggests that this is a rare manifestation.

Adrenergic crisis

Although hypertension and tachycardia were frequently encountered in our patients, the presentation in 1 patient known to have AIP was so extreme as to suggest a diagnosis of pheochromocytoma. She was admitted shortly after undergoing uterine evacuation for an incomplete abortion under general anesthesia. On admission, serum sodium was 130 mmol/L, systolic blood pressure 230 mm Hg, and diastolic blood pressure 130 mm Hg; pulse rate was 144/min. She appeared to have little or no abdominal pain, but was drowsy and confused. A brain CT scan showed multiple areas of attenuation in keeping with ischemia or infarction. The serum sodium level declined to 120 mmol/L despite adequate intravenous rehydration with normal saline, and she developed seizures. The hypertension and tachycardia failed to respond to high doses of combined alpha- and beta-adrenergic blocking agents. We considered the possibility of a coincidental pheochromocytoma. She was admitted to an intensive care unit, intubated and ventilated, and treated with intravenous magnesium sulfate, alpha- and beta- blockers,

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TABLE 2. Patient Characteristics

Patient	Diagnosis	Sex	Ethnicity	Age at First Attack (yr)	No. of Attacks	Additional Information
1	AIP	F	Mixed	22	10	Menstrual attacks. Gonadal suppressive therapy not indicated in view of relative infrequency of attacks.
2	AIP	F	Mixed	24	5	Menstrual attacks: has had subsequent further menstrual attacks treated elsewhere and attacks during mid-pregnancy. Gonadal suppressive therapy not indicated in view of relative infrequency of attacks.
3	AIP	M	Mixed	22	13	Numerous attacks related to recreational drug use, died following an untreated attack at another center.
4	AIP	M	Black	27	1	Single, uncomplicated attack.
5	AIP	F	Mixed	22	1	Severe attack with pronounced autonomic effects mimicking pheochromocytoma. Cerebral ischemia that reversed following heme arginate and magnesium sulfate.
6	AIP	F	Black	36	1	Single, uncomplicated attack.
7	AIP	F	Mixed	26	>100	Developed a pattern of continuous unremitting attacks poorly responsive to heme arginate and tin protoporphyrin. No response to gonadal suppressive therapy. Considered for liver transplantation but condition was too poor to attempt this. Eventually died in an unremitting attack. Data on individual attacks not included in this series.
8	AIP	F	Mixed	20	1	Developed quadriparesis on first admission to another hospital, before diagnosis. Required ventilation for 8 wk. Has had several subsequent attacks treated in another center, which have responded well to heme arginate.
9	AIP	F	Mixed	23	33	Numerous recurrent attacks. No response to gonadal suppressive therapy. Received numerous courses of heme arginate and tin protoporphyrin. Eventually died.
10	AIP	F	Black	29	1	Menstrual attack: has subsequently developed a problem of recurrent menstrual attacks treated in another center but has not responded to gonadal suppressive therapy.
11	AIP	F	Black	25	4	Prolonged course complicated by staphylococcal septicemia and seizures during first admission. Subsequent attacks have responded well to heme arginate.
12	AIP	F	Mixed	21	6	Menstrual attacks. Gonadal suppressive therapy not indicated in view of relative infrequency of attacks.
13	AIP	F	White	28	8	Menstrual attacks with eventual complete response to gonadal suppressive therapy.
14	AIP	F	White	34	1	Single, uncomplicated attack.
15	AIP	F	Mixed	20	1	Single, uncomplicated attack.
16	VP	M	White	24	8	Repeated attacks related to recreational drug use: no further attacks following behavior modification.
17	VP	F	White	34	1	Single, uncomplicated attack.
18	VP	M	White	31	6	Repeated attacks related to recreational drug use: no further attacks following behavior modification.
19	VP	F	Black	27	1	Single, uncomplicated attack.
20	VP	F	Mixed	27	1	Initial pain appeared to settle but was followed by quadriparesis. Ventilated for 12 weeks: eventual recovery in 12 months.
21	VP	M	White	27	1	Single, uncomplicated attack.
22	VP	F	Mixed	30	1	Single, uncomplicated attack.
23	VP	F	Mixed	30	3	One attack during pregnancy.
24	VP	M	White	32	2	Uncomplicated attacks.
25	VP	M	Mixed	36	1	Abrupt cessation of pain was followed by the onset of moderate neuropathy with full recovery.

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and heme arginate. This regimen was highly effective in controlling both the adrenergic features and the seizures. Recovery was rapid and she was discharged, neurologically intact and completely asymptomatic, after 9 days. A repeat CT scan was completely normal, and she remained well 4 years later.

Biochemical and Electrolyte Disturbances

ALA and PBG values were significantly higher in AIP than in VP. Mean values were, for AIP and VP respectively, as follows: for ALA, 386.1 (SD 226.5) and 189.1 (SD 115.7) ($p = 0.02$); for PBG, 544.9 (SD 242.0) and 168.9 (SD 122.3) ($p = 0.02$). Hyponatremia was common during the attack. A sodium value below 135 mmol/L was recorded in 31.3% of cases at some stage of the admission. Mean sodium levels did not differ between AIP and VP. Severe hyponatremia (Na < 125 mmol/L) was noted in 5 admissions: 3 of these admissions were complicated by seizures, and 4 were complicated by neuropathy. The lowest sodium values noted were 100 and 104 mmol/L. In all 5 cases of severe hyponatremia, urine sodium concentrations were found to be markedly increased. The serum sodium failed to improve in response to fluid restriction alone, and rose only after the infusion of hypertonic saline. In 2 instances, urinary sodium loss was accompanied by marked kaliuresis and calciuresis, suggesting a primary tubular defect.

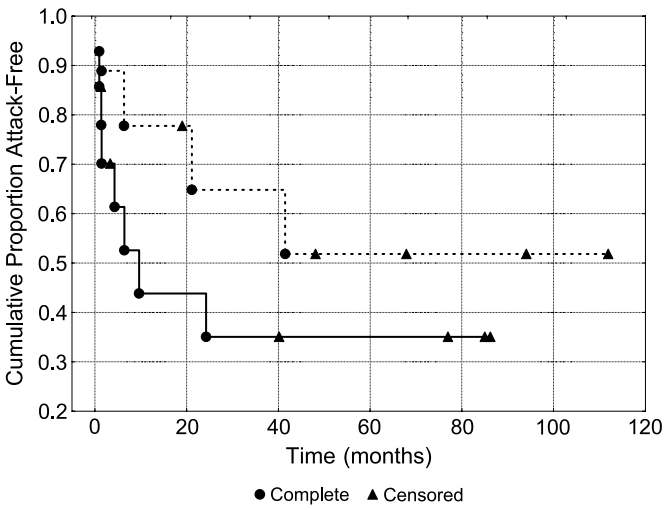

FIGURE 1. Kaplan-Meier survival curve, dated from the time of discharge after the first admission for an acute attack. The horizontal axis represents the interval in months from the date of discharge after the first attack before admission for a second and subsequent attack. Patients with acute intermittent porphyria are represented by the solid line, and patients with variegate porphyria, by the dashed line. The difference in the 2 curves is not significant ($p = 0.17$).

TABLE 3. Presenting Symptoms and Signs in 112 Acute Attacks

	No. (%)
Pain	109 (97.3)
Nausea and vomiting	88 (78.6)
Hypertension (systolic bp > 130)	83 (74.1)
Tachycardia (heart rate > 100)	42 (37.5)
Hyponatremia (sodium < 135 mmol/L)	35 (31.3)
Constipation	30 (26.8)
Psychosis	1 (0.9)

The mean urea and creatinine concentrations on admission were 8.0 (SD 2.9) and 114.6 (29.8), respectively; urea levels were elevated in 52.7% and creatinine values, in 46.4% at some stage of the admission. This may represent, in part, dehydration, since values typically improved rapidly following admission and intravenous fluid administration. No consistent changes in potassium, calcium, or magnesium levels were noted.

Therapy

Opiates were required in 98% of cases; the total meperidine dose required varied from 50 mg to more than 10,000 mg per admission, with a median dose of 1200 mg per admission. All patients received intravenous normal saline-dextrose for at least 48 hours following admission. Beta-blockers were prescribed in 35% of admissions (AIP, 43%; VP, 8%; $p = 0.002$). Antiemetics were administered in 54% of admissions (AIP, 51%; VP, 68%; $p = 0.35$).

Heme arginate was used in 75 admissions (67%). A standard dose of 125 mg, irrespective of body mass, was used: this is an empirically chosen dose, convenient in that it represents a 5-mL aliquot from a 10-mL ampoule, which we have found effective in practise. The number of doses required to abort the attack varied: 5 doses: 5 (7%), 4 doses: 40 (53%), 3 doses: 23 (31%), 2 doses: 8 (11%). Four attacks, all in patients with AIP, required a second course of heme arginate following an inadequate response to the first course. Infusion of heme arginate was complicated by phlebitis at the site of infusion in 14 of 79 instances, all occurring early in this series when heme arginate was administered in saline. Heme arginate was later administered in suspension with 20% human serum albumin, and no further cases of phlebitis were observed.

The median time from admission to commencement of heme arginate was 24 hours (range, 2 h to 12 d). In many instances, initiation of heme therapy was delayed, either to assess whether symptoms would settle on conservative measures alone, or because of delays in obtaining the medication from suppliers. This gave rise to an unplanned experiment that has allowed us to make some assessment of

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the efficacy of heme arginate. Figures 2 and 3 show the symptom severity score and the meperidine requirement by treatment day, ranging from Day 6 pretreatment (Treatment Day −6) to Day 8 after initiation of heme therapy (Treatment Day +8). We note that heme therapy had an early beneficial effect on both the severity of the attack and the requirement for meperidine, both of which decreased promptly once heme arginate was administered. The decline in both severity score and meperidine requirement is highly significant ($p < 0.0001$). Posthoc analysis recorded a significant deterioration in symptoms in the days preceding initiation of therapy as reflected by analgesic requirement, followed by a highly significant improvement after initiation of treatment with a lag phase of 24–48 hours.

Course and Complications

The median time from admission to resolution of symptoms was 6 days (range, 1–19 d). The median length of hospital stay was 7 days (range, 1–56 d). Three patients remained longer than 30 days: 1 developed profound quadriparesis requiring ventilation; a second developed moderate paralysis complicated by staphylococcal septicemia requiring prolonged intravenous therapy; and a third needed treatment of unrelated medical problems. This excludes the 2 patients described above who eventually became hospital-bound.

Eleven of the 24 patients, 8 with AIP (57%) and 3 with VP (30%), demonstrated neuropathy. The neuropathy developed before admission to our hospital, usually under the care of another hospital, in all subjects except 2. In most cases the neuropathy had therefore developed before porphyria had been diagnosed, and in only 2 of 112 admissions did neuropathy supervene during the course of admission to our hospital. Neither patient had received heme arginate.

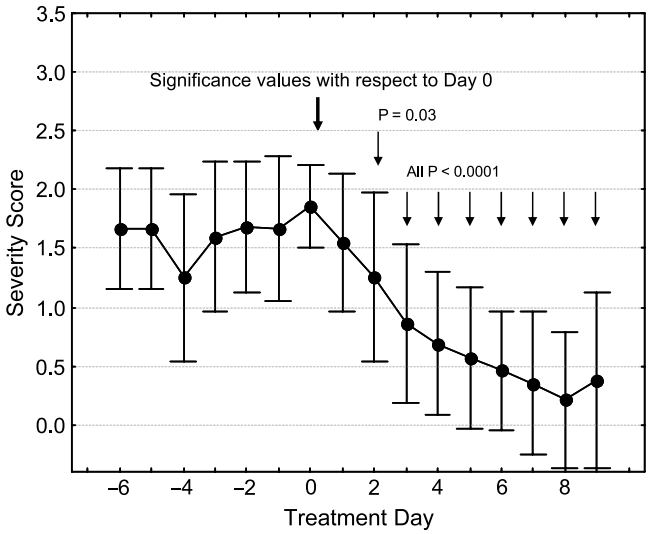

FIGURE 2. Effect of heme therapy on symptom severity score. Treatment was commenced on Day 0. Symptoms were maximal on Day 0. Values on Days 2–9 are significantly lower as shown. The arrows refer to the respective p values with respect to Day 0 as returned by posthoc analysis.

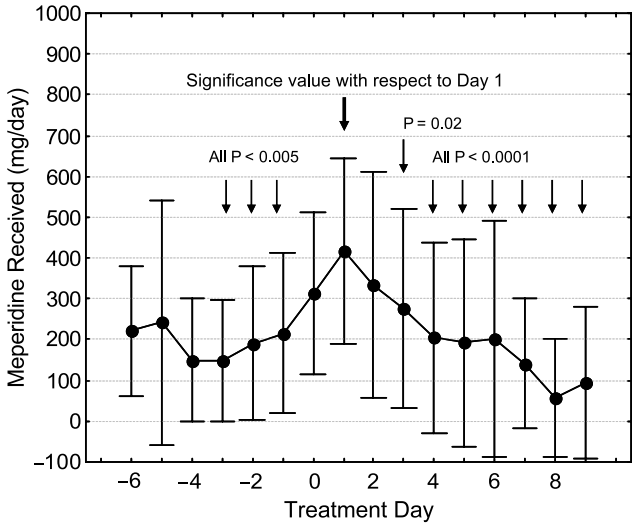

FIGURE 3. Effect of heme therapy on meperidine requirement. Treatment was commenced on Day 0. Analgesic requirement was maximal on the day following the first dose of heme. Values on Days 3–9 are significantly lower as shown. Values on Days −3, −2, and −1 are also significantly lower, indicating an increasing severity of symptoms before heme arginate was commenced. The arrows refer to the respective p values with respect to Day 1 as returned by posthoc analysis.

Neuropathy was in most cases limited to mild weakness of the extremities manifesting as wrist-drop and foot-drop. We encountered 3 patients with quadriparesis, 2 of whom developed this complication during their initial attack elsewhere, and who were diagnosed as having porphyria only after the development of quadriparesis. The third became quadriparetic while under our care. All 3 improved with physiotherapy and orthopedic supports and eventually regained the ability to walk. The frequency of neuropathy and seizures did not differ between patients with AIP and those with VP.

We noticed an interesting phenomenon among our patients with preexisting neuropathy and recurrent attacks. Shortly after the start of a new attack, a rapid diminution in distal motor power was frequently demonstrable. When heme arginate was administered, there was a prompt return to the status quo ante.

Three patients with neuropathy had a striking clinical picture apparently resulting from a small-fiber neuropathy. They reported severe pain and discomfort in response to trivial stimuli over the whole body, such as intense discomfort resulting from tight underwear or even a fold in the bed sheets. In 1 of these patients the complaints were

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wrongly ascribed to repeated acute attacks, and she received repeated doses of meperidine and heme arginate inappropriately. With adequate explanation, reassurance, and simple analgesics, she required no further opiates, and her condition improved over several months. One patient had striking peripheral features of autonomic nerve dysfunction: light stroking of the dorsal surface of the forearm would bring about dramatic piloerection and profuse sweating in that arm. We conclude that in some patients, acute attacks may result in a complex regional pain syndrome that should not be mistaken for evidence of ongoing acute attacks.

Seizures were encountered in 6 attacks (5 AIP, 1 VP). Three of these were associated with hyponatremia. One was associated with a prolonged acute attack complicated by systemic staphylococcal septicemia. Two other episodes, in a single patient with severe AIP, were related to the use of large doses of meperidine; 1975 mg total dose in 1 attack, and 10,650 mg total dose in the second, and were preceded for several hours by myoclonic jerks. Both the seizures and the myoclonus were easily abolished by clonazepam.

Three patients died, all with AIP. Two required permanent admission for unrelenting symptoms of the acute attack. Prophylactic administration of heme arginate in the interval between attacks, parenteral GnRH agonist therapy, and a subcutaneous implant of testosterone[53] were ineffective. Both patients demonstrated a pattern of severe, unremitting attacks such that courses of heme arginate were required at intervals of 7–10 days; with time, a progressively poorer response to heme arginate was observed. We developed a protocol whereby the heme oxygenase inhibitor tin protoporphyrin in a dose of 25 μg was injected intravenously for 3 daily doses at the start of every second course of heme arginate. Tin protoporphyrin was given simultaneously with heme arginate and was well tolerated other than for photosensitivity, which was not a problem provided the patients avoided direct sunlight. This appeared to augment the symptomatic relief afforded by heme arginate, but in both patients the course was one of inexorable decline and finally death. The third patient, a 22-year-old man admitted on 13 occasions over 25 months with acute attacks, most of which appeared to follow alcohol and cannabis abuse, subsequently died following an acute attack in another city; he had not received heme arginate during that admission, although this would appear to have been indicated.

Contrasting Severity of AIP and VP

Some markers of severity of the acute attack are summarized in Table 4. Blood pressure, pulse rate, and heme arginate requirement were significantly higher in patients with AIP than in patients with VP. No significant difference could be shown, however, in the length of admission, the time to resolution, or the meperidine requirement.

DISCUSSION

Incidence and Severity of Acute Attacks

Our study clearly suggests an increased risk of acute attacks in patients with AIP compared with those with VP. Although VP was diagnosed nearly 15 times more often than AIP in our population, the ratio of patients with VP with acute attacks to those with AIP was 1:1.4, indicating a 14-fold increase in risk. Furthermore, the patient profile is dissimilar in that our patients with AIP were predominantly young women, whereas patients with VP were, on average, 7 years older, with an equal sex-ratio. Thus, while we have confirmed the greater susceptibility of women to acute attacks reported for AIP elsewhere[16,45], this would not appear to be true of VP. Furthermore, the small number of patients we observed with acute attacks of VP suggests that the acute attack itself is currently a rare manifestation of VP. This conclusion is supported by our own work on the clinical expression of VP, where we found that, in contrast to the 40% of adults with VP who exhibit skin disease, acute symptoms were uncommon[28].

Recurrent attacks are a significant feature in some patients. Kauppinen and Mustajoki[33] have emphasized that recurrent acute attacks are less common where porphyria is

TABLE 4. Relative Severity of the Acute Attack: Parameters Observed in Attacks Associated With AIP and VP

	Acute Intermittent Porphyria			Variegate Porphyria			
	Mean	**SD**	**n**	**Mean**	**SD**	**n**	**p**
Maximal systolic bp (torr)	156.5	22.00	83	145.7	20.63	23	0.036
Maximal diastolic bp (torr)	98.2	16.09	83	86.7	14.74	23	0.002
Maximal pulse rate	93.3	14.18	83	85.2	12.75	23	0.015
Doses of heme arginate	3.9	1.14	69	2.7	0.90	11	0.002
Total meperidine requirement (mg)	1746	1620	83	1278	1053	20	0.22
Length of admission (days)	8.3	6.8	87	8.0	9.4	25	0.89
Interval before improvement (days)	6.3	3.3	85	5.4	3.7	25	0.21

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diagnosed in asymptomatic patients, in contrast with those diagnosed during an established attack. In a series reported in 1999[16], 81% of symptomatic patients with AIP developed recurrent attacks. Although we observed a lower proportion of recurrent attacks in patients with VP than in patients with AIP, the difference was not significant. This may relate to our observation that most recurrent attacks in VP were associated with drug ingestion and were therefore preventable, whereas the same association was not observed in AIP.

Precipitating Factors

In patients with VP, acute attacks were strongly associated with medication, whereas acute attacks in patients with AIP were more likely to be associated with the menstrual cycle or with an unproven etiology. Despite the high prevalence of porphyria in our population, precipitation of the acute attack by drugs appears to be rare. To our surprise, the drugs most commonly implicated in precipitating the acute attack were the recreational drugs alcohol and cannabis. Such exposure was frequently associated with recurrent episodes. In 2 subjects in whom we noted this association, all further attacks ceased once they desisted from exposure to these agents. The third subject subsequently died following an attack in another city. The effect of cannabis on heme synthesis has not been reported, whereas several authors have discussed the effects of alcohol on porphyrin metabolism[38,44,52]. Although alcohol in moderation is probably safe, there is evidence that alcoholic binges may be associated with acute attacks[33,59].

A striking feature is the number of women with AIP in whom attacks appear to have been menstrually related. Indeed, the number may be higher than we report, since it is possible that hormonal effects may have contributed to some of the attacks in women for which no definite cause could be ascribed. Our definition of a menstrually related attack was restrictive in that we described as menstrually related only attacks that were recurrent, with a clear onset of symptoms in the late-luteal phase of the cycle. Yet we were unable to link a single attack in women with VP with the menstrual cycle, suggesting that this association is a very uncommon feature of VP. We treated 3 patients with AIP and apparent menstrually induced exacerbations with gonadotrophin-releasing hormone agonists[1]. Only 1 responded with a complete remission, whereas the other 2 patients continued to experience monthly attacks despite amenorrhea and documented hormonal suppression. Such an unpredictable response has been reported by others[26].

Certain factors commonly stated to aggravate porphyria were notably absent in our series. In the Argentinean series[16], 20% of attacks were ascribed to infections and 30% to starvation. Neither of these played a significant role in our series. We recorded a single attack associated with pregnancy. Subsequent to the termination of the present study, 1 of our patients, who had revealed a pattern of menstrual attacks (Patient 2) became pregnant and experienced acute attacks in the late second trimester; we will report our experience with her management in the future. With this exception, we are unaware of any attacks in pregnancy occurring in South Africa during the past 15 years. It is clear that early reports, which suggested that approximately 50% of women with the acute porphyrias would develop a complicating acute attack in pregnancy[9,30], overstated the risk. A 1992 report from Finland[33] reported a rate of 8% in patients with porphyria followed prospectively, whereas our observed rate is very low indeed.

Clinical Features

The cardinal features of the acute attack have not changed since those described in previous series, with abdominal pain being nearly universal[16,20,47]. Although pain is the most common presenting feature, clinicians should be aware that exceptional patients will present atypically. Thus we have learned that the sudden cessation of abdominal pain may not indicate improvement, but may provide warning of incipient quadriparesis. Pain was not prominent in 2 of our patients, which led us to withhold heme arginate with unfortunate consequences. Pain was not noted at all in a third, who presented with psychosis alone. Presentation without pain is therefore highly atypical and may lead to a delay in starting therapy[2].

Hypertension is common during the attack. Antihypertensive therapy with beta-blockers was used in approximately half the admissions, overwhelmingly in patients with AIP. However, we have learned that in most cases, both blood pressure and pulse rate will subside spontaneously as the attack improves, and there is little need for specific antihypertensive therapy in the early phase of the attack. In only 1 instance was the hypertension sufficiently severe to warrant treatment in its own right. An association between AIP, chronic hypertension, and chronic renal failure, possibly related to protracted vasospasm, has been shown[3]. Three of our patients with AIP, all of whom have had repeated episodes, appear to illustrate this.

We identified 1 attack in which the presentation was predominantly of an acute psychosis without the classic features of the acute attack. Similar cases have been reported[56], but this must be regarded as an exceptional and extremely rare mode of presentation, which probably has been overstated in general reviews of porphyria. It is notable, too, that the psychosis regressed completely with recovery from the acute attack.

Hyponatremia is a common manifestation of the acute attack that deserves more attention than it is usually given. About one-third of the attacks in the current series were accompanied by hyponatremia; Morales Ortega et al[45]

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encountered hyponatremia in 53% of the acute attacks they described. Severe hyponatremia is dangerous and is a marker of a particularly severe attack. Of 5 admissions marked by severe hyponatremia, 4 were complicated by neuropathy, whereas the fifth demonstrated a severe course marked by profound adrenergic activity. Hyponatremia may be due in part to dehydration, although other factors may be operative, as suggested by Eales et al[20]. In the 5 patients we describe with severe hyponatremia, the biochemical findings were more in keeping with a primary tubular defect with salt-wasting, as previously suggested[53], than with the syndrome of inappropriate ADH[62]. We therefore recommend that severe hyponatremia be treated with hypertonic saline from the beginning, rather than fluid restriction. Hyponatremia must be corrected slowly and cautiously since rapid correction of hyponatremia in patients with AIP has resulted in central pontine myelinolysis and cortical laminar necrosis[55]. Furthermore, intravenous hypotonic dextrose solutions should be avoided in the acute attack in view of the risk of aggravating hyponatremia. We recommend the use of intravenous normal saline. Carbohydrates may be given orally if tolerated, or as a saline-dextrose solution. Our experience has shown that heme arginate is so effective in terminating the attack that additional carbohydrate loading is not necessary. Serum sodium levels should be checked frequently in patients with more severe forms of the acute attack.

Several lines of evidence suggest that the average severity of the acute attack in the current series was worse in patients with AIP than in those with VP. The mean systolic and diastolic blood pressures, pulse rate, and the proportion of patients requiring heme arginate were all significantly higher in AIP than in VP. We noted a trend to higher analgesic requirements, length of hospital stay, and duration of symptoms, although these did not reach statistical significance. However, the overall incidence of significant complications, such as seizures and neuropathy, is similar, and it is clear that a fully developed acute attack poses the same risk to the patient with VP as it does to the patient with AIP.

Complications

The incidence of severe complications of the attack is markedly lower in the current series than in those described by Eales et al[20] and Mustajoki[47]. Neuropathy was a rare occurrence in patients primarily admitted and managed by us, and it is notable that in the 2 patients seen by us who developed severe neuropathy, heme arginate had not been given. In both instances this was because we had been misled by the absence of ongoing pain into believing that the attack had settled. In most instances, neuropathy was mild and was limited to wrist- and foot-drop. This confirms the trend toward an increasingly favorable outcome for the acute attack noted in more recent reports[5,32,33]. During this time, several factors have changed that may have led to a better outcome. There is a greater awareness and understanding of porphyria among both doctors and patients. Diagnostic tests for porphyria and for the acute attack have become more reliable and accessible. Patients understand their illness better and are perhaps more likely to present to hospital early. Management protocols for the acute crisis have been refined, and specific therapy, heme arginate, is now available.

Our experience in patients with preexisting neuropathy and recurrent attacks suggests that these patients operate just below a threshold of clinically evident nerve damage: any subsequent acute attack results in immediate deterioration in nerve function, which is reversible provided that heme arginate is infused promptly. In light of this observation, it is our standard practise to ensure that every patient with a history of previous neuropathy receives heme arginate without delay, whereas other patients are allowed 24 hours to determine whether spontaneous remission will occur.

A 1996 study[10] reported that 10 of 268 (3.7%) Swedish patients with porphyria had experienced seizures; in 6 patients, these were associated with an acute attack of AIP, and 3 patients had been severely hyponatremic. Seizures were rare in our patients. In 3 cases, seizures accompanied severe hyponatremia, an association noted previously[18,62]. In 2 further instances, we ascribed the seizures to the use of high doses of meperidine. Meperidine is metabolized to normeperidine, a metabolite that is epileptogenic[40], and meperidine-related seizures have been reported in a patient with hereditary coproporphyria[15]. Seizures relating to meperidine should be suspected in any patient receiving high doses in whom myoclonic jerks are noted. We have found clonazepam to be a safe and effective agent, for both the prevention and the termination of seizures. We conclude that in most instances, seizures during the acute attack are associated with an identifiable precipitating cause.

We encountered 1 patient who manifested a severe adrenergic crisis. Acute hypertension mimicking pheochromocytoma as the main presenting feature of AIP has been reported[18,54]. In our patient, intravenous magnesium sulfate[57] was highly effective in controlling the autonomic features, and we now recommend its use, along with heme arginate and beta-blockade, in any patient in whom adrenergic or cerebral features dominate the presentation. This patient demonstrated reversible neurologic deficits and neuroradiologic defects, presumably related to cerebral vasospasm and ischemia. Both reversible and irreversible findings have been described in case reports[4,11,34,36,37,63].

Mortality

Of the patients described by De Siervi et al[16] and Morales Ortega et al[45], approximately 15% died during an

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acute attack. Most of these deaths resulted from respiratory failure, usually during the first attack, implying that the diagnosis was made too late for effective suppressive therapy. Certainly our results support the belief that the prognosis of the acute attack has improved greatly over the past 20 years[31,33]. None of our patients died during a ''routine'' acute attack, but rather after a protracted and difficult course of repeated acute attacks, in 1 instance totaling more than 100 consecutive attacks.

Treatment

Heme Arginate

The beneficial effect of exogenous heme in porphyria is mediated via a repression of ALAS by a process of negative feedback. Since the first reported use of hematin in acute porphyria[6], numerous reports have attested to its efficacy in aborting the acute attack. Heme arginate was introduced subsequently, and has greater stability and lower incidence of complications[49]. Heme arginate is effective in rapidly reducing ALA and PBG levels in the acute attack[21,29,35]; this biochemical improvement is typically followed within 48 hours by evidence of clinical resolution. Neuropathy, once established, is not necessarily reversed by the administration of heme[48,51], which should therefore be administered before neuropathy develops. The only controlled trial of heme arginate[25] was unable to show a significant difference in outcome, although it suggested an improvement in symptoms following treatment. Our experience, reflected in Figures 2 and 3, supports the hypothesis that heme arginate is responsible for a rapid and reliable improvement in symptoms. Furthermore, none of our patients developed serious complications such as hyponatremia, neuropathy, or seizures once heme arginate had been initiated; we have no doubt that it represents highly effective therapy for the acute attack.

Typically the effect is short lived, and ALA, PBG, and porphyrin levels begin rising within 48 hours of the last of a four-day course of injections[25,60]. Thus the role of heme arginate is to abort a crisis rather than as a prophylactic measure in patients with porphyria. Since heme is known to induce the enzyme heme oxygenase and thus to mediate its own catabolism, tolerance would appear a reasonable assumption. In 2 of our patients, prolonged, repeated use of heme arginate led to an apparent decrease in efficacy, suggestive of tolerance. This led us to combine the heme oxygenase inhibitor tin protoporphyrin with the heme arginate, with some apparent benefit.

Despite the suggestion that heme arginate infusion is associated with a lower rate of thrombophlebitis than hematin[50,58,61], we frequently recorded severe thrombophlebitis at the infusion site when heme arginate was given in saline, whereas administration in 20% human serum albumin appeared to prevent this. We have not encountered renal failure[17], coagulopathy[46], or anaphylaxis[13] in association with heme arginate.

Heme arginate is expensive. The current price in the United Kingdom for 4 250-mL ampoules is [£]4500 (approximately 8200 United States dollars)[8]. We have been able to reduce the cost to our service by using a standard dose of 125 mg per patient irrespective of body weight. Nor do we consider it necessary to treat every acute attack with heme arginate. In our series, approximately 30% of attacks responded to conservative measures alone. We have refined our indications for initiation of heme arginate therapy as follows. Treatment is begun immediately in any patient with severe symptoms who shows evidence of incipient complications such as neuropathy, hyponatremia, or seizures; in patients with recurrent attacks who have required heme arginate previously; and in any patient with evidence of residual neuropathy from a previous attack. In other patients, particularly those with VP, we treat expectantly for the first 24 hours. If there is no improvement, we begin heme arginate after 24 hours; since our experience has suggested that rapid spontaneous resolution is unlikely in those who fail to improve within this period.

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