



A review of the clinical presentation, natural history and inheritance of variegate porphyria: its implausibility as the source of the 'Royal Malady'

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ABSTRACT

It has been suggested that King George III of Great Britain suffered from the haem biosynthetic disorder, variegate porphyria. This diagnosis is pervasive throughout the scientific and popular literature, and is often referred to as the 'Royal Malady.' The authors believe it inappropriate to view the case for porphyria purely in terms of symptoms, as has generally been the case in his presumptive acute porphyria diagnosis. Accordingly, this review provides a current description of the natural history and clinical presentation of the porphyrias, against which we measure the case for porphyria in George III and his relatives. The authors have critically assessed the prevalence of porphyria in a population, the expected patterns and frequency of inheritance, its penetrance and its expected natural history in affected individuals, and conclude that neither George nor his relatives had porphyria, based on four principal reasons. First, the rarity of the disease mandates a very low prior probability, and therefore implies a vanishingly low positive predictive value for any diagnostic indicator of low specificity, such as a historical reading of the symptoms. Second, penetrance of this autosomal dominant disorder is approximately 40%, and one may expect to have identified characteristic clinical features of porphyria in a large number of descendants without difficulty. Third, the symptoms of both George III and his relatives are highly atypical for porphyria and are more appropriately explained by other much commoner conditions. Finally, the natural history of the illnesses reported in this family is as atypical for variegate porphyria as are their symptoms.

became the dominant power in Europe with the defeat of Napoleon. George III's reign was punctuated by several prolonged episodes of ill health, documented in detail by his attending physicians. From 1811, his son ruled in his place as Regent in view of George's increasing mental incapacity. The poet Shelley captured the effect of George III's illness on the King and on the nation he ruled in the evocative lines which head this review.

In 1966, Ida Macalpine and Richard Hunter put forward a confident claim that George's symptoms were due to acute intermittent porphyria (AIP),¹ subsequently amending their diagnosis to variegate porphyria (VP).² This diagnosis has persisted in the scientific literature and has stimulated a number of speculative articles right until the present.³ In addition, George III's presumptive porphyria was popularised in Alan Bennett's successful stage play *The Madness of George III*, which premiered in 1991, and was subsequently adapted for the screenplay of a 1994 film directed by Nicholas Hytner, *The Madness of King George*, a popular science work, *Purple Secret—Genes, 'Madness' and the Royal Houses of Europe*⁴ and a number of television documentaries. For many people, the symptoms portrayed in these popular works have come to define the clinical presentation of porphyria. That a number of authorities have questioned^{5–8} and indeed rejected the hypothesis is not generally appreciated.^{9–14}

It is not our intention to repeat these arguments. In this review, we will provide an authoritative description of the natural history and clinical presentation of the porphyrias as currently understood, a description against which the case for porphyria in George III and his relatives must be measured.

PORPHYRIAS

The porphyrias are a group of metabolic disorders which arise from enzymatic defects in the haem biosynthetic pathway. Defects in any of these eight enzymes may result in the accumulation of porphyrins and their precursors in a pattern specific to the enzyme involved, and this in turn may result in clinical manifestations.¹⁵

VP results from mutations in the *PPOX* gene, which codes for protoporphyrinogen oxidase, the penultimate enzyme on the haem biosynthetic pathway. The molecular sequence for human *PPOX* was first described in 1995,¹⁶ and molecular techniques for the diagnosis of VP had been available since 1996.^{17–19} Identification of the specific *PPOX* mutation present in individual patients with VP now forms part of standard diagnostic practice.

An old, mad, blind, despised, and dying king,
Princes, the dregs of their dull race, who flow
Through public scorn, mud from a muddy spring,
Rulers who neither see, nor feel, nor know,
But leech-like to their fainting country cling,
Till they drop, blind in blood, without a blow...
Percy Bysshe Shelley: Sonnet: England in 1819.

INTRODUCTION

King George III of Great Britain reigned from 1760 until his death in 1820. During his reign, Great Britain and Ireland amalgamated to form the United Kingdom of Great Britain and Ireland. Britain lost her American colonies with the American War of Independence but eventually

Given the very high sensitivity and specificity of a molecular diagnosis for VP, it is now possible to prove or disprove the presence of VP with near-absolute certainty. Thus, we are able to delineate the clinical presentation of VP accurately.

PREVALENCE AND PENETRANCE OF VP AND THE RELIABILITY OF A DIAGNOSIS BASED ON CLINICAL SYMPTOMS

The gene prevalence of VP in most European countries, including the UK, is now estimated at 7 per million.¹⁵ The prevalence in South Africa is much higher at approximately 1200 per million of the European immigrant population,²⁰ owing to a founder effect resulting from the introduction of the R59W mutation into the Dutch settler community of Cape Town in 1688.¹⁷ The clinical penetrance of VP among adults is approximately 40%: thus, 40% of adults carrying a PPOX mutation express clinical disease, while the remainder are asymptomatic.^{21–23} This contrasts with earlier studies suggesting a rate of symptomatic disease of 70–80%.^{24 25} In large part, this lower rate is likely due to the advent of DNA testing, which has allowed identification of the 60% of carriers who are clinically silent unexpressed carriers.

The case for VP in the British Royal House rests wholly on the symptoms reported in this family. Thus, the presence or absence of symptoms constitutes the diagnostic test on which the diagnosis of VP in George III and his relatives is based. As with all diagnostic tests, Bayes' rule should be applied in order to estimate the accuracy of the resultant diagnosis. Given the prevalence, sensitivity and specificity of any test, its predictive values can be calculated.

The prevalence of VP in Europe is known. The sensitivity of clinical symptoms in predicting a diagnosis of VP has an absolute upper limit of 0.4, corresponding to a penetrance of 40%. The specificity of clinical symptoms for the diagnosis of VP is unknown. Skin problems and abdominal pain are common in the population, and the contemporary reports of the symptoms of George III and his relatives lack the detail which might tighten up their specificity for VP. For the purposes of our calculation, we have set the specificity of clinical symptoms for VP at 50%, suggesting that 50% of all people with the symptoms described by Macalpine and Hunter do indeed have VP. In practice, specificity will be far lower than this optimistic figure.

Table 1 shows the application of Bayes' rule to this problem, using the observed prevalence of VP in Europe of 7×10^{-6} , a sensitivity of clinical symptoms for a diagnosis of VP of 0.4 and a specificity of 0.5. The calculated probability that clinical symptoms will correctly identify porphyria is vanishingly small; indeed the probability of a false positive exceeds 99.999%. This is an expected consequence of a diagnostic test of imperfect specificity applied for a disease with a low prevalence. On statistical grounds alone, the case for the correct diagnosis of VP in the Royal Family is extraordinarily weak.

PROBLEM OF MISSING CASES

Approximately 200 years have elapsed since the death of George III, and we estimate that his living relatives now number nearly

900 individuals. (George III had 15 children, two died in infancy, nine married and had legitimate offspring. George himself had eight siblings of whom three had legitimate offspring.²⁶) Given a 50% transmission rate for this autosomal dominant disorder and the 40% clinical penetrance alluded to earlier, we would therefore expect approximately 450 currently living relatives to carry the mutation and 180 to manifest the illness clinically. Yet, to our knowledge, not one of the many patients identified in recent years in Europe, in whom VP has been reliably confirmed by genetic testing, has claimed kinship with the House of Hanover. Indeed, MacAlpine and Hunter claimed to have identified symptoms suggestive of VP in fewer than 10 of George III's relatives spanning numerous generations over several 100 years. If the diagnosis of VP in the Royal house is to be sustained, a convincing explanation for the large discrepancy between the expected number of affected family members and the handful for whom a claim of VP has been made is required.

By contrast, a large pedigree of patients with VP has risen in South Africa in the 320 years which followed the introduction of the R59W mutation.⁶ Given the observed gene prevalence of the R59W mutation in the South African population of European extraction, we estimate that the original founder couple now have more than 6000 descendants carrying the mutant gene alive today. Indeed, we have no difficulty in identifying clinically expressed VP in large numbers of their descendants, and this in the descendants of a modest farming couple, lacking the public prominence of a king and his family.

Is it possible that large numbers of affected relatives indeed exist but have not been recognised? Currently the proportion of expressed relatives who present with acute attacks runs at roughly 10%,^{21 23} whereas previously it was higher.^{23–25} Authoritative series published 30 years ago suggested that between 60% and 80% of all attacks in that era may have resulted in paralysis, with an extraordinarily high incidence of respiratory failure and death of between 27% and 80%.^{25 27} Even in the South African population of the mid-20th century, families were aware of a complex of symptoms with an excess mortality among their relatives, even though the illness had yet to be defined and named. There is nothing in the historical record to suggest a morbidity and mortality of this magnitude in the Royal Houses of Europe.

The incidence of acute attacks may have been lower before the era of modern pharmacotherapy. Eales suggested that the introduction of modern medicines, particularly barbiturates, had led to an increased frequency of acute and often fatal attacks in the 1920s in families in whom symptoms had previously been confined to the skin.²⁸ Skin disease is nearly always present in clinically expressed patients.^{21 29} Certainly, in our most recent series, we have not seen patients with VP without skin symptoms.^{21 30} Even in Europe, at least 80% of clinically expressed patients with VP will manifest typical skin disease despite the lower intensity of solar irradiation in comparison with South Africa.²²

We can therefore expect that 50% of all George's descendants should have inherited his putative VP-associated mutation, and that 40% of these should be clinically expressed, with acute attacks, skin disease or both. Yet this is not what is observed.

CLINICAL FEATURES OF PORPHYRIA

The diagnosis of VP has been plagued by two mutually reinforcing problems. For much of the latter half of the 20th century, porphyria testing rested on imprecise biochemical analyses,³¹ a situation which is now improving with international standardisation of diagnostic testing using quantitative

Table 1 Application of Bayes' rule to the use of clinical symptoms as a diagnostic test for variegate porphyria in a European population

Disease prevalence in the population	0.000007
Sensitivity of clinical symptoms as a diagnostic tool	0.4 (40%)
Specificity of clinical symptoms as a diagnostic tool	0.5 (50%)
Probability that a positive test is a true positive	0.00056%
Probability that a positive test is a false positive	99.99944%

chromatographic analytic methods for porphyrin measurement, supported by molecular studies. Second, many patients with vague symptoms and uncertain laboratory results have been erroneously labelled as having porphyria. This has led to a self-reinforcing cycle, with the nosology of porphyria being ever more stretched to include an extraordinary variety of vague and imprecise clinical features.

The clinical presentation of VP is now well understood. It is clear that, for the overwhelming majority of patients with this disorder, the symptoms are consistent and reproducible. In our own experience, patients referred for diagnosis on the basis of vague symptoms of abdominal pain, abnormal reactions to drugs and a variety of neurological and psychiatric disorders, will prove not to have porphyria.⁵² Indeed, the further a patient's history diverges from the prototypical presentation, the less likely the diagnosis becomes. Yet the patient often clings strongly to the erroneous diagnosis—'delusional porphyria' as memorably termed by one exasperated colleague (Marsden JT, personal communication).

When the diagnosis is overlooked, it is due to unfamiliarity of the attending clinician with porphyria rather than any particular ambiguity in the symptoms. The presentation can be divided into two groups: photosensitive skin disease and the acute attack.³³ The cutaneous symptoms are stereotypic: a propensity to develop fluid-filled blisters which give rise to small erosions and which heal, leaving persistent hypo- and hyperpigmented patches. Milia, frequently limited to the interdigital clefts, may accompany this.³⁴ Lesions are found only in sun-exposed areas, typically the backs of the hands, the forearms and, to a lesser extent, the back of the neck and the feet in people who wear open shoes or sandals (figure 1). These lesions are readily identifiable and highly suggestive of VP or PCT.³³ Other skin afflictions have no diagnostic value in terms of VP whatsoever—hence the scepticism attracted by Macalpine and Hunter's advancement of rashes, erythaema, weals and oedema as evidence in support of their hypothesis. These are not associated with VP and clearly suggest alternative conditions such as skin allergy, acne and even sunburn.

The acute attack is a specific manifestation of AIP and VP, as well as less common disorders hereditary coproporphyrin and ALA dehydratase porphyria.¹⁵ It is associated with elevated levels of the porphyrin precursors delta-aminolaevulinic acid (ALA) and porphobilinogen (PBG), and presents with a characteristic constellation of neurovisceral and motor symptoms



Figure 1 Hands of a patient with variegate porphyria showing blisters, premature ageing and changes in pigmentation.

believed to result from a biochemically mediated autonomic and motor neuropathy.³⁵ The acute attack is frequently triggered by exposure to a variety of drugs which appear to have in common their ability to induce particular classes of cytochrome P450 enzymes, with resultant increases in haem requirement and upregulation of ALA synthase 1.³⁶ Precipitation by stress, infection and starvation have also been listed as causes of the acute attack.^{24 37 38} A small number of female patients with AIP experience attacks in response to pregnancy and the menstrual cycle. The mechanism is thought to be analogous to that of attacks in response to exogenous medicinal agents, here replaced by endogenous production of oestrogen and progesterone.³⁹

The cardinal feature of the attack is abdominal pain. This is stereotypical in its presentation and easily recognisable by the expert, though frequently a source of diagnostic confusion to those less experienced with these patients. It is felt diffusely throughout the abdomen and often extends into the lower back and thighs. It is severe and only relieved by opioid analgesics. It is continuous, unrelenting and most certainly not colicky or cramping. It is poorly localised and is unassociated with signs of peritoneal irritation.⁵⁰

The autonomic disturbance typically manifests with hypertension and tachycardia but only in the most severe cases are these striking. Typically, there is a mild rise in blood pressure and pulse rate, which is then seen to decrease as the attack abates. Patients with longstanding clinically expressed AIP are increasingly recognised to develop chronic sustained hypertension and renal impairment.⁴⁰ Nausea, vomiting and constipation are common but are entirely non-specific and of little diagnostic value in themselves; as symptoms, they are completely overshadowed by the abdominal pain. Severe attacks progress to quadriplegia and respiratory failure. Before the introduction of modern methods of artificial ventilation, motor neuropathy was commonly fatal.³⁰

These, then, are the clinical features of VP. Unfortunately, there is still a tendency to regard any combination of skin problem, abdominal pain and neuropsychiatric disturbance as highly suggestive of VP.

Many symptoms and signs which do not form part of the clinical spectrum of VP have been put forward in support of the George III claim, including abnormal constitution of the blood with severe anaemia, malarial feverishness, neuralgia, biliousness, fainting fits, redness between the breasts, itchy rashes, swollen legs, cloudy urine, shooting labour-type pains and even a raging pain in the feet. Indeed, many of the symptoms adduced in George and his relatives are more appropriately ascribed to such common conditions as acne, skin allergies, sunburn, obstructive jaundice and urolithiasis. As clinicians with a wide experience in porphyria and a proper concern for the correctness of our diagnoses, we believe the time has come to call a halt to such nosological incontinence. Waldenstrom, who described porphyria as 'the little imitator',⁴¹ meant this in the restricted sense that some of the cardinal manifestations might be misinterpreted as a feature of a more common disorder, for example, the quadriplegia of the acute attack being mistaken for the Guillain-Barré syndrome, and did not mean to imply that 'anything goes' when matching symptoms to porphyria.

Bipolar illness has been suggested as a more convincing explanation for George III's mental problems.⁹⁻¹³ His first so-called acute attack, marked by colicky upper-abdominal pain and discoloured urine, may well have reflected obstructive jaundice and was diagnosed at the time by Sir George Baker as 'Concretions of the Gall Duct.' James I, a relative also claimed to have had VP, suffered abdominal pain, vomiting and diarrhoea associated with repeated attacks of left-loin pain radiating to the

bladder and glans penis, with production of dark urine and was found to have calculi in a kidney at autopsy. The most superficial reading of this suggests urolithiasis as a far more likely cause of his symptoms than porphyria. The evidence for the final illness of Edward Duke of Kent (1767–1820), a son of George III and father of Queen Victoria, overwhelmingly favours acute pneumonia. The Duke had caught a cold, which deteriorated over several days, culminating in a final illness marked by delirium, vomiting, high fever, severe chest pain, a cough, pain in the side and hoarseness. Autopsy revealed a large lung abscess. Yet his symptoms too were put forward in support of a porphyria diagnosis.

NEUROPSYCHIATRIC SYMPTOMS IN PORPHYRIA

Nowhere has the concept of porphyria as ‘the little imitator’ been more enthusiastically embraced than in the field of psychiatry⁴² which is, perhaps not coincidentally, the discipline in which Macalpine and Hunter were trained. Indeed, the psychiatric associations of porphyria are among the most misunderstood and misattributed symptoms related to this disorder. The psychiatric manifestations of porphyria may be divided into two groups. First, an association between chronic porphyria and mild anxiety and depression has been postulated.^{43–46} A careful study has reported anxiety and depression in up to 46% of patients with AIP and VP where it was found that anxiety appears to represent a ‘relatively stable personality trait’, rather than a ‘transitory emotional state,’ implying that it is an intrinsic personality trait rather than occurring secondarily to the porphyria.⁴⁷ The nature of this association is yet to be explained.

Second, during the active phase of the acute attack, mental disturbances in the broadest sense are common and may be present in up to 30% of patients.¹⁵ The cause is almost certainly multifactorial and may include common effects of medication used in the management of the acute attack, such as sedation and disorientation arising from the use of opioids, and the effects of the metabolic disturbances associated with the acute attack, including hyponatraemia. Acute psychotic manifestations such as paranoia and hallucinations are occasionally encountered but are very uncommon. In our series of 112 acute attacks, an acute psychosis was noted in a single attack (0.9%) and resolved within 48 h as the attack settled.³⁰

Severe acute attacks are associated with serious central nervous system symptoms, including acute confusion, seizures and coma. Acute porphyria is a well-described precipitant of the posterior reversible encephalopathy syndrome (PRES).^{30 48–53} Patients show a characteristic appearance on CT or MRI scanning suggestive of severe, reversible cerebral ischaemia. About 70 to 80% of all patients with PRES demonstrate moderate to severe hypertension, which probably explains the link with the acute attack of porphyria. PRES may result from disordered cerebral autoregulation or cerebral endothelial dysfunction in the face of hypertension, manifesting as vasospasm and vasogenic cerebral oedema.⁵⁴ It is completely reversible, and all the neurological manifestations of acute porphyria disappear promptly once the attack has settled, with the exception of established peripheral motor neuropathy.

The widely held belief that there is a link between porphyria and insanity is not supported by current evidence. Jara-Prado *et al*⁵⁵ studied 300 psychiatric patients and 150 controls, and found a similar frequency of AIP in both groups: two patients in the patient group and one in the control group. Patience *et al*⁵⁶ studied the case records of 344 consecutive patients with AIP seen by the porphyrias research group in Glasgow between 1950

and 1988. They identified 16 individuals who had had contact with psychiatric services, and were able to study the records of 12. One patient among their 344 cases had been diagnosed as schizophrenic. Bipolar disorder was identified in two, both of whom had a positive family history, and in these families the bipolar disorder did not segregate with AIP. The commonest psychiatric diagnosis in their sample was generalised anxiety. They therefore concluded that there is no evidence for an association between AIP and chronic psychotic illness such as schizophrenia or bipolar disorder.

Yet the belief that chronic psychosis is a feature of latent porphyria has proved difficult to dislodge. A widely quoted study by Tishler *et al*⁵⁷ introduced the discussion with the following sentence: ‘(Our) study of the prevalence of intermittent acute porphyria in patients with psychiatric illness was based on the hypothesis that intermittent acute porphyria may commonly present only as chronic and debilitating psychopathology.’ This belief had been strengthened by a number of early studies, including that of Kaelbling *et al*,⁵⁸ who in 1961 reported 12 patients with porphyria among 2500 patients admitted to short-term American psychiatric units, McEwin *et al*⁵⁹ in 1972, who reported seven patients among 1774 patients admitted to psychiatric wards in Australia, and Wetterberg who detected three cases among 1907 patients in Swedish psychiatric hospitals.⁶⁰ Although, in each study, this was a handful of cases among large numbers of psychiatric patients, the observed frequencies, of 0.48%, 0.4% and 0.16% respectively, were felt to exceed the prevalence of AIP in the general population. Tishler *et al*⁵⁷ studied 3867 psychiatric inpatients in 1985. They identified eight subjects as carrying AIP, a prevalence of 0.05%, suggesting an over-representation compared with the population.

With the benefit of hindsight, it is clear that these studies were unintentionally misleading. The diagnostic methods employed in these studies, including simple urine-screening tests for PBG and blood-spot tests for reduced hydroxymethylbilane synthase activity, do not meet the standards of sensitivity and specificity that would be required for publication today. Furthermore, the psychiatric patients identified as ‘carriers’ of AIP constituted a diverse group of patients who appeared to share no other features in common: none had any other symptoms of porphyria (such as a history of the acute attack), and the psychiatric diagnoses attached to these patients spanned the entire psychiatric spectrum, from personality disorder to depression, hysteria, dementia, head trauma and epilepsy. The association between chronic psychosis and porphyria apparently identified in these studies is hopelessly compromised.

Unfortunately, the supposed link between porphyria and chronic psychiatric illness has become firmly established in the minds of both the public and many professionals. Testimony to this is the following quote written as recently as 1995⁶¹:

Psychiatric manifestations[in porphyria] include hysteria, anxiety, depression, phobias, psychosis, organic disorders, agitation, delirium, and altered consciousness ranging from somnolence to coma. Some patients develop psychosis similar to schizophrenia. Psychiatric hospitals have a disproportionate number of patients with this disorder as only difficult and resistant patients accumulate there... This diagnosis should be entertained in the following situations: (a) unexplained leucocytosis; (b) unexplained neuropathy; (c) aetiologically obscure neurosis or psychosis; (d) ‘idiopathic’ seizure disorder; (e) unexplained abdominal pain; (f) conversion hysteria; and (g) susceptibility to stress.

Are there any patients in psychiatric institutions who do not meet these criteria for porphyria? To conclude: the clinical

presentation of porphyria is straight-forward and rarely problematic: George III and his relatives do not meet clinical criteria for a diagnosis of porphyria.

NATURAL HISTORY OF PORPHYRIA

Porphyria is more than just a complex of symptoms at a particular time. It also has a well-recognised natural history. This implies that the disease should be viewed longitudinally as well as cross-sectionally. The Macalpine and Hunter claim implies that George III's porphyria deteriorated over many years to the point where he became psychotic and demented. Such a pattern is not seen in porphyria. Certainly there are a few unfortunate individuals with severe AIP, almost without exception female, who have frequent attacks, often more than one per month. They do not lapse into insanity. Rather they tend to become increasingly immobilised by motor neuropathy, have a seriously impaired quality of life owing to numerous ongoing painful crises and become dependent for survival on skilled medical care, such as repeated infusions of haem arginate and, more recently, orthotopic liver transplantation,^{62–64} failing which they die.^{15 50}

More recently recognised are an association between chronic AIP and hypertension and eventual chronic renal failure,^{40 43 62} and an increased risk of hepatocellular carcinoma in patients with both AIP and VP.^{45 65–70}

George III's so-called attacks did not follow a typical pattern of attacks—unrelenting pain lasting days to weeks, nor of the discoloured urine which might conceivably represent an attack-associated excess of urinary porphyrins—followed by long periods of remission. Indeed, the natural history of his illness and that of his relatives are as atypical for porphyria as are the symptoms themselves.

LABORATORY EVIDENCE FOR VP

Despite a number of claims, no unequivocal evidence for VP has as yet been adduced in any of George's descendants. Two patients from the house of Hanover were said to have had positive biochemical tests for porphyria.⁴ This claim has been convincingly contested on the basis of insufficient or contradictory evidence.^{5 8} To the best of our knowledge, attempts at a retrospective genetic diagnosis via analysis of the *PPOX* gene from ancient DNA samples have yielded inconclusive or incomplete evidence.⁴

CONCLUSION

We conclude that neither George nor his relatives were afflicted with an acute porphyria, either VP or AIP. First, the rarity of the disease mandates a very low prior probability and therefore implies a vanishingly low positive predictive value for any diagnostic indicator of low specificity, such as a historical reading of the symptoms. Second, penetrance of this autosomal dominant disorder is approximately 40%, and one may expect to have identified characteristic clinical features of porphyria without difficulty in a large number of descendants. Third, the symptoms of both George III and his relatives are highly atypical for VP and are more appropriately explained by other commoner conditions. Fourth, the natural history of the illnesses reported in this family is as atypical for VP as are their symptoms. Finally, no objective, unequivocal, as opposed to circumstantial, evidence has as yet been put forward to support a diagnosis of VP.

We believe that there are three lessons to be drawn from the story of George III and his supposed porphyria. First, it is inappropriate to look at a disease purely in terms of its symptoms. Rather, a rigorous assessment which includes its preva-

Take-home messages

- ▶ Variegate porphyria is not responsible for the 'Royal Malady' nor the 'madness of King George'.
- ▶ The temptation to attach a diagnostic label of 'porphyria' to a wide variety of atypical and non-specific signs and symptoms, especially neuropsychiatric symptoms, must be vigorously resisted.

lence in a population, expected patterns and frequency of inheritance, its penetrance and its expected natural history in affected individuals must be made. Second, rigour in the searching of the available historical information and unbiased reporting of factors that both support and refute the hypothesis are essential.

Third, we believe that the Royal malady hypothesis has unfortunately proved to be more than just a benign and interesting historical footnote. It has served to support serious misconceptions about porphyria. Clinicians with an interest in porphyria are frequently referred patients with a variety of bizarre symptoms (usually with some vague relation to abdominal pain, presumed neurosis or even psychosis, and atypical responses to drugs) with a diagnosis of presumed porphyria. Many of these are psychologically vulnerable patients. Once a diagnostic label of 'porphyria' has been erroneously attached to them, they have great difficulty in letting such a diagnosis go, and therefore of turning their attention to dealing with the real issues. A clear understanding of how acute porphyrias may present, and equally how they do not present, is essential to this.

Competing interests None.

Ethics approval Not required as the study does not involve research on human nor animal subjects

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REFERENCES

1. **Macalpine I**, Hunter R. The 'insanity' of King George 3d: a classic case of porphyria. *BMJ* 1966;**1**:65–71.
2. **Macalpine I**, Hunter R, Rimington C. Porphyria in the royal houses of Stuart, Hanover, and Prussia. A follow-up study of George 3d's illness. *BMJ* 1968;**1**:7–18.
3. **Cox TM**, Jack N, Lofthouse S, *et al*. King George III and porphyria: an elemental hypothesis and investigation. *Lancet* 2005;**366**:332–5.
4. **Röhl J**, Warren M, Hunt D. *Purple Secret—Genes, 'Madness' and the Royal Houses of Europe*. London: Bantam, 1998.
5. **Dean G**. Royal malady. *BMJ* 1968;**1**:443.
6. **Dean G**. *The Porphyrins: A Story of Inheritance and the Environment*. 2nd edn. Philadelphia: Lippincott, 1972.
7. **Dent CE**. Royal malady. *Br Med J* 1968;**2**:118–19.
8. **Eales L**, Dowdle EB. Royal malady. *BMJ* 1968;**1**:841–2.
9. **Brownstein S**. George III: a revised view of the royal malady. *J Hist Neurosci* 1997;**6**:38–49.
10. **Peters TJ**, Beveridge A. The blindness, deafness and madness of King George III: psychiatric interactions. *J R Coll Physicians Edinb* 2010;**40**:81–5.
11. **Peters TJ**. George III: a new diagnosis. *Hist Today* 2009;**59**:4–5.
12. **Peters TJ**, Wilkinson D. King George III and porphyria: clinical re-examination of the historical evidence. *Hist Psychiatry* 2010;**21**:3–19.

13. **Peters TJ**, Beveridge A. The madness of King George III: a psychiatric re-assessment. *Hist Psychiatry* 2010;**21**:20–37.
14. **Peters T**. King George III, bipolar disorder, porphyria and lessons for historians. *Clin Med* 2011;**11**:261–4.
15. **Puy H**, Gouya L, Deybach JC. Porphyrrias. *Lancet* 2010;**375**:924–37.
16. **Taketani S**, Inazawa J, Abe T, et al. The human protoporphyrinogen oxidase gene (PPOX): organization and location to chromosome 1. *Genomics* 1995;**29**:698–703.
17. **Meissner PN**, Dailey TA, Hift RJ, et al. A R59W mutation in human protoporphyrinogen oxidase results in decreased enzyme activity and is prevalent in South Africans with variegate porphyria. *Nat Genet* 1996;**13**:95–7.
18. **Warnich L**, Kotze MJ, Groenewald IM, et al. Identification of three mutations and associated haplotypes in the protoporphyrinogen oxidase gene in South African families with variegate porphyria. *Hum Mol Genet* 1996;**5**:981–4.
19. **Deybach JC**, Puy H, Robreau AM, et al. Mutations in the protoporphyrinogen oxidase gene in patients with variegate porphyria. *Hum Mol Genet* 1996;**5**:407–10.
20. **Koegelenberg AJ**. *Molecular Epidemiological Study of Variegate Porphyria to Determine the Frequency of the Founder Gene Mutation in South Africa* [MSc dissertation]. Stellenbosch: University of Stellenbosch, 2003.
21. **Hift RJ**, Meissner D, Meissner PN. A systematic study of the clinical and biochemical expression of variegate porphyria in a large South African family. *Br J Dermatol* 2004;**151**:465–71.
22. **Whatley SD**, Puy H, Morgan RR, et al. Variegate porphyria in Western Europe: identification of PPOX gene mutations in 104 families, extent of allelic heterogeneity, and absence of correlation between phenotype and type of mutation. *Am J Hum Genet* 1999;**65**:984–94.
23. **Von und zu Fraunberg M**, Timonen K, Mustajoki P, et al. Clinical and biochemical characteristics and genotype–phenotype correlation in Finnish variegate porphyria patients. *Eur J Hum Genet* 2002;**10**:649–57.
24. **Eales L**, Day RS, Blekkenhorst GH. The clinical and biochemical features of variegate porphyria: an analysis of 300 cases studied at Groote Schuur Hospital, Cape Town. *Int J Biochem* 1980;**12**:837–53.
25. **Mustajoki P**. Variegate porphyria. Twelve years' experience in Finland. *Q J Med* 1980;**49**:191–203.
26. **Hibbert C**. *George III: A Personal History*. London: Viking, 1998.
27. **Eales L**, Linder GC. Porphyria—the acute attack. An analysis of 80 cases. *S Afr Med J* 1962;**36**:284–92.
28. **Eales L**. Porphyria and the dangerous life-threatening drugs. *S Afr Med J* 1979;**56**:914–17.
29. **Elder GH**, Hift RJ, Meissner PN. The acute porphyrias. *Lancet* 1997;**349**:1613–17.
30. **Hift RJ**, Meissner PN. 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. *Medicine (Baltimore)* 2005;**84**:48–60.
31. **Hift RJ**, Davidson BP, van der Hooff C, et al. Plasma fluorescence scanning and fecal porphyrin analysis for the diagnosis of variegate porphyria: precise determination of sensitivity and specificity with detection of protoporphyrinogen oxidase mutations as a reference standard. *Clin Chem* 2004;**50**:915–23.
32. **Hift RJ**, Meissner PN, Corrigan AV, et al. Variegate porphyria in South Africa, 1688–1996—new developments in an old disease. *S Afr Med J* 1997;**87**:722–31.
33. **Kirsch RE**, Meissner PN, Hift RJ. Variegate porphyria. *Semin Liver Dis* 1998;**18**:33–41.
34. **Murphy GM**. The cutaneous porphyrias: a review. The British Photodermatology Group. *Br J Dermatol* 1999;**140**:573–81.
35. **Meyer UA**, Schuurmans MM, Lindberg RL. Acute porphyrias: pathogenesis of neurological manifestations. *Semin Liver Dis* 1998;**18**:43–52.
36. **Podvenc M**, Handschin C, Looser R, et al. Identification of the xenosensors regulating human 5-aminolevulinic synthase. *Proc Natl Acad Sci U S A* 2004;**101**:9127–32.
37. **Handschin C**, Lin J, Rhee J, et al. Nutritional regulation of hepatic heme biosynthesis and porphyria through PGC-1alpha. *Cell* 2005;**122**:505–15.
38. **Degenhardt T**, Vaisanen S, Rakhshandehroo M, et al. Peroxisome proliferator-activated receptor alpha controls hepatic heme biosynthesis through ALAS1. *J Mol Biol* 2009;**388**:225–38.
39. **Innala E**, Backstrom T, Bixo M, et al. Evaluation of gonadotropin-releasing hormone agonist treatment for prevention of menstrual-related attacks in acute porphyria. *Acta Obstet Gynecol Scand* 2010;**89**:95–100.
40. **Church SE**, McColl KE, Moore MR, et al. Hypertension and renal impairment as complications of acute porphyria. *Nephrol Dial Transplant* 1992;**7**:986–90.
41. **Bonkovsky HL**. Advances in understanding and treating 'the little imitator,' acute porphyria. *Gastroenterology* 1993;**105**:590–4.
42. **Crimlisk HL**. The little imitator—porphyria: a neuropsychiatric disorder. *J Neural Neurosurg Psychiatry* 1997;**62**:319–28.
43. **Kauppinen R**, Mustajoki P. Prognosis of acute porphyria: occurrence of acute attacks, precipitating factors, and associated diseases. *Medicine (Baltimore)* 1992;**71**:1–13.
44. **Millward LM**, Kelly P, Deacon A, et al. Self-rated psychosocial consequences and quality of life in the acute porphyrias. *J Inher Metab Dis* 2001;**24**:733–47.
45. **Bylesjo I**, Wikberg A, Andersson C. Clinical aspects of acute intermittent porphyria in northern Sweden: a population-based study. *Scand J Clin Lab Invest* 2009;**69**:612–18.
46. **Hift RJ**. *Variegate Porphyria. Molecular Aspects of Variegate Porphyria in South Africa and their Biochemical and Clinical Consequences* [PhD dissertation]. Cape Town: University of Cape Town, 2000.
47. **Millward LM**, Kelly P, King A, et al. Anxiety and depression in the acute porphyrias. *J Inher Metab Dis* 2005;**28**:1099–107.
48. **Hagemann G**, Ugrur T, Witte OW, et al. Recurrent posterior reversible encephalopathy syndrome (PRES). *J Hum Hypertens* 2004;**18**:287–9.
49. **Kang SY**, Kang JH, Choi JC, et al. Posterior reversible encephalopathy syndrome in a patient with acute intermittent porphyria. *J Neurol* 2010;**257**:663–4.
50. **Maramattom BV**, Zaldivar RA, Glynn SM, et al. Acute intermittent porphyria presenting as a diffuse encephalopathy. *Ann Neurol* 2005;**57**:581–4.
51. **Ni J**, Zhou LX, Hao HL, et al. The clinical and radiological spectrum of posterior reversible encephalopathy syndrome: A retrospective series of 24 patients. *J Neuroimaging* 2011;**21**:219–24.
52. **Pischik E**, Kauppinen R. Neurological manifestations of acute intermittent porphyria. *Cell Mol Biol (Noisy-le-grand)* 2009;**55**:72–83.
53. **Shen FC**, Hsieh CH, Huang CR, et al. Acute intermittent porphyria presenting as acute pancreatitis and posterior reversible encephalopathy syndrome. *Acta Neurol Taiwan* 2008;**17**:177–83.
54. **Bartynski WS**. Posterior reversible encephalopathy syndrome, part 1: fundamental imaging and clinical features. *Am J Neuroradiol* 2008;**29**:1036–42.
55. **Jara-Prado A**, Yescas P, Sanchez FJ, et al. Prevalence of acute intermittent porphyria in a Mexican psychiatric population. *Arch Med Res* 2000;**31**:404–8.
56. **Patience DA**, Blackwood DH, McColl KE, et al. Acute intermittent porphyria and mental illness—a family study. *Acta Psychiatr Scand* 1994;**89**:262–7.
57. **Tishler PV**, Woodward B, O'Connor J, et al. High prevalence of intermittent acute porphyria in a psychiatric patient population. *Am J Psychiatry* 1985;**142**:1430–6.
58. **Kaelbling R**, Craig JB, Pasamanick B. Urinary porphobilinogen. Results of screening 2,500 psychiatric patients. *Arch Gen Psychiatry* 1961;**5**:494–508.
59. **McEwin R**, Lawn J, Jonas CT. A survey of porphyria among psychiatric patients. *Med J Aust* 1972;**2**:303–6.
60. **Wetterberg L**. *A Neuropsychiatric and Genetical Investigation of Acute Intermittent Porphyria*. Stockholm: Svenska Bokforlaget, 1967.
61. **Burgovne K**, Swartz R, Ananth J. Porphyria: reexamination of psychiatric implications. *Psychother Psychosom* 1995;**64**:121–30.
62. **Wahlin S**, Harper P, Sardu E, et al. Combined liver and kidney transplantation in acute intermittent porphyria. *Transpl Int* 2010;**23**:e18–21.
63. **Moinia M**, Mistry P, Schilsky ML. Liver transplantation for inherited metabolic disorders of the liver. *Curr Opin Organ Transplant* 2010;**15**:269–76.
64. **Soonawalla ZF**, Orug T, Badminton MN, et al. Liver transplantation as a cure for acute intermittent porphyria. *Lancet* 2004;**363**:705–6.
65. **Kauppinen R**, Mustajoki P. Acute hepatic porphyria and hepatocellular carcinoma. *Br J Cancer* 1988;**57**:117–20.
66. **Dragani TA**. Risk of HCC: genetic heterogeneity and complex genetics. *J Hepatol* 2010;**52**:252–7.
67. **Schneider-Yin X**, Harms J, Minder EI. Porphyria in Switzerland, 15 years experience. *Swiss Med Wkly* 2009;**139**:198–206.
68. **Schneider-Yin X**, Van Tuyl van Serooskerken A-M, Went P, et al. Hepatocellular carcinoma in variegate porphyria: a serious complication. *Acta Derm Venereol* 2010;**90**:512–15.
69. **Innala E**, Andersson C. Screening for hepatocellular carcinoma in acute intermittent porphyria: a 15-year follow-up in northern Sweden. *J Intern Med* 2011;**269**:538–45.
70. **Deybach JC**, Puy H. Hepatocellular carcinoma without cirrhosis: think acute hepatic porphyrias and vice versa. *J Intern Med* 2011;**269**:521–4.