Porphyrias

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Until recently, cases of porphyrias have been considered rare. It has only been within the past decade or so that an increasing number of patients have been diagnosed with this disorder, leading some clinicians to question their prevalence. While allopathic medicine can offer some therapies that are effective in the treatment of these disorders, naturopathic medicine possesses a considerable array of therapeutic modalities that are very effective in combating the disease and preventing recurrence.

Porphyria as a disease was first described 3 centuries ago by Sir Theodore Turquet de Mayerne of France, physician to the English court of King James I. He described accounts of paralysis, bilious urine, colic, insanity fits, permanent insanity, deaths at childbirth and premature death in those afflicted. The disease probably afflicted King George III of England and is felt to have impaired his judgement during the American Revolution. **[1]**

In 1911 Gunther described what is now known as the classic triad of abdominal pain, constipation (or diarrhea), and vomiting. Waldenstrom later added to the understanding of the diseases by describing acute intermittent porphyria as characterized by periods of exacerbation and remission **[2]**.

Various classifications of porphyria were arrived at as greater recognition of their variations occurred. Genetic as well as environmentally induced manifestations of the disease were found, with there being considerable variation in the clinical presentation of the different forms.

The genetic deficits of porphyria affect all tissues but primarily the hematopoietic forming tissues of the bone marrow and the cytochrome P-450 system in the liver because of the greater number of porphyrin precursors required. The liver is the major site where inherited or acquired deficits in heme synthesis manifest. **[3]**

Classifications of Porphyria

Prophyrias are classified as being either of hepatic or erythropoietic in origin. In both classes they are characterized by the

over production of porphyrin or their precursors. Biosynthesis of heme is controlled differently in liver and bone marrow with the rate-limiting enzyme in liver being ALA synthase, while the biosynthesis of heme in the bone marrow is partly regulated by the uptake of iron.

The acute hepatic porphyrias are characterized by a rapid onset of symptoms that are largely neurological while the erythropoietic variety manifest primarily in the skin leading to cutaneous photosensitivity.

Hepatic porphyrias are ALA-Dehydrase-Deficiency Porphyria, Acute Intermittent Porphyria, Porphyria Cutanea Tarda, Hereditary Coproporphyria and Variegate Porphyria.

Erythropoietic porphyrias are further classified as X-Linked Sideroblastic Anemia, Congenital Erythropoietic Porphyria, and Erythrocytic Protoporphyria [4].

Signs & Symptoms of Hepatic Porphyrias

Acute attacks consist of a wide variety of symptomology ranging from skin lesions to abdominal pain to neurological manifestations of varying degrees of intensity. Abdominal, back or extremity pains grow in intensity over a 24 to 48 hour period which may lead the clinician to consider appendicitis or an acute abdomen. Rebound tenderness is not usually present.

Nausea and vomiting are frequently seen as is anxiety and restlessness. Often these patients have some degree of constipation that worsens as the condition develops. Tachycardia may also be present suggesting an infectious process or an increase in bowel toxicity.

In general, the severity of the symptom pattern seems to the clinician to be out of proportion to the presenting signs. It is thought that the bowel symptoms are due to a neurological disturbance of normal function.

Mental abnormalities can range from confusion to acute psychosis and be the first presentations of an attack. With prolonged attacks, sensory and motor function is impaired and can result in respiratory paralysis and death. [5] Many patients are diagnosed with schizophrenia and a considerable number confined to mental institutions are felt to be afflicted with one of the porphyrias. [6, 7]

The majority of carriers are usually asymptomatic except when they are exposed to drugs or chemicals which exacerbate the condition. Neurologic symptoms and the sequelae of an acute and/or prolonged attack can take months to clear but eventual recovery occurs in the majority of cases.

Biochemistry of Porphyria

Biosynthesis of heme is the main purpose for the porphyrogenic pathway. Heme is a large molecular weight metalloprotein which is a member of a group of chemicals which include cytochromes (oxidation/reduction reactions) chlorophyll (photosynthesis) and vitamin B_{12}. Heme is formed from succinyl CoA and glycine and is ultimately involved in aerobic metabolism after it is combined with globin chains that are synthesized on the ribosomes in the plasma of the developing erythrocyte. In the liver, heme production is largely utilized for the production of cytochrome P-450 in response to the over abundance of toxic substances that the body needs to eliminate. Heme synthesis begins and ends in the mitochondrion with part of it occurring in the cytopalsm. All tissues form heme but the primary sites are the bone marrow and liver.

The rate-limiting enzyme for heme synthesis is ALA synthase, which is the initial enzyme in the cascade. ALA synthase requires vitamin co factors and energy input. All other reactions in the sequence are the result of thermodynamics and are irreversible once initiated.

ALA synthase is regulated by a feedback mechanism which is responsive to the tissues demand for heme production. With the formation of uroporphyrinogen, branching occurs resulting in different porphyrin isomers. Isomer I proceeds only as far as coproporphyrin I and normally is considered inconsequential. Isomer III results in the formation of uroporphyrinogen III which undergoes modification to render it more lipophilic so it can be excreted from the body. Thus the majority of the pathway favors heme production.

Heme Formation

Final heme formation is regulated by the action of ferrocheletase in the mitochondria. Reducing substances such as ascorbic acid, cysteine, or glutathione are required. Iron must be in

the ferrous rather than ferric form. Ferrocheletase activity is inhibited by high concentrations of heme, thus the feed back system preventing further formation. Heme concentration also feeds back on ALA synthase, the rate-limiting step in the biosynthetic pathway.

As heme formation is essential for aerobic metabolism, an absence would be lethal. Therefore, multiple control systems have evolved to regulate the metabolic pathway which has made it difficult to elucidate the exact mechanism of the deficit, be it genetic or acquired. Recent advances in identifying specific DNA's encoding the heme biosynthetic enzymes however, has resulted in a more precise diagnosis of the specific genetic deficit.

Red blood cell incorporation of heme, iron and glycine occur in maturing cells up through and including reticulocytes, but is eventually lost as the red cell ages. Hypoxia and erythropoietin will increase ALA synthase activity in RBC's but not liver while drugs and chemicals will affect liver but not erythropoietic tissues.

Specific genetic or acquired deficiencies limit the flow of heme precursors through the cascade of steps needed to form hemoglobin. The deficiency can become manifest due to an increased demand for heme precursors. Certain drugs, chemicals, steroids, estrogens, oral contraceptives, progesterone, testosterone or any substance, which places an excess burden on the cytochrome P-450 system, can act to precipitate an acute attack. This results from the partial removal of the feedback mechanism on delta-ALA synthase (ALA-S). Depending upon the specific enzyme deficit present, heme precursors follow different pathways resulting in their accumulation in the tissues. Their presence affects the skin and nervous system and manifests as the signs and symptoms of the disease.

Attacks occur more frequently in women than men, especially premenstrually. As the person ages, the likelihood of exposure of an underlying porphyria deficit increases because of increased exposures to environmental toxins and the aging bodies decreasing ability to adapt.

Cutaneous manifestations occur because some porphyritic precursors absorb light at 400 nm resulting in photosensitivity. Absorption of light causes a raising of the potential energy of the molecule to an "excited" state resulting in a highly reactive oxygen species. A histamine and proteolytic enzyme release resulting in

oxidative damage follow this. Beta-carotene protects against these injuries. [3, 4, 8]

Neuropsychiatric changes occur in the hepatic porphyrias (ALA-Dehydrase-Deficiency Porphyria, Acute Intermittent Porphyria, Porphyria Cutanea Tarda, Hereditary Coproporphyria and Variegate Porphyria) with excess production of ALA and PBG and there is a somewhat linear relationship between their concentration and the severity and duration of symptoms. A build up of porphyrin intermediaries have been found in a variety of tissues and may induce the neuropsychiatric symptoms accompanying acute flare-ups [9, 10]. The exact mechanism of how porphyrins affect the central nervous system is not well understood.

Patients with familial porphyria cutanea tarda usually present at a younger age than patients who spontaneously develop porphyria cutanea tarda despite there being no difference in biochemical features of the disease. [11] This may be due to a corresponding genetic predisposition to sequestering ferritin in the liver or due to an increased sensitivity to ethanol ingestion [11, 12]. Additionally, even in families with known genetic deficits, manifestations of the disease among family members varies.

Etiological agents triggering Porphyria

Numerous agents that trigger an episode of porphyria have been identified and patients afflicted must be careful when taking prescription medications, estrogens, some herbal medicines, and of environmental exposures to heavy metals, organo-phosphates or any substance which places an excess burden on the cytochrome P-450 system. In particular, exogenous estrogens, be they oral contraceptives, estrogen patches or with estrogen replacement therapy are strong contributors to an underlying porphyria deficit [13, 14]. This is one of the reasons why acute porphyria attacks are seen more often in women than men, especially premenstrually. Additionally, it has been suggested from studies that estrogens enhance the porphyrin inducing activities of other agents making women more vulnerable to environmental exposures than their male counterparts [15, 16].

Herbicide induced porphyria has been shown to decrease activity of several enzymes involved in the prophyritic pathway as

well as increasing the porphyrin content in nerve tissue [16, 17]. A considerable number of chemicals have also been linked to porphyria or porphyrinuria in humans and generally involve chronic industrial exposures or environmental exposures. An example of an epidemic of porphyria cutanea tarda produced by accidental ingestion of wheat treated with the fungicide hexachlorobenzene occurred in Turkey in the 1950's.

It has been hypothesized that several otherwise unexplained chemical-associated illnesses, such as multiple chemical sensitivity syndrome, may represent mild chronic cases of porphyria or other acquired abnormalities in heme synthesis [18, 19].

According to William Morton, M. D., who has studied and written on porphyrias extensively, multiple chemical sensitivity syndrome (MCS) first described by Cullen in 1979, may in fact be porphyria. He speculates that exposures to porphyrogenic chemicals, medications or severe infection, overpower the already deficient enzyme system resulting in accumulation of the specific porphyrin because of diminished enzyme function. He proposed that the resultant symptoms are due to an increase of the porphyrinogen and not an accumulation of the toxin itself. "Many diagnosticians have tried to expedite the distinction between "real" porphyria and secondary porphyrinopathies by requiring that a porphyria diagnosis be based on urinary and/or fecal porphyrin excretions 2-20 times the upper limit of normal. This classification would exclude individuals demonstrating lesser degrees of porphyroinogenic activity, possibly some of those whose conditions are in remission or not subject to environmental exposures" [20].

Intensities of porphyria symptoms vary widely. About 10% of the cases present with acute severe attacks, while approximately 25% are seen with chronic symptomology of varying degrees. The remaining percentage (65%) presents with no symptomology but may become susceptible under the right circumstances [21].

Not all researchers agree with Morton's and others' premise that environmental toxicity's induce underlying genetic deficits leading to symptomatic porphyria. According to Hahn and Bonkovsky, "patients with multiple chemical sensitivity syndrome may, at times, have modest increases in urinary coproporphyrin excretion, this is a common finding found in many asymptomatic subjects or patients

with diverse other conditions (e.g., diabetes mellitus, heavy alcohol use, liver disease, and many kinds of anemia). Such secondary coproporphyrinuria does not indicate the existence of coproporphyria "[22].

Regardless of which "school of thought" is correct, an increasing number of cases are being diagnosed by clinicians. Certainly, with the increasing levels of pollutants in the environment, hormone additives to the food chain, and the unmonitored multiple pharmacy prescriptions encountered by most humans, the potential for unmasking an underlying deficit increases.

Laboratory diagnosis of Porphyria

Small amounts of porphyrins are excreted in normal human urine; the most predominant of which is coproporphyrin. Coproporphyrin is also present in the bile and feces. ALA, PBG and uroporphyrin are largely excreted in the urine while coproporphyrin is preferentially and protoporphyrin exclusively excreted in the bile and feces.

Fecal excretion is also affected by diet and bowel flora, thus contributing to its wide variation. Geographic distribution, dietary preferences, ethnic diversities and differences in test methodologies make it difficult to arrive at "normal" values.

PBG excretion in the urine of healthy individuals is usually below 1.5 mg per day and is undetectable by conventional testing. The Watson-Schwartz qualitative test for PBG will be positive in acute intermittent porphyria in acute attacks and variegate porphyria and hereditary coproporphyria in latent periods [23]. There is a high false negative rate due to its subjective nature. A false increase in porphyrins from a substance present in yeast tablets has been demonstrated to provide a false positive Watson-Schwartz test [24].

A cost-effective strategy for diagnosis of porphyric syndromes when presented with acute symptoms has been suggested. " If neurovisceral features suggest an acute porphyric syndrome, a rapid screening test for urinary porphobilinogen should be performed. If clinical features suggest a cutaneous porphyria, then for solar urticaria and acute photosensitivity (suggesting protoporphyria) screening tests for increased erythrocytic porphyrins should be done; for vesiculobullous formation (suggesting porphyria cutanea tarda,

hereditary coproporphyria, or variegate porphyria) a screening test for urinary porphyrins should be done. Positive screening tests should be confirmed with targeted quantitative testing." [25]

Enzymatic assays and DNA-based testing are not usually needed for rapid diagnosis or management of symptomatic subjects when presented with acute disease. They are however useful for evaluation and genetic counseling. Isolation of specific DNA encoding the heme biosynthetic pathway enzymes makes it possible to now provide precise heterozygote identification as well as providing prenatal diagnosis in families with known defects [4, 25, 26].

Other cell markers may also help in identifying porphyria patients in the absence of symptomology. Leukocyte concentrations of manganese, calcium, iron and zinc, as well as erythrocyte calcium have been shown to be present at different concentrations between groups classified as acute intermittent porphyria gene carriers. Of the cell markers, manganese was found to be the most discriminative component of all the variables investigated. An increase in cellular manganese by a factor of four suggests an increase in the likelihood of development of acute intermittent porphyria [27].

Because of the many possible genetic deficits leading to porphyria, it is important that the specific deficit is determined as successful treatment out comes depends upon the correct diagnosis.

Case Management:

Identification of those patients predisposed and susceptible to the development of porphyritic episodes is important. Patients with a past medical history of periodic psychotic episodes or nervous break downs, unexplained abdominal pains, or unusual symptoms that have lead to numerous diagnosis', should alert the physician to the possibility of an underlying porphyria. Prevention is clearly the first option as porphyritic episodes can be very difficult to control once initiated [28].

Treatment of patients afflicted with acute episodes can be quite demanding on the clinician and difficult to manage due to the severity and frequently changing clinical picture. Each patient presentation will be different depending upon the degree of toxicity, genetic component and patient response to therapy.

Homeopathic treatment has proven successful but different homeopathic medicines will be required depending upon the clinical picture, which, as has been mentioned, can often change very quickly. Constitutional prescribing does not seem to work as well while the person is in an acute state and several prescriptions may be needed for the patient to stabilize. The prescriptions may need to be changed frequently as the patient progresses through the varying stages of the disease.

Antioxidant therapy, along with homeopathy, is the mainstay of case management during acute porphyritic episodes. Once the patient has stabilized, an on-going regime of antioxidants such as vitamin C, vitamin E, glutathione, beta carotene, and N-acetyl cysteine should be undertaken in order to prevent recurrence [29]. In particular, vitamin C has been found to be low in porphyria cutanea tarda patient's [30].

During an acute episode, frequent follow up is needed in order to assess the clinical state. In some cases, patients will need to be seen daily and medications altered depending upon the presentation.

Education of the patient as to their condition is one of the most important things that can be done for them. Often the patient does not want to believe they have a genetic affliction and will seek another diagnosis. They often have received a variety of different diagnoses and may still want to believe that they have another disorder. It will be important to delineate which symptoms go with each condition but they will all probably be related to the porphyria. Additionally, informing other physicians the patient is seeing as to their condition will help keep prescription drugs to a minimum, thus decreasing the likelihood of an exacerbation.

The course of therapy in order for the patient to reach a state where they are not as susceptible to environmental toxins is usually long and has periods of exacerbation's and remissions. Helping the patient to understand this will help in their recovery.

Eliminate environmental and chemical exposures by identifying offending agents and limiting exposures. Lists of prescription medicines and environmental toxins that cause exacerbation of porphyria are available (see table). A complete history as to environmental and work related exposures is in order. Often, simply

changing the patients work environment will decrease exposure, eliminating attacks.

As panthothenic acid is required for the formation of succinyl CoA (generated by the tricarboxycilic acid cycle) and glycine, which are the precursors to formation of aminolevulenic acid (ALA), supplementation is helpful. Additionally, a step in the transformation of succinyl CoA requires a vitamin B_{12} dependent enzyme and evaluation of vitamin B_{12} and folic acid status may be in order. The initial reaction is oxygen dependent which may mean that oxygen therapy is contraindicated in delta-ALA porphyria.

ALA formation requires, and is dependent upon pyridoxal-5'-phosphate, and any substance which inhibits enzyme systems, is countered in part by the addition of pyridoxal-5-phosphate. However, experimental models suggest that P5'P does not play an important role. **[3]**

Constitutional hydrotherapy during an acute flare up is very effective in normalizing liver function as well as neurological symptoms. Daily sessions may be needed to accomplish this while allowing the physician to monitor the patient closely. **[31]**

During attacks of acute intermittent porphyria, increasing complex carbohydrates in the diet helps to alleviate symptoms. Often the patient will be ingesting very high amounts of carbohydrates when first seen and weight gain often follows. Intravenous glucose can also be given (300 gm/day). A more complete parenteral nutritional regime is preferable however. Fasting or rapid weight loss diets can precipitate AIP and should be avoided.

Detoxification of the liver and colon is indicated as an on going process as this helps to eliminate toxins from the body which may precipitate an exacerbation of the condition. Regardless of whether the toxin actually precipitates an attack of porphyria, elimination on an on-going basis reduces the chance of an acute flare-up of the disease. Detoxification can be achieved through colon hydrotherapies, constitutional hydrotherapy's, sauna's, antioxidants or oxygen therapies such as ozone.

Ozone therapy is primarily indicated when there is a deficit of coproporphyrinogen oxidase resulting in a deficit of coprophyrinogen in hereditary coproporphyria. It is contraindicated when there is a

deficit of ALA synthase as higher amounts of oxygen will enhance the pathway resulting in an exacerbation of symptoms.

Supplementation with lipotrophic factors that enhance the function of the livers cytochrome P-450 system are contraindicated during acute attacks but are useful when the patient is in a period of normality. Incorporating them, as well as high doses of anti-oxidants will help decrease the episodes of acute attacks.

Additionally, chelation therapies with EDTA, as well as ethanol extracts of botanical medicines are contraindicated in patients with a predisposition to develop porphyria.