Porphyria: A difficult disease to diagnose

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To the faculty of Washington State University:

The members of the committee appointed to examine the Intercollegiate College of Nursing research requirements and manuscript of MARELDA MARY ABNEY find it satisfactory and recommend that it be accepted.

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Abstract

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Porphyria describes a group of disorders in which there is an inborn error of heme metabolism. The error is deficient or defective enzymes needed in the production of heme. There are at least seven different known types of porphyria based upon which enzyme is affected. Essentially, the person who is suffering with porphyria has a build up of enzymatic particles, called porphyrins, due to the defective pathway (Thadani, Deacon & Peters, 2000).

All of the porphyrias are rare, some more than others. They are mainly an inherited, but may be acquired (Rich, 1999). Because of their rarity, clinicians often forget to include them in their differential diagnosis (Crimslick, 1997). The clinical manifestations of porphyria are easily misinterpreted for other illnesses.

There is no cure for porphyria, but early diagnosis and treatment can reduce the number of hospital admissions and potential for death and disfigurement (http://www.cpf-inc.ca/guide.htm). Most treatment usually consists of avoidance of triggers factors such as alcohol, specific drugs, and sunlight. In acute porphyrias the use of phlebotomy or administration of heme can be used. (Thadani et al., 2000).
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Introduction

Porphyria results from an inherited or acquired error in heme metabolism. There are eight known types of porphyria namely congenital erythropoietic porphyria (CEP), hereditary coproporphyria (HCP), variegate porphyria (VP), erythropoietic protoporphyria (EPP), delta-aminolevulinic acid dehydratase (ALAD), acute intermediate porphyria (AIP), and porphyria cutanea tarda (PCT). PCT is further subdivided into I PCT, II PCT also known as hepatoerythropoietic porphyria (HEP), and III PCT. Some name confusion exists depending on the literature reviewed and the country in which the literature is published (Table 1). Types of porphyria are also categorized in many ways; by their clinical presentations; cutaneous or neurologic, or a mix of both, their functional site, hepatic or erythropoietic, or their type of attack, acute or non-acute (Table 2). Classification in the United States (U.S.) is usually either acute or non acute depending on presenting symptoms (Desnick, 2001).

Regardless of how porphyria is classified, the disease is caused by the accumulation of the by-products of a disrupted metabolism. These by-products or enzymatic substrates are called porphyrins, hence the name porphyria. As the system of heme synthesis is disrupted, an accumulation of porphyrins or their precursors are deposited in different bodily tissues such as urine, bone, skin, liver and kidney. The buildup of porphyrins causes the clinical picture seen in practice, such as severe abdominal pain, purple urine,
mental disturbances, skin disease or parathesias (Canadian Porphyria Foundation, n.d.). Porphyrins cause urine to look red or purple in sunlight due to fluorescent properties (Kamel, 1998). King George III of England is thought to have had porphyria because he had “purple urine” and sporadic bouts of madness (Arnold, 1996).

In general, all types of porphyria are influenced by genetic function. Each individual gene influences several enzymes and each porphyrin is generally influenced by more than one gene (Canadian Porphyria Foundation, n.d). All of the porphyrias are rare and if averaged together the incidence is about 1:100,000. These are the people who actually manifest the disease. Some forms of porphyria are recessive and some forms are dominant. People who have porphyria, but never express the disease are called “latent porphyrics” (Crimslick, 1997). As many as 80% of family members may be “latent”, having the genetic predisposition, but not the disease (Crimslick, 1997).

Porphyria is primarily inherited, but one form, porphyria cutanea tarda (PCT) can be acquired. Porphyria is also a disease of percentages, meaning that at least 50% of an enzyme must be dysfunctional, before the disease will express itself. Even then, porphyria is only expressed when the body is put under unusual stress.

Manifestation Theories

There have been many studies worldwide that have looked at the prevalence of porphyria. Of greatest concern and confusion are the acute porphyrias, as they are sporadic and often can be life threatening due to their neurological consequences. Because there is evidence that the number of cases are growing, new research is attempting to answer why.
One popular theory for the increase of porphyria, especially Porphyria Cutanea Tarda, is the increasing use of drugs, specifically those that use the cytochrome P450 (CYP450) system. The CYP450 system in the liver is critical in the production of certain cytochromes needed for cellular function. Drugs that induce the CYP450 system are the same drugs that increase the synthesis of amniolevulinic acid dehydratase (ALA) (Adams, 2001). The increase in ALA synthesis causes the system to be overwhelmed and the porphyrin by-products to build up, which triggers the disease. The increase in ALA synthesis may be the trigger that exposes “latent porphyrics” and disease manifestation (Thadani, Deacon & Peters, 2000).

The use of certain herbicides may also have an affect on heme biosynthesis in humans. Studies on mice at Charles University in Prague, Czech Republic, have shown that certain herbicides cause an oxidative reaction that inhibits protoporphyrinogen oxidase (Krijt, 1999). This inhibition disrupts heme biosynthesis and causes II PCT.

Another theory focuses on the overproduction of delta-amniolevulinic acid dehydrase (ALAD) and porphobilinogen (PBG). These enzymes are released into the circulation and are taken up by the nervous system, causing the neurological symptoms seen with the acute porphyrias, such as mental disturbances and severe peripheral neuropathy (Krijt, 1999).

Other studies are trying to find the reason for the seemingly unexplainable neurological symptoms associated with acute porphyrias. The hope is that answers regarding triggers and ways to prevent reoccurrences will be developed (Krijt, 1999). More research needs to be done to determine what environmental factors and drugs interfere with heme biosynthesis.
Definitions and Pathogenesis

There are eight enzymatic pathways used to create one porphyrin molecule. Each pathway creates and uses porphyrinogens which are reduced enzymes (Desnick, 2001). Porphyrinogens are tetrapyrrole pigment enzymes that serve as intermediaries in the heme biosynthesis pathway (Desnick, 2001). It takes eight enzymatic processes to create one oxidized porphyrin, which then binds with iron to create heme (Desnick, 2001). Each pathway is associated with an individual type of porphyria. If just one enzyme is missing or in short supply, the associated porphyrin is diverted out of the main heme pathway into side pathways that will produce porphyrin by-products (Rich, 1999). Most of these degraded porphyrin by-products are water soluble, and are excreted, as quickly as they are formed in urine and stool (Canadian Porphyria Foundation, n.d). The energy, created as the cells attempt to return the dysfunctional molecules to their original state, bind with oxygen and create free radicals (Kamel, 1998). Free radicals are the cause of most of the physiologic damage, and signs and symptoms of porphyria.

The heme pathway is vital to all organic life. Heme is made up of a molecule of iron and four molecules of porphyrins namely porphobilinogen, uroporphyrin, coproporphyrin, and protoporphyrin (Canadian Porphyria Foundation, n.d). The heme molecule makes blood red and plants green. Heme joins with protein globulins which in turn bind with oxygen to form oxyhemoglobin (Canadian Porphyria Foundation, n.d). The ability of the body to transport oxygen via oxyhemoglobin to every cell in the body is dependent on this system.
Heme is also necessary in the production of cytochrome and tryptophan pyrrolase, both of which are manufactured in the liver and are necessary for other cellular activities (Krijt, 1999). Erythroid cells in bone marrow produce about 85% of heme used to make hemoglobin (Desnick, 2001). The remainder of heme is made in the liver, which is under the control of a negative feedback system responding to levels of free heme, and suppressing alpha-aminolevulinic acid (ALA) (Desnick, 2001). ALA is the starting point of the heme biosynthesis pathway. ALA synthesis can be increased by many of the same drugs that influence cytochrome P450 (CYP450) system. Most of the heme in the liver is used to synthesize enzymes for the CYP450 system. The mechanism of porphyrin production is both mitochondrial and cytoplasmic and takes place in both the liver and bone marrow.

Each of the porphyrias is made up of the overproduction, accumulation, and excretion of the byproducts of heme biosynthesis (Desnick, 2001). The point in the pathway at which the mutation occurs, can often be the deciding factor in the severity of the disease. The heme pathway can still be completed successfully with as much as a 50% reduction in normal enzyme activity (Krijt, 1999). Any enzymatic reduction causes a compensatory increase in the substrates via a negative feedback mechanism (Elder, Hiff & Meissner, 1997). However, when the body is under increased stress such as acute illness, there is an increased need for energy. The increased energy demands increase and eventually overwhelm the heme biosynthesis pathway, specifically the CYP450 system, which in turn begins the overproduction of the entire heme pathway (Desnick, 2001).
Etiology and Epidemiology

Scientists have found through genome projects, as well as other research, the specific genes and alleles that are responsible for the porphyrias. Most cases of porphyria are inherited in an autosomal dominant way. Porphyria is found in every country and race, but the type of porphyria and country of origin will significantly affect the prevalence of the disease.

Although there is no official registry in the US, Acute Intermittent Porphyria (AIP) (gene location 11q23-q24.2) has an estimated prevalence of 5 per 100,000 people. Some literature state incidence rates as high as 1 in 10,000 (Sacher & McPherson, 2000). Some research shows upward of 90 different mutations of the porphobilinogen deaminase gene which is associated with AIP (Elder, Hiff & Meissner, 1997). AIP is autosomal dominant and affects women more than men (Shah, Remoza & Aziz, 2002). Acute Intermittent Porphyria is also the most common porphyria in Scandinavia and perhaps Great Britain (Desnick, 2001). There is also a higher incidence of AIP in the psychiatric patient population. Shah et al. (2002) report AIP in the general population at 1.5 per 100,000 and 2.1 per 100,000 in the psychiatric population. Crimslick (1997) makes note of several studies that report higher incidences of AIP in the acute mentally ill. Kaelbling, Craig and Passamanect first attempted to look at the prevalence of porphyria in the psychiatric population in 1961 (Crimslick, 1997). Their study demonstrated that 35 out of 2500 patient admitted for acute psychiatric problems had positive Watson-Schwartz reactions. The study used a screening test only and failed to do any diagnostic follow up (Crimslick, 1997). Tishler, Woodard and O’Connor in 1985 tested 4000 psychiatric patients for porphyria. Initial screening was done with a Watson-Schwartz
with further testing in all positive cases using 24-hour urine analysis of 5-aminolaevulinic acid (ALA) and porphobilinogen (PBG) (Crimslick, 1997). Of the 70 who screened positive, eight were believed to have acute manifestations of AIP based upon further enzyme assay of PBG and physical manifestations. Ten other patients were believed to be latent carriers, but not to manifest symptoms of acute porphyria, as their urine porphyrins were negative.

These studies show a definite increase in the prevalence of AIP in those patients tested upon admission to a hospital for acute psychiatric illness, such as schizophrenia, schizoaffective disorder and atypical psychoses (Crimslick, 1997). They show an incidence rate in the psychiatric population much higher than the general population. These studies however were flawed in their design. They lacked any control groups, did not have long term follow up, nor were they repeated in another geographical area. Making any direct correlation to AIP and acute psychosis therefore is inconclusive.

South Africa has the highest incidence of Variegate Porphyria (VP) (gene location 1q14). Whites are affected at 1:250 which can be traced back to one Dutch immigrant in 1688 (Crimslick, 1997). In the US, the prevalence of VP is 1:100,000 with women affected more than men (Desnick, 2001).

Delta-amniolevulinic acid synthase deficiency (ALAD) has both hepatic and erythroid aspects depending on which type of cell is affected (Desnick, 2001). The erythroid type is located in the bone marrow. The erythroid ALA (gene location Xp11.21) disease is an X-linked recessive sideroblastic anemia which is extremely rare (The Merck Manual, n.d.). As of 1997, there were only six known hepatic cases of delta-amniolevulinic acid dehydratase deficiency (ALAD) (gene location 9q34) worldwide
Because there have been so few cases there is no real pattern to describe. ALAD is autosomal recessive, and the first known cases were in two unrelated teenagers in Germany and an infant in Sweden (Desnick, 2001). There have been two reported cases of men in their 60’s from Japan and Belgium (Desnick, 2001).

Research continues to discover new combinations and alleles that have an effect on heme biosynthesis and the genetic causes of porphyria. Rates for all types of Porphyria Cutanea Tarda include (gene location 1q34) 4 per 1,000 people in some references and 1 in 25,000-50,000 in others (The Merck Manual, n.d.; Frye & DeLoughery, 2002). There are three types of Porphyria Cutanea Tarda (PCT) described in the literature. PCT is both an acquired and inherited disease, but all types have a deficiency in uroporphyrinogen decarboxylase (URO-D) (Desnick, 2001).

I PCT is spontaneously acquired, usually triggered by an environmental element and URO-D is deficient in all cells, except erythrocytes (Desnick, 2001). I PCT is the most common of all of the Porphyria Cutanea Tardas accounting for about 80% of all cases (Kim & Lim, 1999). II PCT is autosomal dominant and the URO-D enzyme is deficient in all tissues (Kim & Lim, 1999). III PCT is deficient in URO-D only in the liver (Desnick, 2001).

In Turkey in 1954, an accidental exposure to the chemical hexachlorobenzene (HCB) caused 5,000 people to develop I PCT (Kim & Lim, 1999). The Turkish people ingested wheat seed that was treated with a fungicide using HCB. The seed was originally intended to be planted, not eaten directly and it overwhelmed the CYP450 system in the liver and triggered PCT (Kim & Lim, 1999).
Hereditary Coproporphyria (gene location 3q12) is autosomal dominant with an incidence of 1:100,000 (Frye & DeLougherty, 2002). Age of onset is usually early adulthood, although there are rare cases in children (Frye & DeLougherty, 2002).

Erythropoietic Protoporphyria (EPP) (gene location 18q21.3 or 22) is an autosomal dominant disorder and is the third most common porphyria (The Merck Manual, n.d.). There are many possible mutations for each gene. The type of mutation, gene affected, and number of defects inherited predict the severity of porphyrias symptoms, especially with EPP (The Merck Manual, n.d.). The prevalence of EPP can not be definitively stated, because there is no national clearing house for porphyria statistics. Some literature suggests the prevalence at 2:10,000 (Frye & DeLougherty, 2002). The disease affects men and women equally and presents in early childhood with photosensitivity changes (The Merck Manual, n.d.).

Congenital Erythropoietic Porphyria (gene location 10q25.2->q26.3) is a rare autosomal recessive disorder with fewer than 200 known cases in the US (The Merck Manual, n.d.). It affects all races and males and females equally. There are many different mutations of any one gene and patients usually need to inherit two different mutations to produce CEP. Symptom severity depends on the degree of enzyme deficiency, which is determined by the combination of gene mutations inherited (The Merck Manual, n.d.).

Within all types of porphyria there are several factors thought to trigger the onset of illness. Hepatic or erythropoietic cells can usually function with 50% of a particular porphyrin without any difficulty. It is therefore very important to know what triggers the clinical picture of porphyria. All porphyrias can be triggered by drugs, alcohol, liver
disease, fasting, infection, smoking and sex hormones (Thadani, Deacon & Peters, 2000). Sunlight also triggers attacks in most of the porphyrias, but has no effect on Acute Intermittent Porphyria (AIP) and delta-aminolevulinic acid dehydratase deficiency (ALAD) which manifest with neurologic disorders only (Crimslick, 1997).

Clinical Features in Diagnosis

There is no universally accepted classifications system for porphyria. Literature uses presentation of the illness as one way of classifying porphyria, with location of the defective enzymes or whether there are cutaneous symptoms as some of the factors considered (Table 2). The difference between acute and non-acute porphyrias is that acute disease manifests neurological symptoms and non-acute does not. Neurological symptoms that manifest rapidly can be life threatening.

Acute Porphyrias include delta-aminolevulinic acid dehydratase deficiency (ALAD), Acute Intermittent Porphyria (AIP), Variegate Porphyria (VP), and Hereditary Coproporphyria (HCP). All these types present with attacks of acute abdominal pain, limb weakness or parathesias and various mental status changes (Adams, 2001). Neurological and gastrointestinal symptoms are thought to result from neuronal dysfunction caused by irregularity of the myelin sheaths, degeneration and axon abnormalities (Crimslick, 1997). Photosensitive changes are seen in all acute patients except those with AIP and ALAD.

Non-acute Porphyrias include Congenital Erythropoietic Porphyria (CEP), Erythropoietic Protoporphyria (EPP) and Porphyria Cutanea Tarda. These porphyrias present with cutaneous changes and have no neurological symptoms. Why a porphyria
presents with neurological versus cutaneous symptoms has to do with the type of porphyrin involved. Each type of porphyrin is excreted in a different way. Some of the porphyrins are deposited in the epidermal layer of the skin. These porphyrins are highly reactive to sunlight releasing free radicals, which are the cause of the skin damage. Some porphyrins react with neurological tissues, causing neurovisceral and mental status changes. The provider can often determine what type of porphyria a person has by the presenting symptoms.

The Acute Porphyrias

Acute Intermittent Porphyria (AIP), a hepatic porphyria, is the most common and severe of the acute porphyrias (Adams, 2001). Normally, onset is in early adulthood. Patients will present with acute abdominal pain that is usually constant and poorly localized. It is often described as colicky or cramping pain. Decreased bowel sounds, ileus and edema are common and the patient may or may not have nausea, vomiting and constipation (Desnick, 2001). Patients may also present with neurological signs, such as limb weakness or parathesias. Patients will not have increased abdominal tenderness with palpation, fever or leukocytosis as the gastrointestinal symptoms are of a neurologic origin, not inflammatory (Desnick, 2001). Presentation with sympathetic over-activity such as hypertension, tremors, excess sweating and tachycardia are also very common (Desnick, 2001). Many people will present with limb weakness and mental status changes. Of greatest concern, are the possibilities of seizures and truncal weakness leading to respiratory paralysis (Adams, 2001). Lab values are usually normal with the exception of hyponatremia caused from syndrome of inappropriate anti-diuretic hormone
(SIADH) secretion (Shah, Remoroza, & Aziz, 2002). It is unknown why SIADH occurs only in AIP, but autopsy findings have shown damage to the supraoptic nuclei of the hypothalamus, which may trigger anti-diuretic hormone release (Shah, Remoroza & Aziz, 2002). The loss of sodium may be a precipitating factor in the development of seizures (Shah, Remoroza & Aziz, 2002).

Urine color may often be the first visible indicator of the disease. If the urine is collected during an acute attack and left in the sun it will often change colors. In AIP, urine may be dark brown, red or any combination of these colors. Urine is not always discolored with porphyria so lack of color shouldn’t dissuade a practitioner from including porphyria in the differential diagnosis. Patients may present with any variety of symptoms or with only one or two. All symptoms are manifestations of a neurovisceral and neuropsychiatric origin (Shah et al., 2002). The exact pathology that triggers neurological symptoms is unknown. Severe acute diffuse abdominal pain with other gastrointestinal symptoms are the most common and have been mistaken for an acute abdomen, and surgery has been performed (Shah et al., 2002).

Delta-amniolevulinic Acid Dehydratase Deficiency (ALAD) is the rarest of all of the porphyrias (The Merck Manual, n.d.). The earlier the presentation of symptoms, the poorer the prognosis. ALAD presents in much the same way as Acute Intermittent Porphyria, except it may also present with hemolysis and anemia (The Merck Manual, n.d.). The sub-group of ALAD, known as x-linked sideroblastic anemia (XLSA), is a deficiency of ALA in the bone marrow affecting red cell production (Desnick, 2001). XLSA affects males who usually present as infants with pallor, weakness and anemia (Desnick, 2001). Patients usually develop secondary splenomegaly, iron overload and
can develop hemosiderosis (Desnick, 2001). This disease can only be diagnosed with a bone marrow biopsy and genetic tests as all standard porphyria tests are normal.

Variegate Porphyria (VP) is a hepatic porphyria. Patients may have a homozygotic or heterozygotic form (Desnick, 2001). VP is usually first seen in young adults and presents in the same way as AIP, but may have photosensitivity, as well. Neurovisceral symptoms and cutaneous symptoms usually don’t appear together, so it is not uncommon for the initial diagnosis to be Porphyria Cutanea Tarda, if the patient presents with skin lesions (Desnick, 2001). Further testing must always be done to determine the type of porphyria. Skin manifestations are more prevalent in warmer climates, presumably because people are more exposed to the sun. Interestingly, homozygous patients have a much greater likelihood of having developmental disturbances, such as growth retardation (Desnick, 2001). VP is caused by a deficiency in protoporphyrin, but all cases of homozygous porphyria also have increased levels of erythrocyte zinc protoporhyrins, which is characteristic (Desnick, 2001).

Hereditary Coproporphyria (HCP) is a hepatic porphyria because the over production and accumulation of coproporphyrinogen oxidase occurs in the hepatocytes (Desnick, 2001). Presenting symptoms are nearly identical to AIP, although usually milder (The Merck Manual, n.d.). Symptoms usually present for the first time during puberty and are more common in women (Desnick, 2001). Unlike AIP, photosensitivity may occur, but less frequently than Variegate Porphyria. HCP may appear in early childhood in rare homozygous cases (Desnick, 2001).
Non-acute Porphyrias

Porphyria Cutanea Tarda (PCT) is the most common of all porphyrias. There are three types namely I, II, and III. Classification is based on if they are acquired, type I, or if they are inherited, types II and III. II PCT, also known as Hepatoerythropoietic Porphyria, effects both hepatic and erythropoietic cells (The Merck Manual, n.d.). Type III effects hepatic cells only. The only real difference in the types of PCT is that the hereditary forms may present earlier in life.

PCT is more common in men. Age of onset is usually in the thirties. Women may present at a younger age due to the use of birth control pills which manipulate sex hormones (Fitzpatrick, Johnson, & Wolff, 2001). Estrogen is a known trigger for any of the porphyrias (Fitzpatrick, Johnson, & Wolff, 2001). In some areas of the world, 80% of those with PCT also have hepatitis C (HCV) (The Merck Manual, n.d.). Type I PCT can be acquired and may trigger destruction of hepatocytes. Destruction may eventually lead to cirrhosis or fatty infiltrates requiring a transplant (Figures 2, 3 & 4) (Thadani, Deacon, & Peters, 2000). Human immunodeficiency virus (HIV) is also associated with an increased likelihood of developing PCT (O’Connor, Badley, Dicken & Murphy, 1998). Co-morbidity of HIV and HCV dramatically increases the risk of acquiring PCT. Any young adult diagnosed with PCT should prompt practitioners to further investigate for HIV and HCV infections (O’Connor, Badley, Dicken & Murphy, 1998).

Porphyria Cutanea Tarda patients often present with alterations in skin, specifically bullae in varying degrees of development or healing on sun exposed areas (Figure 5). There are no neurovisceral or mental status changes in PCT. Changes in the skin come on slowly with no real acute phase (Fitzpatrick, Johnson & Wolff, 2001). Early changes
in the skin are erythema, edema, pruritis and blisters (Habif, Quitadamo, Campbell & Zug, 2001). Later changes are erosions at previous bullae sites, milia 1-5 mm and small atrophic scars (Figure 6). They may have waxy yellowish, white areas on exposed parts of the neck, face and trunk (Habif, Quitadamo, Campbell & Zug, 2001). Patients may eventually have excessive facial hair growth, especially the periorbital and temporal areas and in severe disease, the torso (Habif, Quitadamo, Campbell & Zug, 2001). The most commonly affected areas are the dorsa of the hands and feet, as well as the face and neck.

Another common characteristic of PCT is the skin's friability. The smallest scratch may result in large bullae and patients bruise easily (Fitzpatrick, Johnson & Wolff, 2001). PCT may also produce purple urine in an acute attack due to excretion of uroporphyrin, which has fluorescent properties (Rich, 1999).

Another disease to consider in PCT diagnosis is Pseudo PCT. Pseudo PCT will produce blisters that are indistinguishable from PCT (Fitzpatrick, Johnson & Wolff, 2001). Pseudo PCT is brought on by a reaction to drugs (naproxen, dapsone, cyclosporine and others), chronic renal failure with hemodialysis, tanning salon radiation, and other associated conditions (Sjogren's syndrome, lupus, hepatitis C) (Fitzpatrick, Johnson & Wolff, 2001). To differentiate Pseudo PCT from PCT, biopsy and lab tests need to be done.

With Congenital Erythropoietic Porphyria (CEP) symptoms are usually observed shortly after birth, although there have been a few cases of adult onset. Initial symptoms are severe blistering skin and dark red urine followed by anemia (The Merck Manual, n.d.). CEP has no neurological or neurovisceral symptomatology. Severe cases have presented in utero as utero hydrops with amniotic fluid becoming red from high
porphyrin content (The Merck Manual, n.d.). Just as with Porphyria Cutanea Tarda (PCT) the skin is photosensitive, producing bullae and erosions. The main difference between PCT and CEP is the severity and high risk for secondary infections. CEP can be severe enough that the child will have severe scarring with possible loss of facial features or digits (The Merck Manual, n.d.). Changes in skin pigmentation and hirsutism are common. Corneal scarring can be severe enough to cause blindness and the teeth turn red- brown due to porphyrin deposits (The Merck Manual, n.d.). Anemia, hepatosplenomegaly with resultant leukemia, and thrombocytopenia are typical (Desnick, 2001). Ironically, the anemia stimulates bone marrow to produce more erythrocytes, which ultimately increases the amount of porphyrins produced.

Erythropoietic Protoporphyria (EPP) is an erythroid porphyria. The protoporphyrin builds up in the bone marrow and erythrocytes, where it is eventually excreted by the liver into bile and feces (The Merck Manual, n.d.). Clinical features of the disease are pain, itching, edema and redness of the skin immediately after sun exposure resembling angioedema (Desnick, 2001). The skin manifestations are unlike the other cutaneous diseases. EPP rarely produces bullae, pigment changes, friability, severe scarring or hirsutism (Desnick, 2001). Chronic manifestations may produce lichenification, pseudovesicles and nail changes (Desnick, 2001). Anemia or hemolysis rarely occur, but the excessive protoporphyrin can cause chronic liver disease leading to liver failure (Desnick, 2001).
Laboratory Testing

A definitive diagnosis of porphyria is made with laboratory tests (Table 3). Deficiency of a particular enzyme leads to overproduction of porphyrins or their precursors and they can be measured in urine, feces, and blood. The water solubility of individual porphyrins is what determines the route of excretion and therefore where they can be found (Thadani, Deacon & Peters 2000).

Urine porphyrin tests need to be done during an acute attack, as the tests may be normal at other times (Crimslick, 1997). The urine sample must also be protected from light as porphyrins can decrease by up to 50%, if left in the light for 24 hours. Presenting symptoms will determine which tests to order (Figure 7).

Acute neurovisceral symptoms indicate first line testing for urine alpha amniollevulinic acid (ALA) and porphobilinogen (PBG) (The Merck Manual, n.d.). With photosensitivity symptoms, total plasma porphyrins should be checked (The Merck Manual, n.d.). First line tests are generally qualitative, such as the Watson-Swartz test. These tests are known to have significant false positive and false negative results therefore all positive tests should be followed up by quantitative tests (Crimslick, 1997).

Any abnormalities in first line tests should prompt providers to further investigate. Second line testing for acute neurovisceral and photosensitive symptoms include 24 hour urine ALA and PBG, total fecal porphyrins, erythrocyte PBG deaminase and total plasma porphyrins (The Merck Manual, n.d.).

The type of porphyrin in the test samples will be the determining factor as to what type of porphyria the person has (Wallach, 2000). Not all porphyrins are deposited in all
tissues. Skin biopsies may also be done on lesions to determine porphyria, if other lab tests are negative (Fitzpatrick, Johnson & Wolff, 2001).

Differential Diagnosis

Unfortunately for many sufferers the diagnosis of porphyria can take time. The many different ways porphyria manifests itself can lead to a host of misdiagnoses (Crimslick, 1997). The clinical course of acute porphyrias can be sporadic or chronic and present itself in unlimited ways. Mental disturbances can lead to misdiagnoses of schizophrenia and acute psychosis (Crimslick, 1997). Making things more confusing is the apparent "normalcy" of the patient between attacks. Family members of porphyrics have also been shown to have a greater incidence of anxiety disorders, leading many practitioners to wonder if they are latent porphyrics (Crimslick, 1997). Women's hormones can play a big role in confusing clinicians. The monthly luteal phase can sometimes trigger emotional outbreaks and lead to a diagnosis of premenstrual syndrome, premenstrual tension or even cycloid psychoses (Crimslick, 1997). Some small family case studies have shown a wide variety in psychiatric symptoms, such as aggression, impulsive behavior, delusions, paranoia, hyperactivity, emotional lability, insomnia, grandiosity and severe depression (Crimslick, 1997). Unfortunately most of the larger studies of porphyria have been done by neurologists or other physicians and therefore the prevalence of psychiatric disorders may not have been fully examined.

The confusing array of physical symptomatology makes diagnosis very difficult. The symptoms may be mild or severe, as well as chronic. Neurological and dermatologic symptoms are the hallmarks of porphyria. The neurological symptoms encompass both
mental status and physical finding. The neuropathy in porphyria is mainly motor weakness and paresis. Weakness begins proximally and usually in the upper limbs (Crimslick, 1997). Reflexes are often diminished or absent. Paresis is often focal and may involve cranial nerves especially III, VII, and X. Symptoms may progress and cause seizures, cardiac disturbances or respiratory difficulties (Desnick, 2001).Sympathetic nerves are sometimes profoundly affected and may cause sudden cardiac death (Desnick, 2001). Depending on presentation and severity of symptoms, diagnoses such as multiple sclerosis, bells palsy, brain tumors and a host of others have often been the initial diagnosis (The Merck Manual, n.d.).

Abdominal symptoms such as severe colicky pain, constipation, vomiting, distention, and decreased bowel sounds are all common findings (Desnick, 20010). Pain often seems out of proportion to the actual physical findings and has been mistaken for an acute abdomen. Unnecessary surgeries to remove gallbladders and appendixes have been done in cases of Acute Intermittent Porphyria (The Merck Manual, n.d.). Lead poisoning and tyrosinemia must also be ruled out (DeSiervi, Vasquez, Rezaval, Rossetti & del Batlle, 2001). Tyrosinemia is a rare, usually benign, disorder of excessive amounts of the amino enzyme, tyrosine. Lead poisoning may produce the same neurological effects as any acute porphyria.

Dermatological findings are less confusing, as biopsy can determine the disorder in most cases. The condition of the skin at time of presentation might confuse the clinical picture. Patients often present for friable skin or hypertrichosis, both of which can be caused from adrenal dysfunctions (Fitzpatrick, Johnson, & Wolff, 2001). There may be just one crusted lesion or a small blister which could be indicative of contact dermatitis or
impetigo (Fitzpatrick, Johnson, & Wolff, 2001). Often the key to diagnosis is the location of the lesions which are almost exclusively in sun exposed areas. Generally, it is common practice to get a biopsy of any suspicious lesion, which would then be diagnostic of porphyria although not the variety (Fitzgerald, Johnson, Wolff & Suurmond, 2001).

Treatment

There is no cure for any of the porphyrias except for possibly Congenital Erythropoietic Porphyria (CEP). In the early 1990’s, a successful bone marrow transplantation was done on an eighteen month old with CEP. The patient has been doing well and the treatment has proven curative to date (The Doctor’s Doctor, 2002). This research has given some validity to stem cell research into treatment of the erythroid type of porphyrias and other bone marrow disorders (The Doctor’s Doctor, 2002).

Treatment for all of the acute porphyrias is essentially the same. Acute attacks require hospitalization for IV infusion of heme. The heme is taken up by the liver and works on a negative feedback system to reduce production of amniolevulinic acid (ALA) and porphobilinogen (PBG) and slow the heme biosynthesis pathway (The Merck Manual, n.d.). In the USA heme is available in the form of lyophilize hematin, heme albumin and heme arginate (Desnick, 2001). Heme lyophilize is very irritating to the vascular system and phlebitis is common (The Merck Manual, n.d.). Heme should be given, as soon as possible as the treatment becomes less effective with time and permanent nerve damage could occur, if treatment is delayed (Desnick, 2001). PBG urine levels will markedly decrease each day with therapy. IV glucose can also be
given, but is less effective than heme therapy. Treatment for seizures can be difficult as all anti-seizure medications are unsafe except for bromides and maybe gabapentin (Desnick, 2001). Treatment for hyponatremia should be initiated early to help prevent seizure activity. Beta blockers may be used to control hypertension and tachycardia if needed (The Merck Manual, n.d.). Symptomatic treatment for pain with opiates, nausea and vomiting with phenothiazine, and anxiety with low dose benzodiazepines is indicated (The Merck Manual, n.d.).

The best treatment for any of the acute porphyria is strict avoidance of known triggers. Harmful drugs and crash diets must be avoided (Table 4). Patients will need to counseled to maintain a relatively high carbohydrate intake (Desnick, 2001). The brief period of time of fasting before and immediately after surgery has triggered acute attacks (The Merck Manual, n.d.). Menstruation may also precipitate attacks and may be treated with low dose estrogen and gonadotropin-releasing hormones (The Merck Manual, n.d.). Oral contraceptives may help but there is risk that progestin may trigger an attack (The Merck Manual, n.d.).

Alpha amniolevulinic acid (ALAD), Varigate Porphyria (VP), and Hereditary Coporphyria (HCP) all have acute symptoms and are treated the same as AIP. Any cutaneous symptoms with VP and HCP are treated individually.

Porphyria Cutanea Tarda (PCT) presents the classic picture of cutaneous changes associated with porphyria although treatment for any of the cutaneous symptoms is nearly identical. Avoidance of sunlight is critical to prevent the development of skin abnormalities (The Merck Manual, n.d.).
Iron supplementation, alcohol, drugs and estrogens should also be avoided as part of treatment (Desnick, 2001). Phlebotomy may also be needed to reduced iron stores and prevent tissue damage, namely cirrhosis and hepatic fibrosis (The Merck Manual, n.d.). Frequent complete blood counts and ferritin levels may need to be done to monitor for anemia and iron stores (The Merck Manual, n.d.). PCT can also be treated with small doses of chloroquine or hydroxychloroquine, both bind with excess porphyrins and promote their excretion (Desnick, 2001).

Congenital Erythropoietic Porphyria (CEP) is similar to PCT, but much more severe. Because CEP is more sensitive to sunlight, strict avoidance is mandatory. Patients may also benefit from red blood cell transfusions, which suppresses erythropoiesis but leads to iron overload (The Merck Manual, n.d.). CEP can also cause severe hemolysis and splenectomy may be indicated (The Merck Manual, n.d.). The ultimate treatment may be a bone marrow transplant, but it is still experimental at this point.

Erythropoietic Protoporphyria (EPP) is treated the same as PCT. The only difference may be the improved tolerance to sunlight with the addition of beta carotene (Desnick, 2001). For Variegate Porphyria (VP) and Hereditary Coporporphyria (HCP), the only treatment is to avoid sunlight. VP and HCP do not respond to chloroquine, beta carotene or phlebotomy.

For any of the porphyrias avoidance of triggers is the mainstay of treatment. It is also important to provide for genetic counseling for the patient and their family to discover who may be a carrier or be susceptible to the disease.
Conclusion

Porphyrsins are necessary for heme biosynthesis and therefore life. Without porphyrsins, humans can not make heme molecules which are necessary in the transport of oxygen. Fortunately, the heme biosynthesis pathway can be completed without difficulty with as little as 50% of needed enzymes. This fact is what allows most porphyrics to function normally. Research allows us to identify porphyria triggers and ways to treat other disease.

Research is currently being done using porphyrsins to target cancer cells. Work done by De Siervi et al., (2001), shows promise in promoting hepatocarcinoma cell apoptosis with the introduction of alpha amniolevulinic acid (De Siervi, Vasquez, Rezaval, Rossetti & del Batlle, 2001). Their work has been confined to the laboratory, but current results are very exciting.

Another avenue of research involves the use of photodynamic therapy. In the 1970’s while scientists were attempting to find a cure for porphyria, they wondered if porphyrsins could be injected into cancerous tissue (Lane, 2003). The tissue could then be exposed to a light source that would cause destruction of the cancer. This was the beginning of what is now known as photodynamic therapy (PDT) (Lane, 2003). Most recently, PDT is being used for treatment of macular degeneration and pathologic myopia (Lane, 2003). There is current research using PDT for coronary artery disease, AIDS, autoimmune diseases, transplant rejection and leukemia (Lane, 2003). Treatment difficulties in using PDT are the red light used to trigger the porphyrsins can only penetrate a couple of centimeters therefore limiting its use in internal medicine. With the advent of the
laproscope, getting a light source close to target tissue has been much more effective and safer (Lane, 2003). As more is known about porphyrins, their use to treat other disease grows.

Although porphyria cutanea tarda (PCT) is rare, it is on the rise. PCT is not generally life threatening, but it can be physically and emotionally scarring. In Tammy Evans book, Porphyria: The woman who has the vampire disease, she discusses in great detail the emotional scars of being shunned by a society that places such a high value on outward appearances. She tells of her struggles to discover what disease she had and how to treat it. This book reminds all health care providers that compassion is a vital part of any treatment.

More research is needed to discover ways to treat porphyria and prevent reoccurrences. Key to current treatment is first recognizing the disease itself. Porphyria can mimic other diseases, therefore making it challenging for clinicians to diagnose. Health care providers must always consider the interaction of drugs and their effect on the CYP450 system. Early diagnosis can be the difference between life and death in the acute porphyrias. Patient and family education are the corner stone of prevention and treatment of porphyria. All healthcare providers should consider porphyria in their differential diagnoses of unexplained abdominal pain, sudden mental disturbances and scarring skin disorders.
Table 1: Porphyria Synonyms

<table>
<thead>
<tr>
<th>PORPHYRIAS AND SYNONYMS</th>
<th>Uroporphyrinogen III synthase deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital erythropoietic porphyria (CEP)</td>
<td>Hereditary erythropoietic porphyria</td>
</tr>
<tr>
<td></td>
<td>Congenital hematoporphryia</td>
</tr>
<tr>
<td></td>
<td>Erythropoietic uroporphryia</td>
</tr>
<tr>
<td></td>
<td>Gunther Disease</td>
</tr>
<tr>
<td>Porphyria cutanea tarda (PCT)</td>
<td>Symptomatic porphyria</td>
</tr>
<tr>
<td></td>
<td>Uroporphyrinogen decarboxylase deficiency</td>
</tr>
<tr>
<td></td>
<td>Idiosyncratic porphyria</td>
</tr>
<tr>
<td>Hepatoerythropoietic porphyria (HEP)</td>
<td>Homozygous type II PCT</td>
</tr>
<tr>
<td></td>
<td>II PCT</td>
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<tr>
<td>Hereditary coproporphyia (HCP)</td>
<td>Coproporphyria</td>
</tr>
<tr>
<td></td>
<td>Coproporphyrinogen oxidase deficiency</td>
</tr>
<tr>
<td>Variegate porphyria (VP)</td>
<td>Protoporphyrinogen oxidase deficiency</td>
</tr>
<tr>
<td></td>
<td>South African porphyria</td>
</tr>
<tr>
<td></td>
<td>Porphyria variegate</td>
</tr>
<tr>
<td></td>
<td>Protocoproporphyria hereditaria</td>
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<td>Erythropoietic protoporphyia (EPP)</td>
<td>Protoporphyria</td>
</tr>
<tr>
<td></td>
<td>Ferrochelatase deficiency</td>
</tr>
<tr>
<td></td>
<td>Erythrohepatic porphyria</td>
</tr>
<tr>
<td>ALA dehydratase (ALAD)</td>
<td>ALAD deficiency</td>
</tr>
<tr>
<td></td>
<td>PBG-synthase deficiency</td>
</tr>
<tr>
<td></td>
<td>ALA dehydrase deficiency</td>
</tr>
<tr>
<td></td>
<td>ALA-uria</td>
</tr>
<tr>
<td></td>
<td>Doss porphyria</td>
</tr>
<tr>
<td>Acute intermittent porphyria</td>
<td>Hydroxymethylbilane synthase deficiency</td>
</tr>
<tr>
<td></td>
<td>Intermittent acute porphyria</td>
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<td></td>
<td>Waldenstrom porphyria</td>
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<td></td>
<td>Pyrroloporphyria</td>
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<tr>
<td></td>
<td>Swedish porphyria</td>
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References:
**Table 2:** Classifications of Porphyrias

<table>
<thead>
<tr>
<th>Name</th>
<th>Neurologic</th>
<th>Cutaneous</th>
<th>Hepatic</th>
<th>Erythropoietic</th>
<th>Acute</th>
<th>Non-acute</th>
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<tr>
<td>ALA dehydrase (ALAD)</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>Acute intermittent porphyria (AIP)</td>
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<td>X</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Congenital erythropoietic porphyria (CEP)</td>
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<td></td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Erythropoietic protoporphyrion (EPP)</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variegate porphyria (VP)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Porphyria cutanea tarda (PCT)</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hereditary coproporphyrion (HCP)</td>
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<td>X</td>
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References:


### Table 3: Laboratory Testing

<table>
<thead>
<tr>
<th>Type</th>
<th>Urine</th>
<th>Feces</th>
<th>RBC's</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALA Dehydrase Deficiency (ALAD)</td>
<td>ALA, Copro</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Hepatoerythropoietic Porphyria (HEP) (also known as II PCT)</td>
<td>Uro&gt;Copro PBG not increased, ALA may be slightly increased</td>
<td>Iso&gt;Copro</td>
<td>Increased Zinc-proto</td>
</tr>
<tr>
<td>Variegate Porphyria (VP)</td>
<td>Increased ALA and PBG during attacks*</td>
<td>Proto stays constant</td>
<td>Negative</td>
</tr>
<tr>
<td>Congenital Erythropoietic Porphyria (CEP)</td>
<td>Elevated Uro I; Watson-Schwartz negative, Copro increased</td>
<td>Copro</td>
<td>Uro; fluorescent under UV light</td>
</tr>
<tr>
<td>Erythropoietic Protoporphyria (EPP)</td>
<td>Negative</td>
<td>Proto</td>
<td>Proto</td>
</tr>
<tr>
<td>Acute Intermittent Porphyria (AIP)</td>
<td>ALA and PBG increased during attack*; Watson-Schwartz positive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Porphyria Cutanea Tarda (PCT)</td>
<td>Uro&gt;Copro is elevated; PGB is normal; ALA may be slightly increased</td>
<td>Iso&gt;Copro</td>
<td>Negative</td>
</tr>
<tr>
<td>Hereditary Coroporphria (HP)</td>
<td>Increased Copro; ALA and PGB are increased during acute attack*</td>
<td>Copro is constant</td>
<td>Negative</td>
</tr>
</tbody>
</table>

ALA=Delta-amniolevulinic acid
Iso=Ispoproporphyrin
PGB=Porphobilinogen
Copro=Coproporphyrin
Uro=Uroporphyrin
Proto=Protoporphyrin

Watson-Swartz test is a test based on the premise that porphobilinogen is insoluble in chloroform and butanol.

References:

### Table 4: Drug safety

<table>
<thead>
<tr>
<th>Drugs Thought to be Safe</th>
<th>Drugs Thought to be Unsafe</th>
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<tbody>
<tr>
<td>Acetaminophen</td>
<td>Amiodarone</td>
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<tr>
<td>Aminoglycosides</td>
<td>Barbiturates</td>
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<td>Amitriptyline</td>
<td>Bromocriptine</td>
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<td>Aspirin</td>
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<td>Atropine</td>
<td>Carisoprodol</td>
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<tr>
<td>Bromides</td>
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<td>Diclofenac</td>
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<td>Digoxin</td>
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<td>Diphenhydramine</td>
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<td>Thyroxin</td>
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<tr>
<td>Vitamins A,B,C,D, &amp; E</td>
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</tbody>
</table>

References:

**Figure 1:** Heme Biosynthesis

THE HEME BIOSYNTHETIC PATHWAY

**DISEASES & INHERITANCE PATTERNS**

ALAD dehydrase deficiency (ALAD) ........................................... *Delta amino levulinic acid (ALA)*

(AR, 9q34)

MITOCHONDRIA

Acute intermittent porphyria (AIP) ........................................... *Porphobilinogen (PBG)*

(AD, 11q23-q24.2)

Congenital erythropoietic porphyria (CEP) ............................. *Hydroxymethylbilane*

(AR, 10q25.2-q26.3)

Porphyria cutanea tarda (PCT) .............................................. *Uroporphyrinogen III*

(AD, 1q34)

Hereditary coproporphyria (HCP) ......................................... *Coproporphyrinogen III*

(AD, 3q12 & 9)

CYTOSOL

Variegate porphyria (VP) .................................................... *Protoporphyrinogen IX*

(AD, 1q24)

Erythropoietic protoporphyria (EPP) ...................................... *Protoporphyrin IX*

(AD, 18q21.3 & 22)

MITOCHONDRIA

* Representation of the sequential order of enzymatic reactions in the production of heme. The heme pathway takes place in both the mitochondria and the cytosol of the cell.

AD: Autosomal Dominant; AR: Autosomal Recessive; numbers in parenthesis represent the gene loci

References:

**Figure 2:** Liver cirrhosis as seen by CT

Destruction of hepatocytes leading to cirrhosis and liver failure. In this picture the liver is enlarged, which is seen with cirrhosis.

**Figure 3:** Fatty liver as seen by CT

*As the hepatocytes are destroyed, plaques of fat are laid down causing the infiltrates seen on CT. In this picture the liver is enlarged and the white streaks represent fatty infiltrates.

*It is believed that the excessive levels of porphyrins, specifically ALA, cause oxidative damage to cellular proteins and DNA. The abnormal DNA can trigger cancer.

**Figure 5:** Bullae of the skin

* Large clear fluid filled blisters in areas of sun exposure.

**Figure 6:** Hand scaring and lichenification of PCT

* Areas of sun exposed skin will have old healing sores, discoloration and thickening of the skin as well as small scars.

**Figure 7: Algorithm**

Subjective: severe abdominal or peripheral pain, nausea, hallucinations, depression, anxiety, limb weakness, constipation, itching, burning sensation

Objective: changes in color of urine, mental status abnormalities, sensory changes, hypotension, anemia, parasthesias, skin changes in sun exposed areas, decreased bowel sounds, ileus, vomiting, diarrhea, tachycardia, hypertension, tremors, seizures

History: Medical History, especially any history of unexplained symptoms. Family history of skin disorders? Family history of Porphria?

Skin Changes
(Bulles, scaring, itching or erythema in sun exposed areas)

No current or History of Skin changes

Abdominal Pain?

YES

Mental Status Changes?

YES

Urine ALA & PBG

NO

Unlikely Acute Porphyria
(If high suspicion based on other s/s or family Hx do Urine ALA & PBG)

YES

Urine ALA & PBG Analysis

NO

Biopsy Lesions
(Positive results do follow up blood tests)

Total Plasma Porphyrins

References:


References


