Emma Hoover

Dr. Van Laar

BIOL 3350

13 July 2023

Disease Paper: Porphyria Variegata

**Description**

Porphyria variegata is a rare metabolic disorder caused by a single gene mutation. This specific type of porphyria is a variety of acute porphyria of which there are three additional forms (Norton *et al*. 2016). Porphyria variegata occurs due to a rare mutation in the protoporphyrinogen oxidase (*PPOX*) gene which leads to mutated enzymes that normally function to synthesize heme, a component of hemoglobin. (Vafaee-Shahi *et al*. 2022). The *PPOX* gene is located on the q arm of chromosome one at location 22, 1q22 (Besur *et al*. 2015). The mutation of this gene results in partial deficiency of the seventh enzyme, protoporphyrinogen oxidase, in heme biosynthesis. As a result, aminolevulinic acid (ALA), a porphyrin precursor that is the rate-limiting step in heme synthesis, and porphobilinogen deaminase (PBG), the third enzyme involved in heme synthesis, are overproduced, leading to porphyrin over-production (Norton *et al*. 2016). These porphyrins and porphyrin precursors accumulate in the body. In addition, deficiency of *PPOX* causes porphyrins to oxidize and turn into protoporphyrin and coproporphyrin, resulting in the affected person’s skin being more sensitive to sunlight (Vafaee-Shahi *et al*. 2022).

Although porphyria variegata is caused by the mutation of one gene, there can be two different mutations of the *PPOX* gene that result in the disorder. Homozygous porphyria variegata has been correlated with the missense mutations in exons six and ten where G to A transitions occurred, coding for the wrong amino acid. On the other hand, heterozygous porphyria variegata has been correlated with the missense mutations D349A and A433P (Vafaee-Shahi *et al* 2022). For those diagnosed with this genetic disease, being heterozygous is more common than homozygous cases. In the case of heterozygotes, the activity of *PPOX* is about 50 percent in the patient’s tissue and mitochondria since they will have inherited one fully functioning gene from an unaffected parent (Norton *et al*. 2016).

**Transmission**

Porphyria variegata is not spontaneous nor a disease that is developed later in life after the accumulation of mutations. Instead, it is an autosomal dominant trait that is inherited. Any offspring of an affected individual with porphyria variegata have a 50 percent chance of inheriting the genetic mutation themselves, however, the severity of the disease may differ from that of the parent (Vafaee-Shahi *et al.* 2022). Usually, one parent of a person diagnosed with porphyria variegata is heterozygous for the *PPOX* mutation, but they may or may not have been symptomatic (Singal and Anderson 2019). If a family member is affected by porphyria variegata, prenatal testing can be conducted to determine if the offspring has an increased risk of the disease. However, the presence of a mutated PPOX gene in a fetus does not predict when, or if, symptoms will show later in life (Singal and Anderson 2019).

**Symptoms**

The symptoms of porphyria variegata fall under two categories: cutaneous, or skin-related, and acute, or neurovisceral. Of the four types of acute porphyrias, porphyria variegata is one of two that display both cutaneous and neurovisceral symptoms (Norton *et al.* 2016). The neurovisceral symptoms are caused by increased ALA and PBG levels, while the increased porphyrins cause the cutaneous conditions (Vafaee-Shahi *et al*. 2022). Symptom severity can depend on the type of mutation of the *PPOX* gene, as discussed earlier (Vafaee-Shahi *et al.* 2022). Furthermore, symptoms, both cutaneous and acute, rarely occur before puberty and are more commonly observed in women compared to men (Singal and Anderson 2019). Porphyria variegata has low penetrance, so many carriers never show symptoms, however, they may have complications, such as hepatocellular carcinoma, or liver cancer, later on in life (Norton *et al*. 2016).

The cutaneous symptoms most commonly include lesions that occur when exposed to sunlight, blisters, hyperpigmentation, scarring, thickening of the skin, and hypertrichosis, or extreme hair growth on the extremities of the body (Norton *et al*. 2016). These symptoms occur when the skin is exposed to sunlight because the exposure causes the porphyrins in the body to activate which makes the skin fragile and liable to blistering (Singal and Anderson 2019).

As well as suffering from cutaneous symptoms, those diagnosed with porphyria variegata struggle with neurovisceral symptoms. The most common acute symptom of porphyria variegata is severe abdominal pain accompanied by nausea, vomiting, and constipation (Norton *et al*. 2016). The abdominal pain that accompanies an acute attack can last for several days and sometimes longer (Schulenburg-Brand *et al*. 2022). Unfortunately, the abdominal pain is not caused by inflammation and is instead neuropathic, so physical examinations of the abdominal area reveal minimal results compared to the severity of pain (Singal and Anderson 2019). In 85 percent of acute attacks, nausea and vomiting are symptoms and half of the cases also include constipation, while 60 percent of cases include hypertension, or high blood pressure, and tachycardia, or abnormally high heart rate, as symptoms (Schulenburg-Brand *et al*. 2022). In addition, 30 to 40 percent of attacks are shown to have hyponatremia, or low sodium level in the blood, as a symptom while seizures are present in 5 to 10 percent of attacks and may be linked to hyponatremia (Schulenburg-Brand *et al*. 2022). Although these acute symptoms are due to porphyria variegata, outside factors, such as alcohol, drugs, female hormones, smoking, infection, or stress, may trigger or worsen attacks (Schulenburg-Brand *et al*. 2022). As mentioned previously, female hormones can affect the acute symptoms. As a result, when pregnant, the hormonal changes in women make them more susceptible to attacks, but, in most cases, does not affect the pregnancy itself (Schulenburg-Brand *et al.* 2022).

**Epidemiology**

As stated earlier, porphyria variegata is a rare condition, consequently, it only has a prevalence of 0.5 per 100,000, but can be as high as 3 per 1,000 in South Africa (Vafaee-Shahi *et al*. 2022). This greater prevalence in South Africa is due to the genetic mutations linked to a Dutch immigrant dating back to the 17th century (Norton *et al.* 2016). Moreover, porphyria variegata is more commonly observed in South Africa, compared to other parts of the world, and affected individuals display less acute or neurological symptoms than they do cutaneous symptoms (Singal and Anderson 2019). In addition, cases of porphyria variegata have been diagnosed in Europe where the prevalence is 3.2 to 1,000,000 (Singal and Anderson 2019).

**Screening**

Acute porphyria, of which porphyria variegata is one type, is known as “the little imitator” because it can be hard to diagnose and sometimes is misdiagnosed as major trauma (Norton *et al*. 2016). In order to diagnose this genetic disease, samples of a patient’s urine, blood, fecal matter, and plasma can be tested.

To test for porphyria variegata, the urine of a patient can be examined for increased levels of PBG and ALA, the fecal matter can be examined for increased level of protoporphyrin and coproporphyrin, and the plasma can be tested using plasma fluorescence spectroscopy for a peak between 624-627 nm (Norton *et al.* 2016). When testing, samples taken from the patient should be protected from light because ultraviolet light can affect the samples. For example, if exposed to ultraviolet light, urine samples taken during a symptom attack will turn dark red or purple due to the porphyrins in the urine oxidizing (Norton *et al*. 2016). Furthermore, in regards to urine, fecal, or blood samples, they should be tested as soon as possible since, after 2 days, PBG levels will decrease by 20 percent, however, ALA levels can be stable for 7 days (Schulenburg-Brand *et al.* 2022). Again, the urine and plasma samples should not be exposed to light as the porphyrins will decrease 37 to 50 percent in urine when exposed to light for 24 hours and 50 percent in plasma when exposed to light for 6 hours (Schulenburg-Brand *et al.* 2022). Additionally, when screening for cutaneous porphyrias, samples of the urine or plasma are tested for porphyrin levels while levels of PBG and ALA are tested in the urine when screening for acute porphyrias (Singal and Anderson 2019). If there are elevated PBG levels in the urine, the patient can start treatment right away while other tests are conducted to determine the type of porphyria (Singal and Anderson 2019). On the other hand, if PGB levels in the urine are normal, then further testing can be done on ALA and total porphyrins (Singal and Anderson 2019). The latter tests can be helpful when determining a diagnosis because the levels of total porphyrins often remain elevated longer than the levels of PBG alone (Singal and Anderson 2019). For similar reasons, any samples taken from a patient should be collected when the patient is showing symptoms since the PBG levels in the urine may return to normal after the symptomatic attack resolves (Schulenburg-Brand *et al.* 2022).

Once testing is done on the urine, further testing, including plasma fluorescence scanning and fecal porphyrin analysis is needed to distinguish porphyria variegata from other porphyrias (Singal and Anderson 2019). While these screenings are helpful in determining a diagnosis, the tests should ultimately be confirmed through genetic testing of the *PPOX* gene.

**Treatment**

There is not a cure for porphyria variegata, but actions can be taken to reduce the chance of a symptom attack. For example, eating carbohydrate-rich foods can reduce symptoms since carbohydrates reduce the activity of ALA (Norton *et al.* 2016). Also, patients should refrain from drinking alcohol and check the medication they are currently or will be taking prior to consumption since many common prescription drugs can trigger symptom attacks (Norton *et al.* 2016). Drugs that should be avoided include progestins, barbiturates, most anticonvulsants, rifampin, and sulfonamide antibiotics (Singal and Anderson 2019). Birth control pills should also be avoided due to their hormone regulation, however, low-doses of hormonal preparations can be permissible (Singal and Anderson 2019).

In the past, injecting a glucose and water solution was used to increase carbohydrates and treat attacks, however, this had the risk of worsening hyponatremia. Now, hematin injections are a preferred treatment since it suppresses ALA, the rate-limiting enzyme in heme synthesis (Norton *et al.* 2016). Moderate or severe acute attacks are most commonly treated with human hemin which, to be most effective, should be administered in the first few days of the attack beginning (Schulenburg-Brand *et al.* 2022). For instance, normosang is a human hemin solution that contains 250 mg of heme with arginine to stabilize it. The dosage for this solution is 3 mg/kg body weight, not exceeding 250 mg, and is mixed with 100 mL of saline. This heme and saline solution is then administered through a central line over the course of 30 to 40 minutes and, once finished, the vein is immediately flushed thoroughly with normal saline (Schulenburg-Brand *et al.* 2022). Another treatment is carbohydrate loading in which 2 liters of saline, 10 to 20 percent of which is glucose, is administered through a central line over the course of 24 hours. This treatment is used more commonly for minor attacks or when human heme is not available (Schulenburg-Brand *et al.* 2022). Additionally, monthly injections of givosiran, a type of small interfering RNA that degrades ALAS1, can help prevent frequent acute attacks (Singal and Anderson 2019).

Unlike acute symptoms, there is no treatment for the cutaneous symptoms, but these problems can be reduced by avoiding sunlight exposure and wearing protective clothing (Singal and Anderson 2019). More severe symptoms such as seizures and hyponatremia should be treated in the ICU since these symptoms point to more extreme manifestations of porphyria variegata. Hyponatremia should be treated slowly and the medications chosen to treat seizures should not be ones that can make the porphyria worse (Singal and Anderson 2019). Furthermore, liver transplantation is an option for those who do not respond well to other medical therapy and have severe and repeated acute attacks (Singal and Anderson 2019).

Works Cited

Besur, Siddesh, Schmeltzer, P. and H.L. Bonkovsky. 2015 Sept. Acute Poryphias. J Emer Med 49(3): 305-312. www.sciencedirect.com/science/article/abs/pii/S0736467915003819?casa\_token=RJS0ku2UQBYAAAAA:1emKvUXKhkFolMVggF0YTF6\_uce5VVtICVSFdpE5dzvE0KUJAC0G1R0PrDKUnMV73cNJWyZYwQ.

Norton, Joel, Hymers, C., Stein, P., Jenkins J.M. and B. Duncan. 2016 Nov. Acute porphyria presenting as major trauma: case report and literature review. J Emer Med 51(5): 115-122. www-sciencedirect-com.lib.proxy.csustan.edu/science/article/pii/S0736467916303869.

Schulenburg-Brand, Danja, Stewart, F., Stein, P., Rees, D. and M. Badminton. 18 May 2022. Update on the diagnosis and management of the autosomal dominant acute hepatic porphyrias. J Clin Pathol 75(8): 537-543. jcp.bmj.com/content/75/8/537.

Singal A.K. and K.E. Anderson. 2019. Variegate porphyria. In: Adam M.P., Mirzaa G.M., Pagon R.A., et al. Seattle: University of Washington, Seattle. www.ncbi.nlm.nih.gov/books/NBK121283/.

Vafaee-Shahi, M., Ghasemi, S., Riahi, A. and Z. Sadr. 2022 Feb 14. A boy with blistering of sun-exposed skin and finger shortening: the first case of Variegate Porphyria with a novel mutation in protoporphyrinogen oxidase (PPOX) gene in Iran: a case report and literature review. Ital J Pediatr 48(1): 27. www.ncbi.nlm.nih.gov/pmc/articles/PMC8842551/.