Hereditary Coproporphyria Presenting with Weakness and Photosensitive Rash: A case Report and Literature Review

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ABSTRACT

Hereditary coproporphyria (HCP) is a form of porphyria arising from a deficiency of the enzyme, coproporphyrinogen oxidase, which results in the accumulation of coproporphyrin in the heme biosynthetic pathway. In the current study, we report a case of a 22-year-old male with a history of six recurrent intestinal obstructions, mainly presenting with reduced upper limb strength, photosensitive rash, and abdominal pain this admission. The laboratory tests revealed increased levels of coproporphyrin, uroporphyrinogen and porphyrin in stool sample and porphobilinogen deaminase activity was within the normal range. All these led to the diagnosis for HCP. Single intravenous glucose therapy improved the patient’s condition and no relapse was observed during the 3-month follow-up period. Since then, no other pathological or genomic manifestations were observed.

Key Words: Hereditary Coproporphyria, Porphyria, Coproporphyrinogen Oxidase, Coproporphyrin, Treatment

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Introduction

Porphyria, also known as hematoporphyrinism, is a heterogeneous group of metabolic disorders caused by abnormal enzymatic activity in one of the eight enzymes involved in the haem biosynthetic pathway. These altered metabolic disorders lead to the accumulation of different haem intermediates and display of variable clinical manifestations.

Porphyria is mainly synthesized in red bone marrow and liver and can be subdivided into two major categories: hepatic porphyria and erythropoietic porphyria (Singal et al., 2014). Hepatic porphyria is further classified based on clinical manifestations and specific enzyme defects into five subtypes: acute intermittent porphyria (AIP), porphyria cutanea tarda (PCT), variegate porphyria (VP), hereditary coproporphyria (HCP), and aminolevulinic acid dehydratase deficiency porphyria (ALADP) (Roveri et al., 2014).

AIP, the most common porphyria subtype, results from an abnormality in the porphobilinogen (PBG) deaminase enzyme, while HCP is a rare subtype. Importantly, AIP and HCP are both autosomal dominant genetic diseases. VP and HCP subtypes are also referred as neurocutaneous porphyria, because these patients clinically manifest cutaneous symptoms after sunlight exposure and potentially life-threatening neurovisceral symptoms (Frank, 2016). The HCP subtype results from deficiency of coproporphyrinogen oxidase (CPOX) enzyme, the sixth enzyme (Heyer et al., 2006) in the haem biosynthetic pathway, thus leading to accumulation of coproporphyrin, its symptoms are non-specific.
HCP-subtype patients typically show unexplained abdominal pain, neuropsychiatric symptoms, seizures, liver dysfunction, hyponatremia, constipation, vomiting, and seizures. Herein, we report a case of HCP, specifically displaying symptoms such as progressive weakness of both upper limbs as well as photosensitive rash.

Case Report
A 22-year-old male patient was admitted into the Department of Neurology, First Teaching Hospital of Jilin University (Changchun City, Jilin Province, China) due to a 10-day history of weakness in both upper limbs (not over the head) and rashes in the left lower abdomen. Muscle strength analysis in his distal upper limbs showed a score of grade 4, based on Medical Research Council (MRC) criteria, while a score of 3+ was observed in the proximal limbs. The muscle strength in the lower limbs was scored as grade 5 (normal), and muscle tone in the extremities was normal. In addition, we observed an increase in the deep tendon reflexes of the upper limbs, while those of the lower limbs were observed to be normal. Moreover, there were no deficits of superficial or deep sensation and cranial nerve functions. Babinski and Chaddock signs were also bilaterally negative. However, during his hospital admission, the patient displayed sharp pain in the left waist. Patient had no abdominal pain but showed abdominal distension (bowel sounds 1 time/min) without muscle tension and peritoneal irritation. The patient also complained of constipation.

The patient said that he was once diagnosed with porphyria 2 years earlier but we couldn’t demonstrate more details from the previous medical background. Within 6 months of the diagnosis, the patient suffered from six recurrent intestinal obstructions. In addition, the patient had a 14-year history of seizures for which he regularly took antiepileptic drugs (AEDS). Twenty days before this admission to hospital, the patient altered his intake of AEDS to phenobarbital. With this background information, we initially conducted an ultrasound and computed tomography (CT) of the abdomen and the observed results were within normal limits. Furthermore, magnetic resonance imaging (MRI) of the brain (using Siemens Trio Tim 1.5T and 3.0T MRI scanner) was also normal. Likewise, no obvious abnormalities were recorded in the spinal cord. However, electromyography (EMG) results suggested some damage to the nerve fibers of the upper limbs. Moreover, previous blood tests revealed slightly abnormal liver function, for example, r-glutamyl transpeptidase (r-GT) level was 139 U/L (normal range: 10–60 U/L). In addition, when the patient’s urine was exposed to sunlight for 1 hour, it changed color from normal yellow to dark reddish, which indicated increased level of porphyrin.

In addition, measurement of plasma sample showed porphyrin of 67.2 mcg/l (normal range: 1.0-5.6 mcg/l) and coproporphyrin of 59.0 mcg/l (normal value <0.9 mcg/l, level less than 3 times normal is associated with medication use, level greater than 5 times normal is associated with porphyria attacks). Moreover, the level of PBG in urine sample was 3.1 mg/day (normal value <2.0 mg/day). Many other examinations were performed or measured including thyroid function, immunological examinations, rheumatic antineutrophil cytoplasmic antibodies, erythrocyte sedimentation rate, creatine kinase, and rheumatoid factors, and all showed unremarkable results. Additional tests such as heavy metals detection with mercury 0 and lead 0, CD55 and CD59 detection, ANA, and rheumatic and autoimmune tests were also performed for the differential diagnoses of lead and mercury poisoning, rheumatic autoimmune diseases, hemolytic diseases, and other potential diseases. Therefore, the HCP diagnosis was finally established.

Figure 1. Reverse sequencing indicated two missense mutations in the CPOX gene of the patient. A) c.814A>C B) c.880G>A
The genetic sequencing in the CPOX gene identified two mutations, c.814A>C and c.880G>A, as shown in Figure 1, which did not seem to be clinically relevant. Similarly, we also observed a missense mutation c.83G>A in the PBGD gene as shown in Figure 2 and this mutation was not clinically relevant, either (Clin Var database). Since the patient's mother eventually died of lung cancer two years earlier, we did only analyze the PBGD gene from the patient's father and no gene mutations were observed. The patient was treated with single intravenous glucose 200 mg/day therapy as well as oral vitamins C, B1 and B12 for 7 days and obtained an improved condition. At 3 months' follow-up, the patient showed no sign of recurrence.

Discussion

Porphyria is a group of hereditary metabolic diseases that under certain circumstances display metabolic disturbances. Porphyria usually peaks in the third decade of life, it is often latent before puberty and post menopause. Females are more likely to be affected than males (Chen 2013) due to the presence of sex hormones, particularly et al., progesterone.

The variable incidence rate of porphyria has been reported by different studies from different regions. For instance, combined incidence of all forms of porphyria was 1:20,000 (Puy et al., 2010), and AIP and VP were the most prevalent subtypes, while HCP appeared to be rare. However, based on the information from the "Danish Porphyria Register", the total incidence of all porphyria categories was 0.52/100,000 per year, between the years 1989 and 2013 (Christiansen et al., 2016). The incidence rate of AIP in Norway has been reported to be 5/100,000 (Mykletun et al., 2014), without a single incidence of HCP, despite it displaying similar clinical manifestations like AIP.

The most frequent but non-specific symptoms observed in HCP includes abdominal pain, neuropsychiatric symptoms, hyponatremia, constipation, vomiting, and seizures. Furthermore, infrequent photosensitive rash may also occur in HCP, unlike in EPP and PCT. In addition to abdominal distension, no obvious tenderness has been observed, and abdominal pain can be limited. However, pain in the back or the whole abdomen can also be observed in patients without muscle tension and peritoneal irritation. Neuropsychiatric symptoms mainly include central, peripheral, and neurovisceral neuropathy as well as mental disturbance. Central nervous system dysfunction covers seizures, loss of consciousness, and respiratory failure, while peripheral neuropathy signs include sensory loss, numbness, pain in the extremities, and weakness. Neurovisceral symptoms typically include tachycardia, hypertension, and constipation.

The screening test allows the detection of coproporphyrin high level in urine and plasma, especially stool sample. Notably, HCP is inherited in an autosomal dominant fashion, and leads to the accumulation of coproporphyrin in the haem pathway due to deficiency of coproporphyrinogen oxidase (CPOX) enzyme. In most subjects carrying this gene mutation, the disease remains latent and asymptomatic before puberty (Chen et al., 2013), with acute attacks only occurring later in life possibly precipitated by a combination of triggering factors such as use of non-steroidal anti-inflammatory drugs (NSAIDs) (Chen et al., 2013), efavirenz (Grimes et al., 2016), progesterone, erifampicin (Mullin et al., 2012), phenobarbital, phentyoin sodium, and diazepam, environmental stress, and dietary changes (Haimowitz et al., 2015). In addition, some non-specific signs have also been observed during imaging, for example, some cases indicate low perfusion while others show normal during MRI. Based on the literature, we retrospectively evaluated the perfusion defects in HCP patients, which often lead to neurologic and psychiatric symptoms, as noticed by single photon emission computed tomography (SPECT). Perfusion abnormalities are usually mild to moderate and SPECT show higher sensitivity in HCP patients in comparison to MRI. This can probably explain why no obvious abnormalities were observed in MRI studies (Valle et al., 2016).

Importantly, based on the previous report, it was predicted that vasoconstriction pathogenesis included deficiency of nitric oxide synthase, a heme-dependent isoenzyme, which catalyzes the conversion of arginine to vasodilator. Thus, during porphyria, impaired...
supply of this enzyme reduces the availability of nitric oxide, and leads to vasoconstriction (Mullin et al., 2012). Although there are no pathogenomic clinical manifestations or imaging references to determine the specific HCP diagnosis, frequent presentations, laboratory tests contribute much to classifying subtypes for an accurate diagnosis.

In our case report, the patient presented with symptoms that included decreased strength of upper limbs, photosensitive rash, constipation, tachycardia (heart rate 102 times/min), abdominal distension, and pain in the left waist. Mild liver dysfunction was largely due to AEDS. The weakness in both upper limbs represented signs of peripheral neuropathy, and neurologic damage examined by electromyography (EMG) provided enough evidence.

In addition to peripheral nerve dysfunction and neurovisceral damage, this patient also showed uncommon photosensitive rash like eczema. Furthermore, laboratory tests revealed increased level of coproporphyrin, uroporphyrinogen, and porphyrin in urine and stool sample, and PBG deaminase activity was within the normal range, leading to the diagnosis for HCP. We also tested this patient for lead and mercury poisoning, rheumatic autoimmune disease, and hemolytic disease for the differential diagnoses. Moreover, as the patient also altered AEDS to phenobarbital several days before the previous attack, we speculated that phenobarbital could be the predisposing factor for the two acute attacks.

As we treated this patient with intravenous glucose 200 mg/day and oral vitamins such as C, B1 and B12 for 3 days, we observed a slight improvement in the pain of the left side waist area and muscle strength. Also, the patient was instructed to avoid predisposing factors mentioned above and take regular AEDS medication, following the doctor’s advice. Moreover, considering photosensitive rash occurred in the patient, he was also suggested to avoid sun exposure and continue oral vitamins including C, B1 and B12. At 3 months’ follow-up, the patient showed no sign of recurrence.

Porphyria diagnoses are difficult, especially HCP, due to non-specific clinical manifestations and variable imaging findings. This often leads to incorrect or delayed diagnosis and treatment. Once porphyria is suspected, the screening test should be performed followed by further genetic testing to identify the subtype. This will eventually help to design a diagnosis flowchart.

In term of treatment options, the first steps are to relieve pain and elimination of the pain-triggering agents. Intravenous glucose administration terminates mild episodes of acute porphyria, while intravenous heme is required for management of moderate to severe episodes. Heme reduces the accumulation of ALA, coproporphyrin and porphobilinogen. If the disease still progresses, liver transplantation may be the only option for patients with life-threatening acute porphyrina attacks or for patients with recurrent acute attacks refractory to prophylactic treatment (Singal et al., 2014).

No radical option exists for the treatment of porphyria. Elimination of the triggering agents is essential to shorten the course of disease and to reduce the recurrence rate. Most patients are asymptomatic between attacks, and the prognosis is usually good if the condition is recognized early and treated aggressively (Besur et al., 2015).

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