LONG TERM FOLLOW-UP OF FIVE PATIENTS WITH ACUTE INTERMITTENT PORPHYRIA, CASE BASED CLINICAL STUDY

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ABSTRACT

Porphyrias are among rare group of inherited diseases emerging due to decreased enzymes which have the role of the biosynthesis of the hem. The most common and the most serious form is acute intermittent porphyria (AIP) which is an autosomal dominant disease. Gastrointestinal and neuropsychiatric symptoms can be seen at the patients. Five cases who had been followed 2-23 years after the diagnosis, were presented in this paper. Three cases were brothers, one case was father and daughter, and the other case was a male from different family. Symptoms were first seen between ages 15-39. Two cases showed long and severe attacks which were characterized by symptoms of the autonomic and peripheral nervous system. Abdominal pain for other three cases and neurologic signs for the fifth case were distinctive. Porphobilinogen, protoporphyrin and aminolevulinic acide were high in the urine of every patient. All patients were provided benefits from intravenous hem treatment. Second case was deceased on 19th year of the follow-up, due to multi organ failure after myocardial infarction. As a conclusion; even though porphyria is an easily diagnosable disease, main problem is that there is little knowable and little awareness of the disease. Patients can apply with different clinical appearance and it is interesting that the disease is highly sensitive to the environmental factors and comorbidities.

Keywords: *Acute intermittent porphyria, abdominal pain, neuropathy, porphobilinogen deaminase, heme.* ***Nobel Med 2016; 12(2): 69-74***

UZUN SÜRELİ TAKİP EDİLEN AKUT İNTERMİTANT PORFİRYALI BEŞ HASTANIN KLİNİK TEMELLİ BULGULARINA AİT ÇALIŞMA

ÖZET

Porfiryalar, nadir kalıtımsal hastalıklardan olup, hem biosentezinde rol alan belirli enzimlerin azlığına bağlı olarak ortaya çıkar. En yaygın ve ciddi formu otozomal dominant bir hastalık olan akut intermitant porfirya (AIP)'dır. Hastalarda genellikle gastrointestinal ve nöropsikiyatrik belirtiler görülür. Burada tanı konduktan sonra 2-23 yıl izlenen 5 vaka sunulmaktadır. Üç erkek vaka kardeş, bunlardan birisi baba-kız, diğer erkek vaka ayrı bir aileden idi. Belirtiler 15-39 yaşları arasında ortaya çıkmıştı. İki vakada uzun ve ciddi ataklar olup otonom ve periferik sinir sistemi belirtileri ile karakterize idi. Üç vakada karın ağrısı, beşinci vakada nörolojik tablo anamnezi ile birlikte, ön plandaydı. Tüm vakalarda idrarda porfobilinojen, protoporfirin ve aminolevulinik asit yüksek bulundu. Vakalar intravenöz hem tedavisinden yarar gördüler. İkinci vaka takibinin 19. yılında akut myokard infarktüsü sonrası multiorgan yetersizliği tablosunda kaybedildi. Sonuç olarak, porfirya kolay teşhis edilebilir olan bir hastalık grubu olmasına karşın, temel sorun bilinirliklerinin ve farkındalıklarının oldukça az olmasıdır. Hastalar farklı klinik tablolarla müracaat edebilirler, hastalığın çevresel faktörler ve diğer hastalıklarından çok fazla etkilenmesi ilgi çekicidir.

Anahtar kelimeler: Akut intermitan porfiriya, karın ağrısı, nöropati, porfobilinojen deaminaz, hem. **Nobel Med 2016; 12(2): 69-74**

INTRODUCTION

The porphyrias are a group of seven inherited metabolic disorders of hem biosynthesis.[1-3] Totally eight enzymes are involved in this process (Figure-1). All porphyrias are hereditary disorders caused by mutations in the respective genes. The only exception is the sporadic form of "porphyria catenae tarda" (sPCT) which is an acquired hepatic defect of the enzyme "Uroporphyrinogen Decarboxylase" (UROD).[4]

Porphyrias are rarely encountered hereditary disorders of hem metabolism. Acute Intermittent Porphyria (AIP), is an autosomal dominant disease which is the most common and severe form among all the porphyrias. Worldwide incidence of porphyria ranges between 1/100,000 and 2/100,000. Clinical expression of AIP is more common in women of child-bearing age than men.[5] AIP occurs due to the lower enzymatic activity of porphobilinogen deaminase (PBGD); almost less than %50 of normal PBGD. The patients with AIP generally suffer from gastrointestinal complains and neuropsychiatric symptoms.[6] There are many porphyria studies which are showing the clinical and laboratory findings of long term following up the patients in Northern Europe and US.[7-9] However there is no such study that pursues long term porphyria cases (20 years) in Turkey. Characteristics of the 5 cases presented here summarized at the Table.

CASE 1

First patient was 15-year-old boy who was checked during his rehabilitation during in a physical rehabilitation center in 1993. He was confined to the bed and cachectic. There was no muscular activity in both lower and upper extremities, muscle strength was 1/5, and there were significant muscular atrophies in both hands. He had tracheostomy due to respiratory muscle involvement and requirement of tracheal aspiration of the mucous secretions. He had a history of persistent abdominal pain, nausea and apnea three months before he developed quadriplegia. His blood pressure and pulse rate were high (170/100 mmHg and 130/min). The level of urine aminolevulinic acid (ALA) was found to be 25 mg/dl (1-7 mg/dl). Besides this, positive (+++) urine porphobilinogen (PBG) and +++ urine protoporphyrin was detected. With these lab tests, he is diagnosed with AIP. His treatment was initiated with intravenous hem (3mg/kg/day for 8 days). Healing started in the 3rd day of the cure, three years later he went to mandatory military service and completed successfully. He got married, had two children; one girl and one boy. One of these twins, male; ALA: 1-mg/dl, PBG level: normal. Female; ALA and PBG is not at a measurable level. The patient in the year 2009: He started to work in textile industry and had a pain on the right side of his knee. A tear of the meniscus was detected by magnetic resonance imaging (MRI) technique. Additionally, axonal type polyneuropathy was detected as a result of electromyography (EMG). He has been scheduled for a meniscus operation but he refused to be operated. During his physical examination in 2014, a marked arterial hypertension (140/100 mmHg) was noticed. His electrocardiogram (ECG) and transthoracic echocardiography was normal. This is the first time that he developed arterial hypertension since the treatment was begun. Oral nebivolol (5mg per day) treatment was initiated.

CASE 2

Second patient was a 39-year-old man who was admitted to the emergency department with a severe abdominal pain without defense in 1989. He had cold sweats and his arterial blood pressure was found to be (ABP): 70/40 mmHg and Heart Rate: 140 pulse/minute. On the day of admission, his blood hematocrit levels were found to be %30, and it was found to be %25 four hours after the hospitalization. There was no occult blood detected in his stool. He had progressive muscle weakness. His urine acetone and urobilinogen were positive (+ +). The spot urine level of ALA was 25 mg/dl. He had a previous history of AIP attack 3 months before. Besides, at the time of admission, uroporphyrin and porphobilinogen levels were found 3732 ug/24 hours (0.0-60) and 0.30 (0.0-2.0 ug/24 hours urine) respectively. The levels of coproporphyrin were obtained as 4920 ug/24 hours (0.0160). Three units of blood transfusion have been carried out and 10 mg of meperidine was given. The morning after the hospitalization, his urine was put in a glass jar, left under the sun and it is observed that it turned into black completely. The same day, spot urine sample was sent to the occupational diseases and toxicology laboratory. The result in the urine; ALA: 29 mg/L, Protoporphyrin (+++) Porphobilinogen (++++). With these findings, the diagnosis of AIP was confirmed. Intravenous dextrose infusion initiated. Daily, 400 gram of glucose was given for 2 days. Hem cure started on the third day of AIP attack due to the procurement period of the drug since it had been imported from Chicago/ IL, USA. It was administered 3 mg/kg/day for three days. He completely recovered on the 6th day. The patient did not follow the medical suggestions after being discharged from the hospital and smoked 365 packages of cigarettes in a year and alcohol 5-6 g/day. It was understood that he was taking 5 mg/day oral dexamethasone for his itches without recommendation and prescription. He also continued smoking in the following years. Until

2005, he had totally 20 AIP crises. The elder sister of our patient, who was firstly diagnosed with AIP at the age of 42, had gone under operation with the diagnosis of acute appendicitis and later she had paralysis and died at a young age (28 years old, not diagnosed with AIP, died of respiratory failure). Indeed, a very detailed patient history clarified that sister of our patient had AIP. Besides, his two brothers had 2 AIP attacks their life and had treatment of Hem. One of his brothers was 47 years old, had no reported disorder and one of his sisters was 57 years old, Type 2 diabetes mellitus.

He was a cook and retired in 2005; he did not have any AIP attacks in the last four years but its complications hypertension, diabetes and osteoporosis developed respectively after 12 years, 14 years and 15 years. As of January, 2009, 57 years old, he was obese, ABP: right arm: 160/110 mm Hg and left arm: 130/110 mmHg, and had wheezing. Laboratory findings: clearance of creatinine in 24 hours' urine: GFR (Glomerular filtration rate) was 70 ml/mn (N: 85-125) Glucose: 93 mg/dl. Blood tests showed no abnormal finding. Bone Dansitometer showed marked osteoporosis (T score: -3.88). This patient received unsalted and diabetic diet, and has been using oral carvedilol 12,5 mg/day as antihypertansive, alendronat sodium 70 mg/once in a week for osteoporosis and Vitamin D 800 IU/day in last 3 months. In july 2012 he fell down and broke one of his thoracic rib but lately he was hospitalized and diagnosed with acute myocardial infarction (AMI). Before a week of the AMI the urine ALA and PBG was normal. After hospitalization in coronary intensive care unit ALA in the urine increased to 40mg/dl on the 4th day. Acute renal failure, multi-organ failure was observed, and he died 5 days after the hospitalization.

He has two sons and one daughter, they appear completely healthy. The family is conscious about the disease. They follow the medical suggestions about the drugs which they shouldn't receive. One of his sons requested to change his place of military service and told his doctor that his family had AIP. The doctor hospitalized him and found after erythrocyte porphobilinogen deaminase: 1.65 UI/L RBC (>3.85 UI/L reference value) and enzyme activity 50% (reference value: 100%). That means the son of our patient, who was 20 years old, has also AIP but he has not had any attacks yet.

CASE 3

This patient is the younger brother of the second case, he was 39 year-old when he was admitted to our hospital in 1998. He had no complaints apart from abdominal pain and constipation. He had visited many doctors,

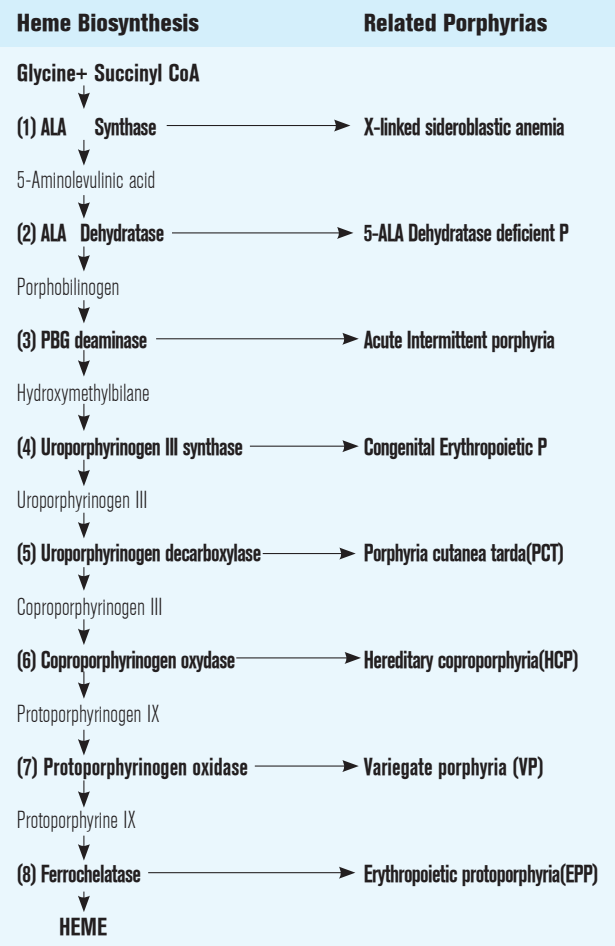

Figure 1. Metabolism of the heme and the mutations of the enzyme in this cascade.

many examinations including intravenous pyelography had been made and all the results were normal. Since the medical history of the patient's family was well defined and known, Watson-Shwarths test was used in order to diagnose AIP. According to test results, ALA, PBG and Proto-PBG were found positive in his urine. Firstly, oral glucose (400 gr/day) was administered and monitored for three days and he recovered. He had the following attack three months later while he was fasting due to the Ramadan but this time he did not respond to the glucose administration. Heme treatment was done as 3 mg/day/kg heme I.V. perfusion for two days and he completely recovered. He has been a healthy person in last 15 years, he only has mild hyperlipidemia. The patient is very careful in his private and working life. He completely changed his life style, he first moved from Istanbul to costal area of the Blacksea region in order to work as an accountant. When he gets any infection he is very careful in choosing the right drug. A complication has not yet been developed. In 2015 he was operated due to prostate hyperplasia.

CASE 4

The forth patient was drinking alcohol and smoking during his daily life and had the first AIP attack in

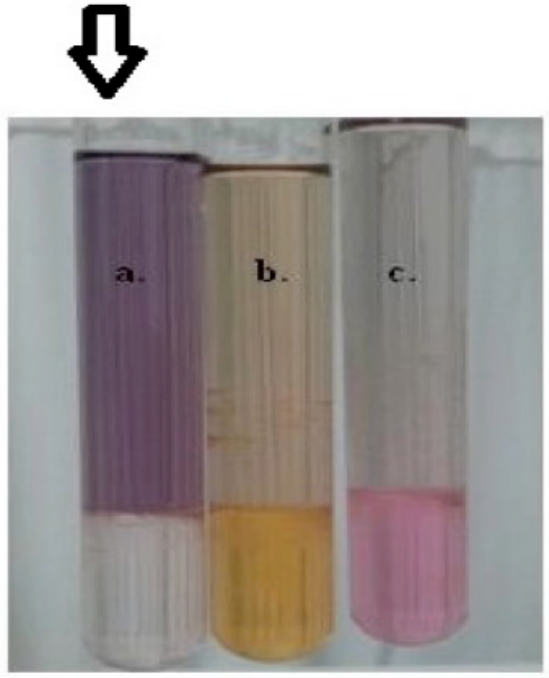

Figure 2. Urine analysis Ehrlich' reagent, (DMAB test) in patients with AIP (a) in normal individual, (b) and treated AIP patient with addition of chloroform (c). The first tube (a) shows purple color because of porphobilinogen positivity. In sample c with addition of chloroform there is no more porphobilinogen but urobilinogen with pink color.

1986. The attack lasted for two months and he could be diagnosed at the end of the 2nd month at the age of 39. Heme treatment was conducted as 4 mg/kg/day for 12 days. He recovered and he was healthy during the following five years. Then AIP attacks were observed in the next years. When the patient was persuaded to enter into hospital in February, 2009, BP was 160/100 mmHg and regular bone densitometer was L3: T-score -3.3 L4:-3.3 Total:-2.8. According to results he had serious osteoporosis. Therefore, the treatment was started as Alendronate sodium 70 mg/once a week, Calcium 1000 mg/day and Vitamin D3 800 IU/day. Additionally, he received antihypertensive propranolol as 40 mg/day. He now lives a retired life and he does sports with regular and proper exercise.

CASE 5

The fifth patient was the daughter of the 4th patient and she had hemiplegia at the age of 26 following her second birth after elective caesarean section. Since doctors were now informed about her family anamnesis, she was now diagnosed with AIP. In diffusion MRI of the brain: arterial embolism was detected in middle cerebral artery. Low molecular weight heparin was administered initially. She had been using acetyl salicylic acid 300 mg for 6 months. Patient's relatives did not notify neurologists who took care of AIP disorder and during hemiplegia attack and ALA and PBG levels were not analysed in the urine. Three months later, she recovered from hemiplegia and the levels of ALA and PBG were found to be completely normal. She had no evidence of AIP attacks for 5 years until she received oral ornidazole 2x500 mg/day for vaginitis. In October 2013, when she was in premenstrual period, she came to our hospital with abdominal pain. Her urine was taken in a small tube and Ehrlich solution was added to it and the color became purple (Figure 2). Upon she was diagnosed with AIP, she started to receive Heme 3 mg/kg/day for three days and she recovered. In november 2014 the attack was repeated and treated for 4 day with the same therapy.

DISCUSSION

Hem is an essential element of the cellular hemoproteins like hemoglobin, myoglobin and drug-metabolizing cytochrome P450. Hem is synthesized from amino acid glycine and succinyl-CoA (Figure 1).

As we observe in the case 1 and the case 4, severe and prolonged attacks of AIP are almost always accompanied by autonomic and peripheral nervous system dysfunctions as well as central dysfunctions, such as seizures and bulbar paralysis. Central nervous system findings point out an urgent clinical presence and must be treated urgently with IV hem, before permanent neuronal damage takes place.

It is interesting to note that, as exemplified in one of our patient's relative (sister of our 2nd patient), in addition to physiologic hormonal changes in women of child-bearing age, fasting for religious purposes, heavy smoking, alcohol consumptions and stress could trigger an acute attack of AIP. Fasting is a common religious practice during the holly month of Ramadan. Our three patients were devoted Muslims and always fasted during the holly month of Ramadan. Only one of them devoloped an acute attack of AIP because of fasting, unfortunately there are no studies in Turkey providing significant data on this regard. It is thought that fasting induces the "hepatic microsomal hem oxygenase" activity resulting in decreased hepatic hem synthesis. Decreased hepatic hem concentration no longer represses the ALA synthetase activity, leading to increased ALA concentration in both blood and urine. This is the reason why glucose infusion is necessary for the AIP treatment.[10]

Heavy alcohol intake, infections, surgery and stress are known to up regulate the hem oxygenase gene expression leading to exacerbation of AIP.[10] Chemicals in tobacco such as polycyclic aromatic hydrocarbons are inducers of hepatic cytochrome P450 enzymes.[11] One of our patients was a heavy smoker and he had over 20 times AIP attacks in 20 years.

Tablo. Clinical and laboratory findings of the patients in long term following

Age/Sex	Presenting Symptoms	Triggering Factors	Clinical Findings	Laboratory (Watson -Schwartz Test)	Family History	Treatment	Complications
15-33/Male	Abdominal pain, muscle weakness, polyneuropathy, breathing difficulty, tachycardia, tracheostomy	Sulpha antibiotic	BP: 170/100 mmHg, pulse: 130/min, marked muscle atrophy, quadriplegia, absent deep tendon reflex, dyspnea	Urine: Pbg+++ Protoporhyrin+++ ALA: 25 mg/l	Yes	Heme: 3 mg/kg/day for 8 days, complete response, Cured	Peripheral neuropathy, Hypertation after 16 years
39-57/Male	Severe abdominal pain, generalized weakness, constipation	Smoking, frequent use of outpatient medications, alcohol use	BP: 70/60 mmHg, pulse: 140/min, abdominal tenderness no rebound	Urine: Pbg+++ Proto++ ALA:20 mg/l	Yes	IV Glucose: 400 g/day for 3 days, Heme: 3mg/kg/day Response in 6 days, from 1994 to 2012, attacks over 20 times	Osteoporosis after 15 years, hypertension after 12 years, diabetes mellitus after 14 years Death from (MI) in 2012
39-52/Male	Abdominal pain	Unknown	Normal physical findings	Urine: Pbg++ Proto++ ALA:15 mg/l	Yes	IV Glucose: 400 g/day for 3days, Heme: 3mg/kg for only 3 days, Cured	No complication
40-62/Male	Severe abdominal pain, weakness, CVA	Sulpha antibiotic, alcohol use, smoking	Unable to diagnose for 2 months CVA coma	Urine: Pbg+++ Proto+++ ALA:25 mg/l	Yes	IV Glucose: 400 g/day for 15 days, Heme: 4mg/kg-total-12 days/ 2nd attack after 4 years, 8 day IV Heme, Cured	Hypertension, Osteoporosis; both after 16 years
26-33/Female	Severe abdominal pain, constipation, vomiting	Ornidazol 500mg(2x1) for 7 day	Normal pyisical finding	Fresh urine porphobilinogen +++	Yes	Isotonic NaCl 1ltx2 Heme arginin: 3mg/kg IV for 3 day	No complication

BP: Blood pressure, **MI:** myocardial infarction, **CVA:** cerebrovascular accident.

In some AIP patients, no triggering factors could be found. For instance, the sister of our 2nd, 3rd and 4th patients died because of an AIP attack before she was diagnosed with AIP.

Diagnosis of AIP is based on clinical symptoms and proper laboratory tests.[12] AIP mimics many acute clinical conditions such as acute abdomen, cerebrovascular events, respiratory failure, polyneuropathy, quadriplegia, hypertensive crises, chest pains, psychosis.[13] Consequently, it is very difficult to diagnose AIP correctly on an urgent basis. Many times urgent surgical interventions, appendectomies have been performed before AIP could be diagnosed (as done in relatives of our patients 1, 3 and 4) usually resulting in disastrous consequences. If index of suspicion is not high, even a simple test of urinary ALA and PBG, which will be negative in all other serious medical and surgical conditions, will not be ordered and the diagnosis of AIP attacks will be missed. Consequently, wrong tests will be ordered and wrong symptomatic treatments will be started and many of which will cause more severe and prolonged AIP attacks.[14] Therefore, it is always important to make a correct diagnosis, which must depend on knowledge, experience and index of suspicion.

Patients with AIP attacks excrete increased amount of ALA and PBG in the urine. In severe cases, the urine may even develop a dark purple color due to high concentration of porphobilin, which is an oxidation product of PBG (Figure 2). It has been shown that the measuring of urinary PBG levels is the best test for the diagnosis of AIP. During the acute attacks of AIP plasma concentrations of ALA, PBG, and porphyrins are also elevated. For definite diagnosis the amount of ALA excretion in 24 hrs urine (normally less than 7 mg) and the amount of PBG (normally less than 2 mg) should be measured. Additionally, PBG deaminase activity in erythrocytes should be determined as well. The Watson Schwartz screening test is used in urgent circumstances as qualitative screening test for urinary PBG. It must be performed on a fresh urine specimen. It is positive approximately in 50% of the time.[12-15]

As a conclusion porphyrias are a group of rare diseases in this geography. If patients with atypical abdominal pain or atypical neurologic findings were seen, these groups of diseases must be kept in mind.

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