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The most common complication of Acute intermittent porphyria and its occurrence

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Abstract. Porphyria is one of the most common complications related to Heam metabolism, although the incidence of this disease is very rare but due to it is unlimited complications this push the thought to word the concentration about the type of each complication and its type of the disease. Treatment of this disease is not the same as what it was in the past due to that the development of the treatment protocol and the development of genemapping make the incidence of this disease is very rare but still the disease is one of the most important health problems that it occur Method: a study was conducted to follow the most common complication of the type of porphyria and its occurrence in each type of this disease Results : data showed that the most common complication of the acute intermittent porphyria (AIP)is the neurological complications although some researches indicated an occurrence of the abdominal pain, constipation and even intestinal narcosis**.**

Keywords. porphyria , neurological abnormalities , gene mapping, Acute intermittent porphyria, porphobilinogen, Hemoglobin

Introduction

Heam synthesis and catabolism: the synthesis of heme is started from a reaction between theglycine with succinate, by the enzyme ALA synthase with the aid of pyridoxalphosphate as a coenzyme toproduce a 5 amino laevunilate (ALA), this enzyme is the rate-limiting step enzyme of heme synthesisand it is activated by drugs likephenobarbital, griseofulvinor hydantoins, and inhibited by a high level of heme, after that the porphobilinogen (PBG) is formed by the ALA dehydrase which inhibited by lead poisoning and this is one of the reasons of anemia seen in those works in battery factories (note: lead poisoning not only effects on the enzyme ALA dehydrase but also induce an inhibition of ferrochelatase enzyme) , porphobilinogen (PBG) is then converted to uroporphobilinogen III by porphobilinogen

deminase and the last one is converted in to coproporphobilinogen III by uroporphobilinogen decarboxylase . (1)

Coproporphobilinogen III is converted to protoporphobilinogen III by oxidase in the mitochondria andprotoporphobilinogen III is converted to protoporphryrin IX by protoporphobilinogen oxidase, finallyprotoporphobilinogen IX is converted to a haem by ferrochelatase. (2)

The heme is followed by incorporation of Fe^{+2} in its center after the form a ring of four heme molecules to produce a big complex of four heme molecules with Fe^{+2} to form the last product that is called the Hemoglobin(3)

Catabolism of heme

Heme is excreted in the feces, it catabolized into the uroporphyrinogen ALA and even the PBG. Usually the urinary end products of heam are ALA and PBG and URO (uroporphyrin) which are colorless but tend to be darkened when left to stand for along time, while the PROTO (Protoporphyrin) are a faecal end product which have a red dark color and finally coproporphyrin (COPR) are seen in both urine and faeses. (4)

The synthesis pathway is controlled by negative feedback inhibition pathway the inhibit the ALA synthase enzyme so it inhibit the anabolic pathway of the heme. If the synthesis pathway is abnormally impaired, it will end with a clinical abnormality that known as porphyriase.(5)

porphyriase:the word porphyriase comes from a Greek word which means "purple", which refers to the color seen in the urine of these patient suffered from this disease.(5)

the porphyriase is a either a genetic (as an inherited as autosomal dominant disease) or acquired disorder of heme synthesis and so his disease ends wih increase the level of porphyrins or porphyrin precursors, this is due to any reasons or abnormal function of any enzyme of heme synthesis pathway. These enzymes may include: (6)

1-porphobilinogen deaminasedeficiency in the cytoplasm and its deficiency induces acute intermittent porphyria(AIP) which end with increased concentration of both of porphobilinogen and the level of ALA in urine which is darkened when exposed to sunlight or air but here the patient does not suffer from photosensitivity

2-uroporphyrinogen synthase deficiency induces a congenital erythropoietic porphyria which is associated with the accumulation of uroporphyrinogen and coproporphyrinogen I in the urine, in these patients there will not be a symptoms of photosensitivity

3- uroporphobilinogen decarboxylase deficiency is associated with uroporphyrin accumulation in the urine and this case is called porphyria cutanea tarda (PCT).

4- coproporphobilinogen oxidase deficiency in the mitochondria and its deficiency induces a hereditary coproporphyria which associated with coproporphobilinogen III accumulated in the urine

5- protoporphobilinogen oxidase deficiency in the mitochondria deficiency inducesvariegate porphyriase and in these patient, there will be protoporphobilinogen IX accumulation in the urine

6-ferrochelatase deficiency and this one is inducing erythropoietic porphyria at which there will be an accumulation of protoporphyrin in the erythrocyte, bone marrow, and plasma and here the patient is suffer from the photosensitivity(8).

Some drugs or chemical materials (like barbiturates, ethanol, estrogens, sulphonamides, phenytoin,halothane and griseofulvin) may aggravate the occurrence of porphyria because they may increases the cytochrome P450oxidation system. (9)

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Alcohol, smoking may increase the requirement of heme so may aggravate the incidence of porphyriase. Those women who are pregnant and those in the peak of their menstrual life may shows an increasing of the heamrequirement so they are more expose to aggravating the symptoms of porphyriase (10)

Clinical manifestations: (7,11,12)

there are many manifestations depending on the enzyme deficient like

1-photosensitivity, itching and skin burning or rash sensation when exposed to sun light particularly in the early childhood, this due to theses product may induce the formation of free superoxide radicals that ends with a destructive result of the skin membrane and cellular components that induce a photosensitivity

2-cholestatis and hepatic cirrhosis and increased chance of hepatic failure

3- gastric and duodenal abnormality like abdominal pain(Colicky) , vomiting and constipation

4- psychological abnormality like aggressive behavior, confusion

5- fever, cardiac abnormality with increase in the cardiac output and increase the pressure if the blood.

6-the lesion of the skin in some cases of porphyriase particularly most common occurs at porphyria cutanea tarda

7-dark red to brown color in the urine up on exposure to the sun light and red to pink color in the fluorescent light

8- In general Abdominal and neurological symptoms are more common seen in intermittent porphyria (the acute not chronic type); acute variegate, acute coproporphyria (hereditary)

9-the Skin lesions is more common seen in those suffer from acute and latent variegate porphyria.

10- neurologicalsymptoms ranging from peripheral neuropathy toquadriplegia.

10- increase the level of cholesterol with hyperlipidemiais more common seen in cases of Acute intermittent porphyria

11-some cases may suffer from chest pain

prevalence of porphyria:(13)

The incidence of porphyria is varied and not easily to be evaluated, however, it could be considered between one case to even more than one hundred cases are recorded per fifty thousand. The most common cases recorded was belongs to Porphyria cutanea tarda.

Complication of porphyriase:(11)

It may include hyponatremia, seizures attach and sometimeparalysis. Symptoms may be aggravated at smokers, alcoholics, stress, anxiety, sunlike exposure and some medications.hemochromatosis may be seen in some cases of porphyria cutanea tarda. Death may be seen in some cases due to aggravated neuropathy particularly in the respiratory system that could ends with respiratory paralysis and may be accompanied with sever reduce of the blood pressure

Diagnosis: (10)

1-urine sample that shows a dark brown to red color

2- stool sample

3-bolld test including

4-genentic test that reveal the presence of the mutation.

Treatment:

most of strategies of the porphyria treatment base on treating the symptoms or the complication of the disease, it may include:

1-decrease the exposure to the sun light

2-giving the heme to correct the deficiency in its level weather by oral or IV roots, in rare sever cases like the hepatic failure it ends with hepatic replacement.

3-treatment of Convulsions cases by anticonvulsant drugs like vigabatrin or gabapentin

4-Haemarginate, given by(slow IV infusion) can be helpful by decreasing the concentration of PBG or ALA and so reduce the rate of attack incidence

Acute intermittent porphyria(14)

The deficiency of the enzyme Porphobilinogen synthase is a recessive inhirited disease, the concentration of the PBG is remain constant while the other types associated with the dominant inheritance. The biochemical changes with the sign and symptoms may be correlated with the type of the enzyme effected.

Acute phase

Usually there might be neurological complication of the acute phase that may be due to the toxicity of the AL and the PBG. It may be associated with convulsion and hyponatrimia and muscle weakness . The ALA synthase could be in unpredictable way increase due to many medications like estrogen, hormone replacement therapy, phenytoin and others (15)

Porphyria cutanea tarda (16)

In this type the skin may shows a trauma like symptoms with sever skin sensitivity especially in the back of the hand, face with hirisutism in the face and some areas of the body and pigmentation especially under the eyes, it may progressed in to the hepatic enzyme elevation indicating the hepatic abnormalities. It may be due to impairment of the production of coproporphyrinogen from the uroporphyrinogen due to the impairment of the decarboxylation step. Most of the cases of this type is not inhirited but acquired, it increased in alcoholics, hormone replacement therapy takers liver disease espically hepatitis and intoxication of benzene derivatives complications. It associated wiuth increase the porphyrins and uroporphyrinogen that deposit in the skin and could be appeared in the urine that may be associated with microscopic heamaturea.

Erythropoietic porphyria (17)

It tend to be associated with increment in the level if the porphyrins in the RBCs and may be and seen with normal level of PBG and ALA. The congenital type of this Erythropoietic disease is autosomal genetic disease that is recessive attributed to the deficiency of the enzyme responsible of the synthesis of uroporphyrinogen III. It is usually shows an increase of the level of uroporphyrin especially in the teeth (flourcent to brown and even a purple coloration of the front teeth) and bones with photosensitivity, the level is so high that may be seen in the urine and stool (7)

Protoporphyria (18)

It is a dominant inhiroited disease and associated with low function of the ferrochelatase with elevated level of the protoporphyrin in the stool, it might be progressed in to skin damage with a light sensitivity with hepatic damage and proved by a hepatic enzymes elevation that may be ends with a hepatic failure. The light or sun sensitivity can be protected by any kind of sun blocker

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Material and method: a study is designed to study some o complications of porphyriase and its complications and the occurrence of each complication in relation to the type of porphyriase

Results

Table 1 showed that the most common complication is the paralysis, hyponatremia , myelinolysis, seizures and coma, confusion, hallucinations, anxiety and psychosis, total paralysis and crisis of the clonic-tonic types of the convulsive, and polyneuropathy

Tablet 1 neurologicalcomplications of periphrasis

Name of research	Type recognized	Type of complications	Doi
Neurological and neuropsychiatric manifestations of porphyria	AIP	Low Na level associated with Paralysis with myelinolysis, coma and even seizures, confusion, hallucinations, anxiety and psychosis	10.1080/00207454.2019.1655014
Article I. Acute intermittent porphyria: A case report	AIP	quadriparesis and presented single generalized tonic-clonic convulsive crisis, polyneuropathy	10.7705/biomedica.4767
Article II. Acute intermittent porphyria: Long-term follow up of 35 patients	AIP	peripheral neuropathy	10.1016/j.medcli.2014.06.012
Adrenal hormonal imbalance in acute intermittent porphyria patients: results of a case control study	AIP	neurovisceral attacks	10.1186/1750-1172-9-54

Article III. Porphyria and its neurologic manifestations	AIP, HCP and VP	autonomic neuropathy; encephalopathy	10.1016/B978-0-7020-4087-0.00056-5
Article IV. Clinical Guide and Update on Porphyriase	AIP, VP, , and aminolevulinic acid dehydratase deficient porphyria	serious abdominal, psychiatric, neurologic, or cardiovascular symptoms	10.1053/j.gastro.2019.04.050
Article V. Acute Neurological Manifestations of Porphyriase and its Types: A Systematic-Review			10.2174/1871525718666200910162000

NOTE: AIP: acute intermittent perphyria, VP: variegate porphyria, HCP: hereditary coproporphyria

In the table 2 we see that there is another complication that could be occurred like pain in the abdomen with vomiting, difficulty in evacuation of the stool , elevated the pressure of the blood and increase the cardiac output.

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Tablet 2 abdominal complications of periphrasis

Name of research		Type of complications	Doi
(a) Abdominal painmimics	AIP	Generalized abdominal pain	10.1016/j.emc.2021.07.003
Article VI. Acute abdominal pain caused by acute intermittent porphyria - case report and review of the literature	AIP	abdominal pain, nausea and vomiting, constipation, tachycardia and hypertension	10.17992/lbl.2010.06.301
Article VII. Recurrent abdominal pain caused by acute intermittent porphyria	AIP	recurrent abdominal pain for many years, unexplainable abdominal colic, paresis or psychic symptoms	PMID: 11706487
Article VIII. ‹Acute intermittent porphyria: a possible cause of abdominal pain‹‹	AIP		
Article IX. ‹‹Unsatisfactory pain treatment in attacks of acute intermittent porphyria. Vasodilation an alternative if the pain is shown to be the pain of intestinal angina ‹‹	AIP	visceral ischemia as a possible cause of the abdominal pain with a 20 cm necrotic gangrene in the ileum. A protracted intestinal vasospasm.	PMID: 11292973
Article X. Could attacks of abdominal pain in cases of acute intermittent porphyria be due to intestinal angina?	AIP	intestinal angina could be the cause of the abdominal pain	10.1046/j.1365-2796.2000.00653.x

In the table 3 these is manty other complication that very between a study and another and it differfrom severehydroelectrolytic disorder that may caused by low Na and K+ concentrations, with increased cardiac output with high pressure of the blood, Hepatic complication, serious abdominal, psychiatric, neurologic, or cardiovascular symptoms

Table 3 other complication of porphyriase

Name of research		Type of complications	Doi
Acute intermittent porphyria: A case report	AIP	severe hydroelectrolytic disorder due to hyponatremia and resistant hypokalemia, persistent tachycardia and hypertension	10.7705/biomedica.4767
Article XI. Recurrent attacks of acute hepatic porphyria: major role of the chronic inflammatory response in the liver	AIP	Hepatic complication	10.1111/joim.12750. Epub 2018 Mar 26
Article XII. Adrenal hormonal imbalance in acute intermittent porphyria patients: results of a case control study	AIP	liver and long-lasting deregulation of metabolic networks	10.1186/1750-1172-9-54
Article XIII. Erythropoietic Protoporphyria and X-Linked Protoporphyria: pathophysiology, genetics, clinical manifestations, and management	Erythropoietic Protoporphyria	liver dysfunction that developed to cholestatic liver failure requiring transplantation	10.1016/j.ymgme.2019.01.020
Clinical Guide and Update on Porphyriase	AIP, VP, HCP, and amino-levulinic acid dehydratase deficient porphyria	serious abdominal, psychiatric, neurologic, or cardiovascular symptoms	10.1053/j.gastro.2019.04.050

Discussion

Data showed that the most clinical complication is the neurological abnormalities and particularly the occurrence of the paralysis or aggressive behavior , loose of skeletal and smooth muscular control this support the concept that those patient suffer from this disease may be or may not be responsible of the actions and may need an urgent intervention, photosensitivitymay be occurred in some cases of cutenia tarda and erythropoietic porphyria but not all the cases that had been recorded showed this skin rash and bruising and even the occurred of burning

sensation . on the other and some cases had been reported that showed that the abdominal pain and in general GI disturbance may occur that could be vary between generalized abdominal pain and may even showed an intestinal necrosis. There is many other comlplications that occur in generally like hypertension, cardiovascular and liver dysfunction that developed to cholestatic liver failure requiring transplantation

Recommendation : a further study need to be performed on the personality changes that may occur during the disease attack

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