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Acute Intermittent Porphyria - Overview

Miss .Mansi.P.Akolkar[1]. Mrs.Mali.Shubhangi.Ravsaheb[2]

Student of Pratibhatai pawar college of pharmacy Shrirampur.
Department Of Quality Assurance. Pratibhatai pawar college of Pharmacy Shrirampur.
Corresponding E-mail - Mansiakolkar44@gmail.com

ABSTRACT:-

Acute intermittent porphyria (AIP) is a lowpenetrance autosomal dominant disease caused by mutations in the hydroxymethylbilane synthase (HMBS) gene, whic h codes for the third enzyme in the haem production pathway. In HMBS mutation carriers that are susceptible,OverprUnnoduction is induced by triggering factor s such as hormonal changes and regularly used medicines.In addition, harmful haem precursors can build up in the liver. This manifests clinically as acute assault s.Severe stomach discomfort and a variety of neurological and behavioural symptoms characterise this condition.promotes the development of primary liver canc er, hypertension, and kidney disease in the long term failure.Treatment options are limited, and medications that prevent the onset of symptoms are rare.Long-term problems aren't an issue.

Keywords:- Acute intermittent Porphyria,Haem, Hydroxymethylbilane Synthase, Hepatic Porphyria, Porphobilinogen.

Introduction:-

AIP is an autosomal recessive condition marked by a lack of heam biosynthesis. The Porphyrias are a group of disorders that include AIP. This collection of issues is defined by a high level of porphyria and porphyrin accumulation caused by a lack of particular enzymes required for the synthesis of heam, a component of heamoglobin, and other heamoproteins found in cells. Symptoms associated with different types of Porphyria. Porphyria is divided into two types: hepatic and erythropoetic.Porphyrin and porphyrin precursors, as well as related substances, are produced in large quantities in the liver in the hepatic type, and primarily in the bone marrow in the erythropoetic type. "Cuticular Porphyria" is a term used to describe porphyrin with skin manifestations. Acute Porphyria is a word used to describe Porphyria that is characterised by a quick onset of pain and other neurological symptoms. Porphyria is a metabolic disorder caused by a genetic flaw. Acute hepatic porphyria (AIP) is a type of porphyria that affects the liver. The liver is the source of toxic heam metabolites in AIP, which is a hepatic Porphyria. A genetic mutation causes incomplete function of porphobiliogen deaminase (PBGD), resulting in clinical signs of AIP. Because of this, neurotoxic metabolites accumulate upstream.Long-term consequences associated with AIP include primary liver carcinoma, hypertension, and renal failure .There are few recognised therapy options, and none that prevent clinical disease and long-term consequences in HMBS mutant carriers. To lower their risk of symptomatic disease, patients with AIP and genetically predisposed individuals must adhere to lifelong lifestyle modifications .However, there are numerous potential therapy possibilities for AIP from a mechanistic standpoint. In this review, we focus on HMBS stabilisation and the regulation of proteostasis and present an overview of current techniques, the status of relevant therapy, largely gene-related, developments, and emerging therapeutic alternatives.AIP can be fatal, and the clinical signs and symptoms are frequently varied and non-specific. As a result, it is critical to be able to recognise these patients in order to establish a timely and accurate diagnosis. The epidemiology, pathogenesis, clinical presentation, diagnosis, and therapy of AIP, including the role of liver transplantation, are discussed in this article.

Signs and Symptoms:-

AIP is linked to a variety of symptoms and physical findings that can affect a variety of organ systems in the body. The duration and severity of attacks differ greatly from one person to the next. The disorder can have life-threatening consequences in some circumstances, especially if it is not diagnosed and treated properly. It's crucial to remember that AIP is highly varied, and that those who are affected may or may not experience all of the symptoms listed below. Afflicted persons and parents of affected children should discuss their specific situation, related symptoms, and overall prognosis with their physician and medical team. It's crucial to remember that AIP is highly varied, and that those who are affected may or may not experience all of the symptoms listed below.

1. AIP symptoms commonly manifest itself as episodes or "attacks" that last many hours or days. Individuals who have been affected by an

attack usually recover within a few days.

2. The most common symptom associated with AIP is intense abdominal discomfort, which is often the first indicator of an attack.
3. Nausea, vomiting, constipation or diarrhoea, and abdominal swelling are all frequent gastrointestinal symptoms after a panic attack (distention).
4. Damage to neurons outside the central nervous system can also cause neurological symptoms (peripheral neuropathy). Numbness, tingling, and burning sensations are common symptoms of peripheral neuropathy, which start in the feet and sometimes the arms.
5. Irritability, melancholy, anxiety, insomnia, hallucinations, paranoia, disorientation, and altered consciousness ranging from extreme drowsiness (somnolence) to agitation or, in severe cases, coma are some of the psychological symptoms that people experience during attacks.
6. Long-term effects of chronic AIP include high blood pressure (hypertension), renal damage that can lead to kidney failure, and liver malignancies such as hepatocellular carcinoma (HCC) or cholangiocarcinoma (CC).

Causes:-

AIP is a multifactorial condition, which implies that a mix of elements, such as genetic and environmental factors, is required for the disorder's symptoms to manifest. AIP patients had a mutation in the HMBS gene. Genes give instructions for making proteins, which are essential for many bodily processes. When a gene is mutated, the protein output may be defective, inefficient, or missing. This can have an impact on a variety of organ systems in the body, depending on the functions of the specific protein.

- Excessive alcohol consumption.
- Certain harmonal factors.(Endocrine)
- Fasting and dieting .

Epidemiology:-

Due to its rarity as a disease, diversity in clinical presentations, and penetrance, estimating the prevalence of AIP is difficult. Porphyria cutanea tarda (PCT), Acute intermittent porphyria (AIP), and Erythropoeitic porphyria are the three most frequent porphyrias (EPP). AIP is the most frequent form of acute porphyria, affecting one out of every 20,000 people. 1 In the United States, there are thought to be less than 200,000 AIP patients. In Sweden, where a founder effect has been documented, AIP is more common. The AIP mutation has a frequent origin among families from the country's northern regions, according to haplotype research.Due to its rarity as a disease, diversity in clinical presentations, and penetrance, estimating the prevalence of AIP is difficult.

Pathophysiology:-

AIP is a metabolic condition caused by a lack of the enzyme porphobilinogen deaminase (PBGD), which is one of the enzymes involved in the heme biosynthesis pathway (Figure 1). Mutations in the hydroxymethylbilane synthesis (HMBS) gene cause it, and it usually results in a partial shortage of PBGD. PBGD gene mutations cause a 50 percent reduction in enzymatic function, especially in hepatocytes. AIP is a metabolic condition caused by a lack of the enzyme porphobilinogen deaminase (PBGD), which is one of the enzymes involved in the heme biosynthesis pathway (Figure 1). Mutations in the hydroxymethylbilane synthesis (HMBS) gene cause it, and it usually results in a partial shortage of PBGD. Heme is required for the production of haemoglobin as well as the cytochrome P450 enzymes in the liver. Heme biosynthesis takes place all over the body, however it is most prevalent in the erythroblastic system (80%) and the liver (15 percent) Heme is required for the production of haemoglobin as well as the cytochrome P450 enzymes in the liver. Heme biosynthesis takes place all over the body, however it is most prevalent in the erythroblastic system (80%) and the liver (15 %).The liver is the source of hazardous heme biosynthesis metabolites in AIP, which is one of the hepatic porphyrias. The heme route has seven phases that take place in the mitochondria and cytoplasm. 7 The substrates succinyl CoA and glycine are employed by -aminolevulinic acid synthase (ALAS) to make -aminolevulinic acid in the first step (ALA). ALA is subsequently used by ALA dehydratase (ALAD) to produce porphobilinogen (PBG), which is then used as a substrate by PBGD to produce hydroxymethylbilane. The liver is the source of hazardous heme biosynthesis metabolites in AIP, which is one of the hepatic porphyrias. The heme route has 7 phases that take place in the mitochondria and cytoplasm. The substrates succinyl CoA and glycine are employed by -aminolevulinic acid in the first step.ALA is subsequently used by ALA dehydratase (ALAD) to produce porphobilinogen (PBG), which is then used as a substrate by PBGD to produce hydroxymethylbilane. Hydroxymethylbilane is then used by Uroporphyrinogen III cosynthesase to produce uroporphyrinogen III. Coprophyrinogen III is formed by decarboxylation of uroporphyrinogen III, which then goes through three more stages in the mitochondria to produce heme. Due to a lack of inhibition of ALAS, a partial defect in PBGD causes a buildup of the metabolites PBG and ALA in AIP. 8 Factors that promote ALAS transcription or function, such as hormonal changes throughout the menstrual cycle, medications, fasting, and infections, might trigger acute episodes. The neuropsychiatric and visceral symptoms seen in AIP are caused by the accumulation of these metabolites.

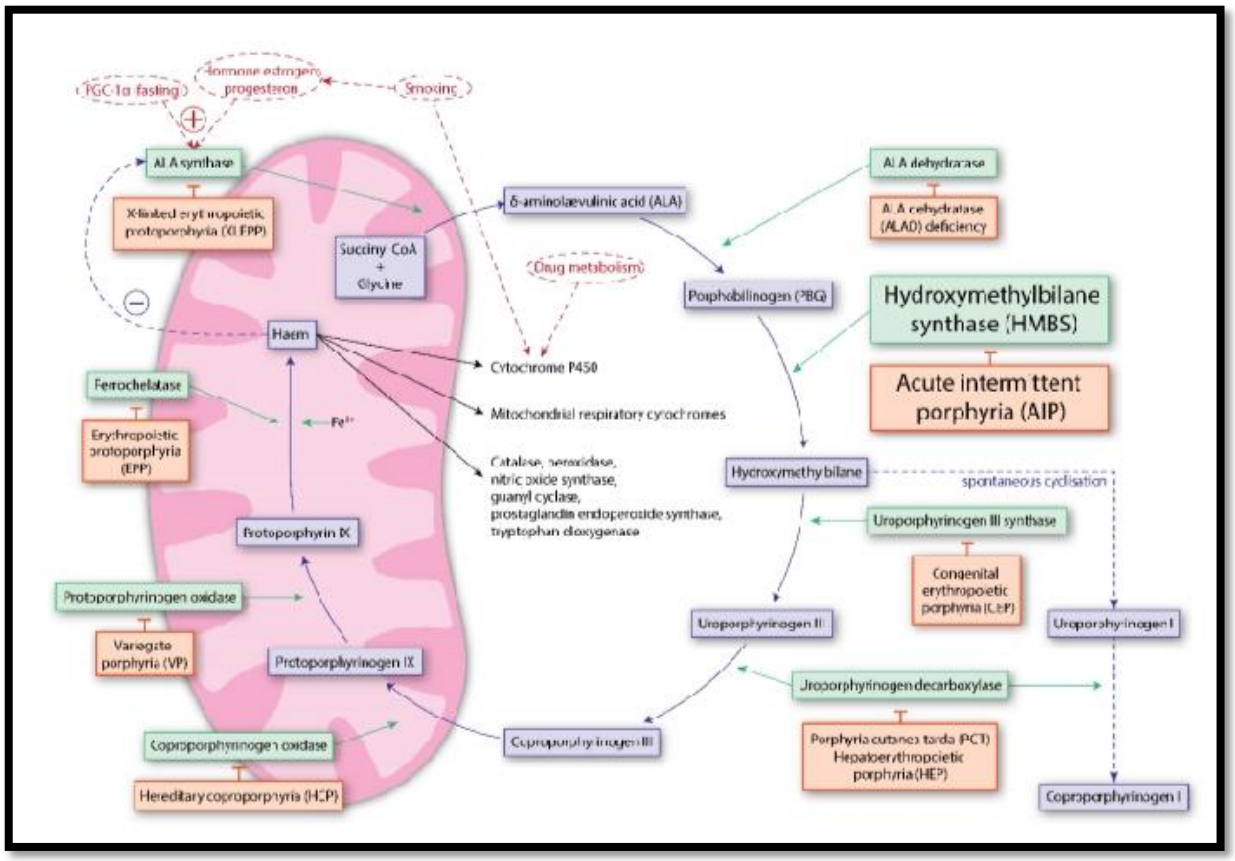

Figure 1:- Heam biosynthesis and associated with the Porphyrias disorder.

- **Current Treatment Options For Acute Intermittent Porphyria:-**

Established Treatment for Sporadic and Recurrent Acute Attack:-

Haem infusions (Panhematin®, Recordati Rare Diseases, Xellia Pharmaceuticals USA, LLC, Buffalo Grove, IL, USA) or haem arginate (Normosang®, Recordati Rare Diseases, Puteaux, France) are currently the chosen specific treatment for sporadic acute attacks in most contexts. Through the negative feedback loop in haem production, haem replenishes hepatic haem and, as a result, downregulates ALAS1 . Infusions of haem are usually well tolerated and effective in treating sporadic acute episodes. When administered as an off-label preventative treatment in individuals with recurrent episodes, however, maintaining central venous access, developing iron overload, and possibly losing efficacy during extended or repeated haem therapy can be difficult . Furthermore, studies show that frequent haem infusions can activate hepatic haem oxygenase 1, resulting in increased ALAS1 activity and consequently disease activity [Infusions of high-carbohydrate foods are popular.also used to treat occasional attacks, either as a stand-alone treatment or in combination with other medications.severe attack, either in conjunction with haem infusions or as the primary treatment in some placeswhere haem isn't present. However, the treatment's effectiveness is debatable. It has been successful.hyperglycemia inhibits the production of peroxisome proliferator activated receptor coactivator 1 (PGC-1), a key transcriptional coactivator factor, in mice.for the regulation of ALAS1 expression . Insulin secretion increases as a result of this. PGC-1 alpha suppression is caused by the protein kinase AKT . ALAS1 expression is controlled . The protein kinase AKT is activated as a result of the following increase in insulin , resulting in inhibition. PGC-1 is a kind of protein kinase C. For women who have repeated attacks associated with their menstrual cycle, aAnalogues of gonadotropin-releasing hormone are available.

Liver And Kidney Transplantation:-

In the recent decade, liver transplantation has been employed as a last-resort therapeutic option for seriously affected AIP patients, particularly those with intense and repeated acute symptoms. The liver is the primary source of haem precursor overproduction in acute hepatic porphyrias, and liver transplantation corrects the metabolic abnormality. ALA and PBG excretion should be normalised . Despite the fact that the majority of people who have had a liver transplantacquire a higher quality of life, with a survival rate comparable to other liver indicationsTransplantation is not without its difficulties and risks, and there is also the possibility of failure. According to a large French AIP cohort, up to 50% of AIP patients would develop porphyria-associated kidney illness, which is thought to be caused by ALA's action on tubular cells . The severity of porphyria-associated kidney illness has been linked to variations in the peptide transporter 2 (PEPT2) gene . PEPT2 has a core component. role in ALA tubular reabsorption, and the use of transporter inhibitors like As a result, the angiotensin II receptor antagonist losartan has been proposed as a possible treatment.AIP has a

nephroprotective approach . AIP patients can develop severe end-stage renal disease in some circumstances. Renal disease In certain patients, kidney transplantation may be therapeutic and eliminate the need for dialysis. In some patients, kidney transplantation may be beneficial, lowering or eliminating AIP attacks and healing skin lesions caused by spontaneously produced uroporphyrins, which are only poorly filtered across the dialysis barrier . The use of a combined liver and kidney transplant has also been described. AIP individuals with renal failure who were seriously afflicted had a successful outcome.

Ribonucleic acid (RNA) Interference therapy:-

Interference Therapy with Ribonucleic Acid (RNA)Givosiran (GIVLAARI®, Alnylam Pharmaceuticals, Cambridge, MA, USA) is an RNAi treatment that reduces hepatic ALAS1 messenger RNA coupled to N-acetyl-galactosamine. for liver-specific delivery. ALAS1 overexpression is induced by phenobarbital in mice.Kidney transplantation may be beneficial in these patients, eliminating or reducing the frequency of AIP attacks, according to Hmbs-deficient mice.As a result, ALA and PBG accumulate in both plasma and urine, resulting in acute attacks . During an ongoing acute assault, siRNA was given to Hmbs-deficient animals, which lowered both ALAS1 expression and ALA/PBG levels.While prophylactic siRNA delivery reduced phenobarbital-induced attack as a result of the drug,The use of siRNA as a method to prevent and treat acute assaults has been demonstrated .Givosiran is a drug that has been licenced to treat adults with acute hepatic porphyria. in November 2019 in the United States and in January 2020 in the European Union for Treatment of adults and adolescents aged 12 and up. The approvals were unanimous. based on the good results of the ENVISION phase III trial.ENVISION included patients with recurrent acute hepatic porphyria, the vast majority of whom had AIP, and notable findings included a considerable reduction in attack rates as well as ALA and PBG levels.When comparing the givosiran group to the placebo group, the concentrations were higher in the givosiran group. the key that has been reportedAdverse effects were linked to liver and kidney function, with serum levels rising.givosiran-treated patients' aminotransferase levels and estimated glomerular filtration rateparticipants. Only data from the first year is available, therefore long-term consequences and efficacy are unknown.The results of the phase 3 study's first six months have been published in detail.Givosiran is already being used to treat seriously impacted patients who have recurrent acute attacks in clinical practise. Based on patient reports of side effects and observation of their treatment,This siRNA therapy necessitates close patient monitoring, with a special focus on kidney function.liver enzymes, lipase, and homocysteine levels.

- **Additional Potential Therapeutic Advancements**

Enzyme Replacement Therapy (ERT):-

Development of enzyme replacement therapy was attempted in the earlyyears of 2000. Treatment with intravenously administered recombinant human HMBSdemonstrated some biochemical evidence and potential in both mice and symptomfree individuals by decreasing the plasma and urinary concentrations of ALA and PBG.However, clinical studies were unsuccessful , presumably due to the intravenous infusion of erythroid HMBS that was not focused to the liver , and it was never further developed.

Gene Replacement Therapy and mRNA Therapeutics:-

To restore normal HMBS activity, the proper HMBS DNA or mRNA sequence is delivered to liver cells via gene replacement therapy were the first to reveal nonviral gene vectors aimed at correcting AIP. Hmbs-deficient mice were protected from attacks generated by transgene-expressing, first-generation recombinant adenovirus in a study utilising transgene-expressing, first-generation recombinant adenovirus. Phenobarbital However, the treatment had no long-term effects and could be harmful.In subsequent studies, utilising a helper-dependent adenovirus containing the HMBS gene, full and sustained protection from both the buildup of ALA and PBG and acute attacks in Hmbs-deficient mice was established. gene and a liver-specific promoter However, this vector was not acceptable for clinical usetrials. Two separate research groups demonstrated non-toxic and long-term effects in the Hmbs-deficient mouse model using an adeno-associated virus (AAV) vector devoid of the genes required for viral gene expression . The AAV2/5-virus is a kind of adeno-associated virus .In cynomolgus, the orphan medication HMBS was found to be safe and effective.Monkeys The recombinant protein was found to be effective in a phase I clinical investigation.The AAV gene vector was found to be safe, although without metabolic correction.that the vector dosages were insufficient to cause adequate liver transduction .This problem was solved by developing a new gene therapy vector with an inducible promotor that responds to oestrogens, hunger, and certain porphyrinogenic compounds.medicines, as well as the development of a hyperfunctional bioengineered HMBS version,In Hmbs-deficient mice, both techniques showed encouraging outcomes. A preclinical investigation using intravenous human HMBS mRNA encapsulated in lipid nanoparticles yielded promising results (Moderna Inc., Cambridge, MA,USA). This study found abundant HMBS protein expression in hepatocytes of Hmbsdeficient mice, as well as rapid normalisation of urine porphyrin precursor excretion in ongoing attacks and in a chemically induced acute porphyria rabbit model, indicating that systemic human HMBS mRNA could be used as a potential therapy for AIP . Repeated dosage in Hmbs-deficient mice resulted in sustained efficacy and therapeutic improvement without indications of hepatotoxicity, and several doses to nonhuman primates exhibited translatability.

Hepatocyte Transplantation:-

Hepatocyte transplantation is less invasive and expensive than liver transplantation, with less side effects and the ability to repeat the engraftment operation ,providing significant benefits over traditional transplantation methods. Hepatocyte transplantation is less invasive and expensive than liver transplantation, with less side effects and the ability to repeat the engraftment operation , providing significant benefits over traditional transplantation

methods.Wild-type hepatocytes were transplanted into the livers of Hmbs-deficient mice.After phenobarbital induction, mice with transplanted livers showed a 50% drop in ALA and PBG in plasma compared to non-treated mice .Furthermore,ALA and PBG that had accumulated in the liver were metabolised by transplanted hepatocytes.Both findings suggest that a modification in a subset of cells may be sufficient to enhance performance.However, no more follow-up trials on hepatocyte transplantation for AIP correction have been reported, and long-term improvement in metabolic deficits is still a topic that needs to be researched .

Conclusion:-

The management of AIP includes treatment of acute attacks, prevention of attacks, long-term monitoring and treatment of chronic complications. Intravenous injection of heme is the most effective method of treating acute attacks. Carbohydrate loading is used when heme is unavailable or in the event of mild attacks. The management of AIP includes treatment of acute attacks, prevention of attacks, long-term monitoring and treatment of chronic complications. Intravenous injection of heme is the most effective method of treating acute attacks. Carbohydrate loading is used when heme is unavailable or in the event of mild attacks.

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