Anaesthetic Considerations in Porphyric Patients

Essay

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بسم الله الرحمن الرحيم

قالوا سبحانك لا علم لنا إلا ما علمتنا إنك أنت العليم الحكيم

صدق الله العظيم

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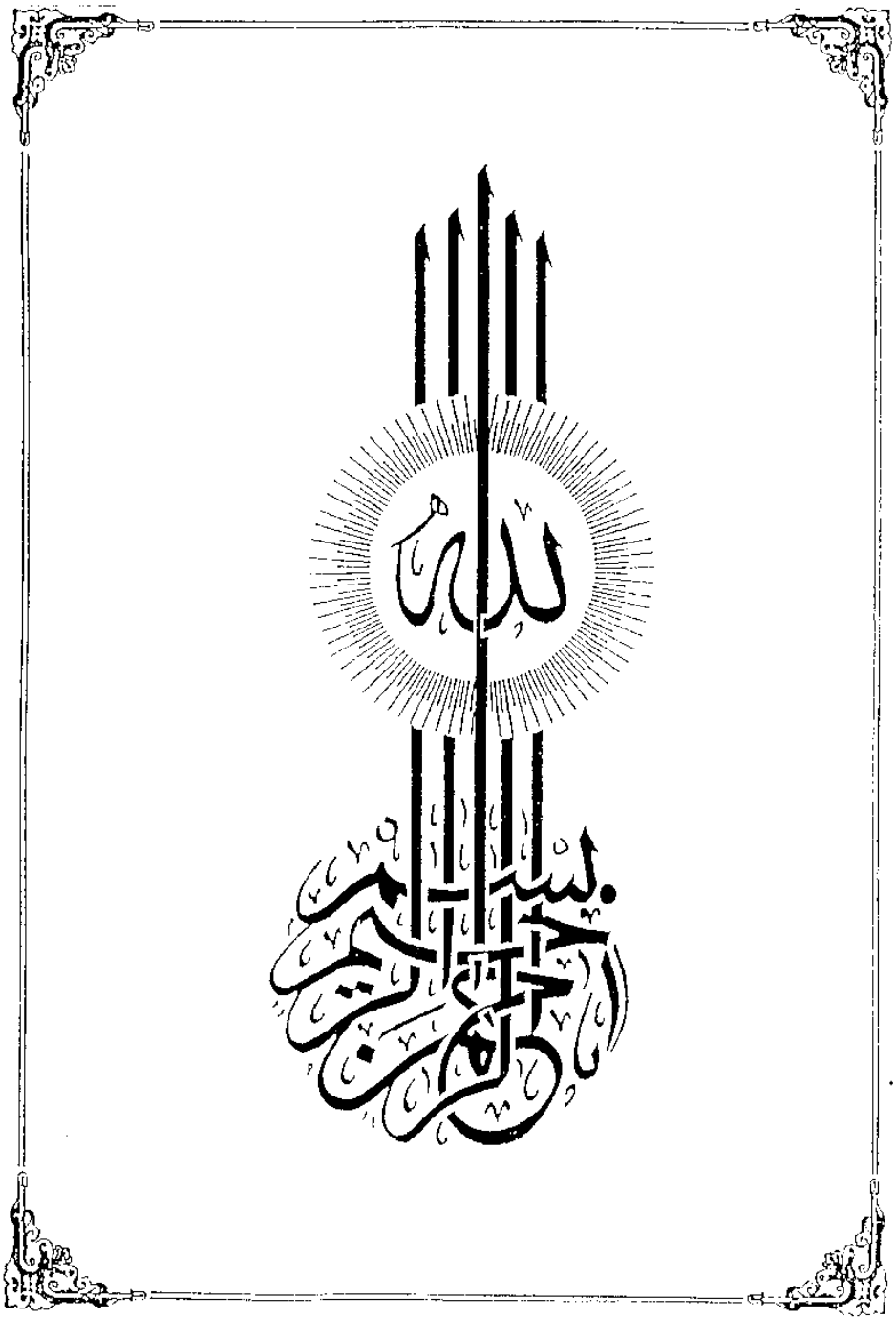

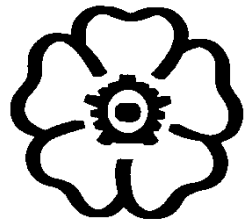

To My Family

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Introduction

Introduction

The porphyrias are group of inborn errors of metabolism characterized by overproduction of porphyrin compounds and their precursors. The first recorded case of acute intermittent porphyria by ***Stokvis*** in 1889 was a woman who excreted dark red urine and died after ingestion of sulfanmethane (sulfonal ®). The term porphyria was introduced by ***Hans Fischer*** and was further popularized by the extensive early clinical and chemical investigations of Waldenstram. The porphyrias are present among the pharmacogenetic conditions of concern to the anaesthesiologists. The drug induced acute attack may be life threatening and some drugs in common use in anaesthetic practice are highly dangerous in porphyria. The real problem anaesthesia once posed for the porphyric patient is reflected in the number of acute porphyric attacks precipitated by the thiopentone induction of anaesthesia in patients admitted to Groote Schuur hospital, Cape Town between 1950 and 1971 when 31 of 145 suffered from acute attack, two proved fatal since that time the identification of patients at risk by the biochemical testing all of members of proband families has lead to dramatic reduction in the number of the acute porphyric admissions ***(Meissner P.N. and Hift R.J., 1991).*** So it is important to the anaesthesiologist to study the types of porphyrias and know how to diagnose it by a combination of family history, clinical and biochemical examination and this will allow them to approach the task of anaesthetizing the porphyric patients safely.

Porphyria

Porphyria

The porphyrias are disorders associated with inherited or acquired disturbances in haem biosynthesis. They are usually inherited and may be associated with striking accumulations of haem pathway intermediates. Porphyrias are more prevalent and more often manifested in adults than as most well characterized inborn errors of major metabolic disorders ***(Anderson, 1991)***. Each of porphyrias is characterized by a unique pattern of overproduction, accumulation and excretion of intermediates of haem biosynthesis these patterns are the metabolic expression of deficiencies of specific enzymes of haem biosynthetic pathway, clinical expression is variable and influenced by factors such as hormones, drugs and nutrition that have regulatory effects on the biosynthetic pathway ***(Bonkowsky and Schady, 1987).***

Haem biosynthetic pathway in porphyrias:

The porphyrins are molecular components of haem serves in aerobic system as the prosthetic group that combines with various apoproteins to form haemoproteins which are large molecules concerned with essential functions of oxidation, electron transport and hydroperoxidation ***(Adler et al., 1975).*** These haemoproteins include haemoglobin, myoglobin, mitochondrial and microsomal cytochromes, catalase, peroxidase and tryptophan pyrrolase. Their basic biochemical functions involve the transport of molecular oxygen, activation of oxygen, and transfer of electrons to oxygen as the final receiver in the electron transport system.

Interestingly, there is no physiological role for free porphyrins which also are chemically related to the plant chlorophylls and the vitamin B12 carrying ring ***(Bissell, 1985).***

According to ***(Kappas and his colleagues, 1983)*** the biosynthesis of haem from eight molecules of amino acid glycine and the carbohydrate intermediary succinyl co-enzyme A is summarized stepwise in the following equations:

1. Succinyl Co-enzyme A + glycine $\xrightarrow{\text{δ aminolevulinic acid synthetase}}$ δ-aminolevulinic acid (ALA) + CO_2

The synthesis of this δ-aminolevulinic acid which is five carbon amino keton is an intramitochondrial reactions and therefore is not present in mature erythrocyte. ALA synthetase is synthesized in cytoplasmic ribosomes and transported to mitochondria.

ALA synthetase has a short half life, a specific protease facilitates its degradation and rapid turnover rate. This is appropriate for the enzyme that catalyze the rate limiting reaction in the biosynthesis of the haem. The Krebs tricarboxylic acid cycle supplies most of the succinyl co-enzyme A.

Pyridoxal phosphatase (vitamin B6) is an obligate cofactor in this condensation step, which is the only reaction in the entire process of haem production that requires a vitamin cofactor and energy. All subsequent

reactions are strongly favored thermodynamically and are therefore basically irreversible. The initial part of this reaction is between pyridoxal phosphate and a sulfhydral group of the active site of ALA synthetase, then follow the formation of a chief base with glycine, and finally a condensation with succinyl co enzyme A. Most importantly, this step is the rate limiting one of the entire haem biosynthetic pathway. This regulation is achieved by controlling the amount of ALA synthetase activity which in turn is thought to be controlled by the rate of synthesis of this enzyme.

The regulatory process involves the biochemical mechanisms of feedback (end product) repression and inhibition as well as substrate hormonal and chemical induction. The direct inhibition of existing ALA synthetase by haem is not of physiological significance.

2. 2 ALA $\xrightarrow{\text{ALA dehydrase}}$ Porphobilinogen (PBG).

This condensation of two molecules of ALA to monopyrrole PBG and the two following reactions are extramitochondrial. The enzyme ALA dehydrase has a reactivity velocity that grossly exceeds that of ALA synthetase,therefore it has no regulatory control on the rate of haem synthesis.

3. 4 PBG-PBG deaminase —(Uroporphyrinogen I synthetase)→ Uroporphyrinogen III.
(Uroporphyrinogen III cosynthetase)

This is a condensation to form a cyclic porphyrin that is a tetrapyrrol-Two enzymes facilitates this reaction in which four possible isomers of uroporphyrinogen could be formed. Initially PBG deaminase converts PBG to the straight chain tetrapyrrole hydroxymethyl bilane, which then spontaneously cycles to uroporphyrinogen I, uroporphyrinogen III cosynthetase converts hydroxymethyl bilane to the macrocyclic tetrapyrrole uroporphyrinogen III isomer prior to the ring closure. A genetic deficiency of the uroporphyrinogen III cosynthetase in human red blood cells results in clinical entity of congenital erythropoietic porphyria. However, it is the genetic deficiency of PBG-deaminase that lead to intermittent acute porphyria. Human chromosome 11 is the site of encoding for PBG deaminase which is reduced to 50 percent of normal activity in the liver, mitogen-stimulated lymphocytes, cultured fibroblasts, amniotic cells, and erythrocytes.

4. Uroporphyrinogen III —(Decarboxylase)→ Coproporphyrinogen III.

Only porphyrin isomers of type III are intermediates in the haem biosynthetic pathway. This inherited disease porphyria cutanea tarada is associated with a deficiency of this decarboxylase.

5. Coproporphyrinogen III —(Coproporphyrinogen oxidase)→ Protoporphyrinogen IX.

This and all subsequent steps are intramitochondrial. The coproporphyrinogen oxidase enzyme is located in the intermembranous space. Hereditary coproporphyrias are the disease associated with the deficiency of this oxidative decarboxylase.

6. Protoporphyrinogen IX —(Coporphyrinogen oxidase)→ Protoporphyrin IX.

Because haem is actually formed within the inner mitochondrial membrane, protoporphyrin IX must cross the inner membrane. Deficiency of this dehydrogenase results in variegate porphyria.

7. Protoporphyrin IX + reduced iron $(Fe)^{++}$ —(Ferrocatalase)→ Haem.

The catabolism of haem produces bile pigments and not porphyrins, because the synthesis of haem is an absolutely essential process (a total blockade of haem biosynthesis is incompatible with life). There are numerous compensatory mechanisms for any genetic and/or acquired enzymatic deficiencies. Thus the maintenance of steady state haem