Anesthetic Considerations In Inborn Errors of Metabolism

Essay

Submitted for partial fulfillment of the master degree in ***Anesthesia***

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ
قَالُوا سُبْحَانَكَ لاَ عِلْمَ لَنَا إِلاَّ مَا
عَلَّمْتَنَا إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيمُ
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Alyeldin Mohamed Mohamed Elgamil

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List of Abbreviations

AIP	:	Acute intermittent porphyria
ALA	:	Amino levulinic acid
BH4	:	Tetrahydrobiopterin
BMT	:	Bone marrow transplantation
CAMP	:	Cyclic adenosine monophosphate
CGMP	:	Cyclic guanosine monophosphate
CNS	:	Central nervous system
Co	:	Cobalt
CoA	:	Coenzyme A
CSF	:	Cerebrospinal fluid
DDAVP	:	Desmopressin
ERT	:	Enzyme replacement therapy
FVC	:	Forced vital capacity
GAGs	:	Glycosaminoglycans
GSD	:	Glycogen storage diseases
GTP	:	Gusnosine triphosphate
HCP	:	Hereditary coproporphyria
HSM	:	Hepatosplenomegally
ICP	:	Intra cranial pressure
IMDs	:	Inherited metabolic disorders
IQ	:	Intelligence quotient
MMA	:	Methylmalonic acid
MPS	:	mucopolysaccharidoses

List of Abbreviations (Cont.)

NAD	:	Nicotinamide adenine dinucleotide
NPD	:	Niemann-Pick disease
OTC	:	Ornithine transcarbamylase
PCT	:	Porphyria cutanea tarda
SIADH	:	Syndrome of inappropriate secretion of antidiuretic hormone
SRT	:	Substrate reduction therapy
UDP	:	Uridine diphosphate
VP	:	Variegate Porphyria

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Introduction

The expression 'Inborn error of metabolism' was coined to describe disorders resulting from the failure of a step or steps within a metabolic pathway. The number and complexity of metabolic processes required to maintain homeostasis is vast and so it follows that the spectrum of human disorders ascribed to inherited defects in metabolism is considerable **(Clarke, 2006).**

Although some of these conditions do not have much impact on the perioperative management plan, others such as the mucopolysaccharidoses (MPS) represent some of the most challenging patients who an anesthetist is likely to encounter. Inherited metabolic disorders (IMDs) are a genetically heterogenous group and may present at any age. Inheritance is often autosomal recessive but this is not invariable. Many conditions are extremely rare and reports of experience of anesthesia in the literature are limited. An overview of some of the commoner IMDs is presented in Table 1 **(Stuart and Ahmad, 2011).**

Inborn errors of metabolism manifest as a variety of metabolic defects that may complicate the management of anesthesia . In some instances, these defects are clinically asymptomatic and manifest only in response to specific triggering events, such as certain drugs or foods **(Tantawy, 2008).**

Inherited metabolic diseases, while individually rare conditions, contribute significantly to pediatric morbidity and mortality. Anesthetists may encounter patients with inherited metabolic diseases presenting for both emergency and elective surgery. The management of these patients is often challenging due to the multisystemic manifestations of many IMDs. Catastrophic metabolic decompensation may occur in the perioperative period and a multidisciplinary approach is

essential to ensure safe management of these patients **(Stuart and Ahmad, 2011).**

Table (1): Overview of inherited metabolic diseases

Metabolic classification of inherited disorders	Clinical examples, inheritance pattern, and incidence	Clinical features
Disorders of amino acid metabolism	Phenylketonuria (autosomal recessive, 1:10 000-150 000)	Mental retardation and seizures
	Homocystinuria (autosomal recessive, 1:200 000)	Marfanoid phenotype, neurodevelopmental delay, high risk of thromboembolism, and cardiovascular disease
Disorders of branched-chain amino acid metabolism	Maple syrup urine disease (autosomal recessive, 1: 180 000)	Hypotonia, hypoglycaemia, ketoacidosis, seizures, coma, sweet smell of urine
The urea cycle disorders	Ornithine transcarbamylase deficiency (X-linked dominant, 1:80 000)	Neonatal hyperammonaemic encephalopathy, seizures, coma. Ataxia and behavioural abnormalities in older children
	4 other urea cycle defects are autosomal recessive	
The organic acidaemias	Propionic acidaemia (autosomal recessive, 1: 100 000)	Similar in both: tachypnoea, lethargy, vomiting, dehydration, metabolic acidosis, hypoglycaemia, ketoacidosis, neutropaenia, hyperammonaemia, encephalopathy
	Methylmalonic acidaemia (autosomal recessive, 1: 48 000)	
Disorders of carbohydrate metabolism	Galactosaemia (autosomal recessive, 1:60 000)	Jaundice, hepatomegaly, hypoglycaemia, seizures, Escherichia coli sepsis, cirrhosis, mental retardation
	Glycogen storage diseases	See Table 3
Lysosomal storage diseases	Lipidoses (Tay-Sachs, Gaucher, Niemann-Pick, Fabry, Krabbe disease)	Lysosomal accumulation of specific sphingolipid substrates, chronic presentation, hepatomegaly, developmental delay
	Mucopolysaccharidoses	See Table 5
Disorders of fatty acid oxidation	Medium-chain acyl-coA dehydrogenase deficiency (autosomal recessive, 1: 17 000)	Acute encephalopathy, seizures, hypoglycaemia, elevated ammonia, cardiovascular collapse

(Stuart and Ahmad, 2011).

Aim of the Work

The aim of the work is to provide the reader with a concise description of some of these rare conditions and highlight some of the key principles of perioperative management.

Anesthetic Considerations in Porphyria

Introduction

Although rare, latent porphyrias may have detrimental effects on patient outcome, in particular during perioperative care. However, due to the rarity of this disease, the literature lacks systematic research concerning the risks of anesthesia in porphyrinic patients. Porphyria originates from the Greek word porphura, which means ‘purple pigment ’and refers to the purple discoloration of skin and urine during an episode of porphyria **(James and Hift, 2000).**

The term porphyria refers to a heterogeneous group of metabolic diseases caused by enzymatic defects in the biosynthesis of haem, the central component of the oxygen transporter hemoglobin. In addition to hemoglobin, haem is an essential component in the synthesis of myoglobin, catalase, peroxidase and respiratory and P450 liver cytochrome **(Ajioka et al., 2006)**.

In porphyrias, haem precursors are excessively produced and they subsequently heap up in various tissues and organs. The accumulation of haem in the body may lead to neurovisceral and/or photocutaneous symptoms and purple colorization of tissues and organs. The physiological disturbances as induced by haem accumulation are associated with increased morbidity and mortality . Porphyrias are classified as hepatic or erythropoietic porphyrias, based on the

characteristic origin overproduction and accumulation. Patients with porphyria commonly present in three different ways with cutaneous lesions, acute attacks, or both . The prevalence of porphyria varies widely from country to country and depends on the type, of which porphyria cutanea tarda (PCT) and acute intermittent porphyria (AIP) are the most widespread **(Thadani et al., 2000)**.

Despite this low prevalence, it is important that anesthesiologists have insight in the pathophysiological process, clinical signs and treatment of these diseases since acute porphyrias may typically be induced by anesthetic strategies. Furthermore, anesthesiologists may be involved in the treatment of this disease during an acute episode, which consists of cardiovascular support, mechanical ventilation and analgesia. Indeed, anesthetic agents like etomidate, barbiturates, clonidine and benzodiazepines are among the drugs that may precipitate acute attacks of porphyria **(Deybach et al., 2006)**.

Physiology and pathophysiology

The porphyrias are a group of inherited or acquired enzymatic defects of heme biosynthesis. Each type of porphyria has a characteristic pattern of overproduction and accumulation of heme precursors based upon the location of the dysfunctional enzyme in the heme synthetic pathway (Fig.1).

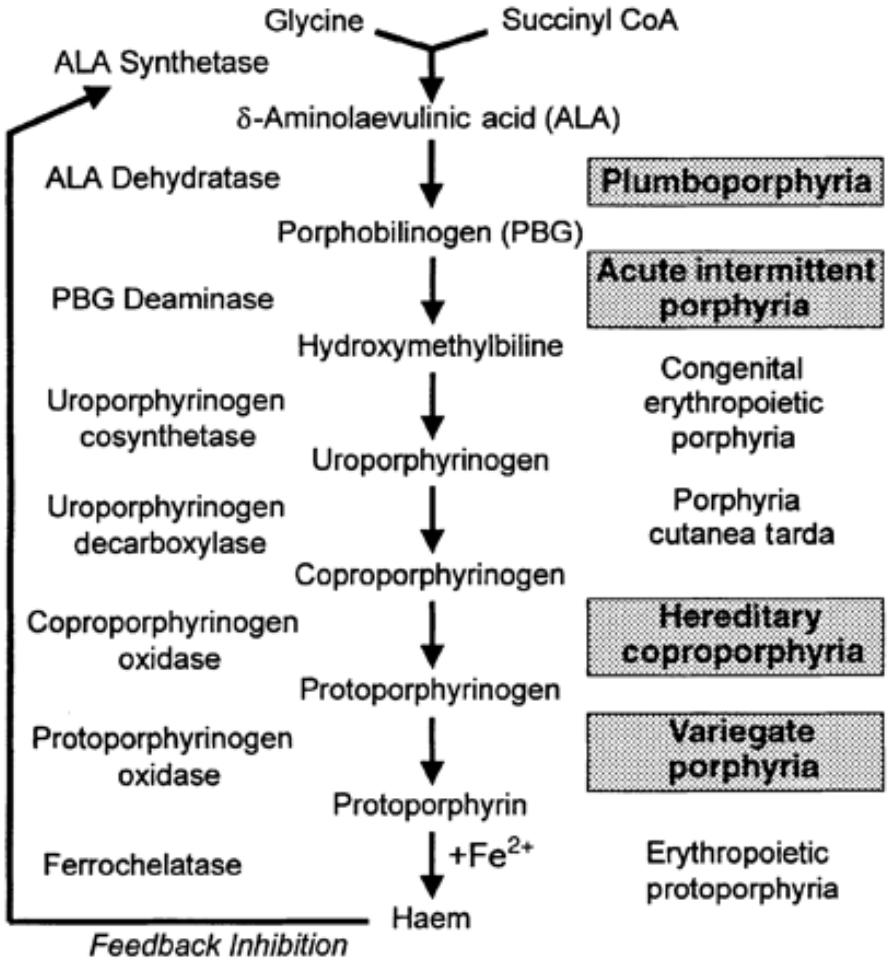

Fig. (1): Metabolic pathways for heme synthesis. Enzymes are noted on the feedback inhibition loop of the sequence, and the type of porphyria associated with the enzyme deficiency is designated on the right. Examples of acute porphyrias are indicated by the boxes **(James and Hift, 2000).**

The rate limiting step in heme synthesis is the condensation of succinyl CoA and glycine to form delta-amino levulinic acid (ALA), catalyzed by the mitochondrial enzyme ALA synthetase. The basal activity of ALA synthetase is substantially lower than that of subsequent enzymes in the synthetic pathway, and therefore changes in ALA synthetase activity are rate limiting, controlling the rate of heme synthesis. Heme, the end product of the synthetic pathway,

exerts negative feedback regulation on ALA synthetase activity. The specific enzyme deficit in each type of porphyria results in a partial block in heme biosynthesis and lower intramitochondrial heme levels (see Fig. 1). Decreased negative feedback from heme contributes to the elevated "baseline" ALA synthetase activity which is characteristic of the porphyrias **(James and Hift, 2000)**.

The manifestions of the disease are thought to be due to increased ALA synthetase activity, increased porphyrin accumulation in the tissues, or decreased heme production. The increased ALA synthetase activity results in elevated levels of heme precursors proximal to the site of the specific enzyme deficiency. These precursors are colorless and nonfluorescent porphyrinogens. Irreversible oxidation of these porphyrinogens causes the formation of porphyrins, which have no known physiologic function but are highly reactive oxidants. The accumulation of porphyrins in the epidermal skin layers leads to cutaneous photosensitivity **(Jensen et al., 1995)**.

Acute porphyria often causes severe neuropathy, the basis for multisystem impairment. Changes in autonomic ganglia, anterior horns of the spinal cord, peripheral nerves, brainstem nuclei, cerebellar axons, schwann cells and myelin sheaths have been demonstrated. Neuronal damage and axonal degeneration may be the primary pathologic lesions, with later axonal changes leading to secondary demyelination **(Jensen et al., 1995)**.

Many hypotheses have been proposed to explain the mechanism of porphyric neuropathy. Two of the most plausible attribute the neuronal dysfunction to direct neurotoxicity of ALA [not porphobilinogen (PBG)], or to diminished intraneuronal heme level or both. In addition, there may be a significant relationship between tryptophan