REVIEW ARTICLE

Elucidating the Possible Mechanism of Renal Dysfunction in Alpha Thalassaemia: A Review

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ABSTRACT

Recent improvement in the treatment and management of α-thalassaemia has enabled patients to live longer and have better quality of life, thus revealing other complications related to the disorder mainly due to the effects of chronic ineffective erythropoiesis and iron overload. We review the renal dysfunction seen in α-thalassaemia as it has been reported (published and personal communication) that the complications presented are more severe than those found in β-thalassaemia patients of similar severity clinically. This review aims to shed light on emerging complications that are currently faced by α-thalassaemia patients as they progress further in life

Keywords: α-thalassaemia, Renal dysfunction, Nephropathy, Complication, Thalassaemia management

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INTRODUCTION

The human haemoglobin (Hb) is a tetrameric protein (a quaternary structure of four subunits) with two alpha (α)-like and two beta (β)-like globin chains. Each folded chain contains a heme protein which binds one molecule of oxygen. Thalassaemia is caused by a decrease or absence of the affected globin chain production and the hallmark of this disorder is ineffective erythropoiesis. Depending on which globin chain is affected, thalassaemia can be categorised into mainly α- or β-thalassaemia. α-Thalassaemia typically occurs in those of African and Southeast Asian descent while β-thalassaemia traditionally affects those of Mediterranean, African and Southeast Asian descent (1). Vichinsky E. (2005) estimated that the incidence of thalassaemia will increase to over 900,000 births in 20 years and changing demographics due to migration will cause the disorder to become more common in many regions including Northern America and Europe. This increase includes β-thalassaemia major births as well as severe α-thalassaemia disorders (2).

With the advancement of treatment and management of thalassaemia, the quality of life for many patients have improved significantly, thus, many other associated complications are now rising in frequency for example renal dysfunction and cardiac disorders. Numerous studies have been conducted on the clinical manifestations of β-thalassaemia, however, there are limited studies on the management of α-thalassaemia especially in terms of renal dysfunction (3, 4, 5, 6). Studies have shown that α-thalassaemia patients with similar severity to their β-thalassaemia counterparts exhibit a more severe renal dysfunction (3, 4).

A review of the possible mechanisms of α-thalassaemia nephropathy could perhaps shed some light on how to improve the treatment and management of α-thalassaemia disorders particularly Hb H disease as the disease progresses and also lead to further investigations in this area.

α-THALASSAEMIA
α-Thalassaemia occurs from the lack or non-existence of α-globin chain generation. α-Thalassaemia carriers make up approximately 5% of the world population and it is considered a common monogenic autosomal recessive gene disorder. Clinical manifestations of this disorder ranges from asymptomatic microcytic, hypochromic anaemia to fatal in utero haemolytic anaemia (7,8). Healthy unaffected individuals have 4 α-globin genes on each allele with a *cis*-pair (αα/αα) found on chromosome 16.

Haemoglobin Synthesis During Development
Haemoglobin subtypes throughout human life are

composed of the embryonic (ζ2ε2, α2ε2, ζ2γ2), foetal (α2γ2, α2β2) and adult haemoglobin (α2β2, α2δ2) (9). The development of haemoglobins specific to the embryonic stage of development was first reported by Huehns et al., 1961 (10). Hb F (α2γ2) increases to be the predominant haemoglobin subtype and by eight weeks of gestation, 90% of the total haemoglobin are Hb F and remain the major haemoglobin throughout rest of gestation (9, 11). After birth, the Hb F declines and by sixth month of age, Hb A begins to be the predominant haemoglobin subtype found (9, 12) (Fig. 1).
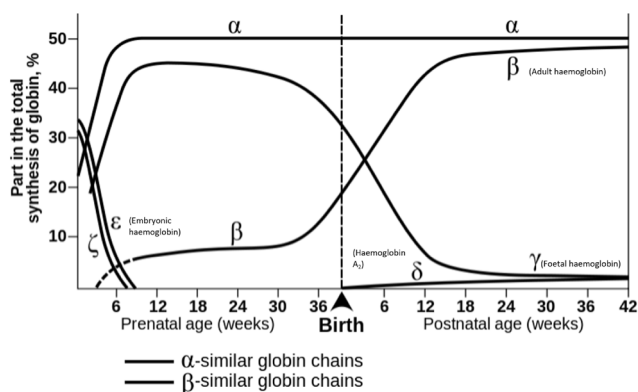

Fig. 1 : Changes in globin chain synthesis in human development

MOLECULAR CLASSIFICATION AND CLINICAL MANIFESTATION OF α-THALASSAEMIA

Currently, there are approximately 128 identified mutations of **α**-thalassaemia, with approximately 50 deletions affecting one (-α/) or both (--) α genes and at least 69 non-deletional α-thalassaemia mutations (7,13,14).

Non-deletional α+-thalassaemia

Non-deletional α+-thalassaemia involves mutations that impair the regulation of gene expression, e.g. mutations in the promoter region, start codon (ATG), splice sites (GT/AG), terminating codon (TAA) and the polyadenylation (polyA) site (AATAA) that inhibit the synthesis of mRNA, the translation of mRNA or the stabilisation of the globin chain. In addition, frameshift mutations, in-frame deletions and nonsense mutations that induce nonsense-mediated decay of mRNA and/or irregular proteins are also included in this category. Such variants can result in a more severe phenotype than deletional mutations. Common non-deletional α+-thalassaemia includes Hb Pakse, Hb Constant Spring, and unstable variants such as Hb Adana and Hb Quang Sze (7,14,15).

Non-deletional Hb H infants, i.e. Hb H-Constant Spring has an average haemoglobin level of 7.0 g/dL with little changes as they develop. Deletional Hb H disease infants, on the other hand, has haemoglobin level of approximately 8.5 g/dL and this rises to about 9.4 g/dL with age (8). Non-deletional Hb H patients typically have associated complications that occur during the first 10 years of life, including growth retardation, requiring

transfusion therapy, cholelithiasis, hepatosplenomegaly, and iron overload (7,8,16). Non-deletional Hb H disease ranges from mild intermediate severity to infants dying in utero (Hb H hydrops foetalis) (16).

Deletional α+-thalassaemia

The α-globin linked genes are found within two nearly identical 4 kb duplication units. These duplication units can be divided into three homologous sub-segments, X, Y and Z punctuated by three non-homologous elements. Reciprocal recombination of the two Z-boxes induces chromosomes with only one α-globin gene (-α$^{3.7}$, rightward deletions) and leads to α-thalassaemia and other genes with 3 α genes (ααanti$^{3.7}$) as the units are separated by 3.7 kb. In the same way, the reciprocal recombination of the X-boxes results in a deletion of 4.2 kb (–α$^{4.2}$ leftward deletion of α-thalassaemia). Recombination may also lead to chromosomes of αααα/αα or even ααααα/αα genes (7,14,16).

Deletional α0-thalassaemia

α-Thalassaemia are commonly caused by deletions. The complete or partial deletion of the α2 and α1-linked genes results in the absence of α-globin chain synthesis. These deletions can be categorised as those which delete only within the α-globin cluster and those which extend approximately 800 kb beyond the α-globin genes, including the flanking regions. Deletion of the HS-40 element and regulatory region α-globin genes also causes α0-thalassaemia even though the α-globin genes remain intact. Heterozygous individuals have mild hypochromic microcytic anaemia, whereas compound heterozygosity of α+-thalassaemia causes Hb H disease.

Deletional Hb H disorder manifests a milder phenotype that rarely needs regular transfusion and has relatively normal growth and development (16). Hb H diseases usually occur in patients with compound heterozygosity of α0-thalassaemia and α+-thalassaemia or less frequently in those with homozygosity of a severe allele. They commonly have less than 30% of usual α-globin production (7). Hb H has red cell inclusion bodies in the peripheral blood smear that can be seen using a light microscope on a supravital stain (8).

Homozygosity of α0-thalassaemia produces Hb Bart's hydrops foetalis syndrome. The most common α0-thalassaemia deletions are $^{--SEA}$, $^{--FIL}$ and $^{--MED}$. A large-scale deletion of 16p13.3 triggers developmental issues with α-thalassaemia intellectual disabilities also known as ATR-16 (15,17). Hb Bart's hydrops foetalis is the most severe type of α-thalassaemia, since there is no production of functional α-globin chains for the formation of haemoglobin. Homotetramers of γ4 and β4 have an extremely high oxygen affinity and are not functional. Homozygous $^{--SEA}$ deletion, which is a common cause of hydrops foetalis, does not affect the embryonic genes, so pregnancy can continue into late

gestation. Hydrops infants are pale and oedematous due to extended intra-uterine anaemia with genitourinary, hepatosplenomegaly, skeletal deformities and enlarged placenta. Affected infants usually die in utero or shortly after birth (7,8). Several reports have documented long-term survival with intrauterine therapy, but these cases are rare (18). Maternal complications including preeclampsia, hypertension, abruption placenta and antepartum haemorrhage, are also implicated.

α-thalassaemia trait is associated with carriers of α-thalassaemia (whether deletional or non-deletional) are generally asymptomatic with minimal reduction in the α-globin chains. They have mild to moderate microcytic haemolytic anaemia that can be seen in a routine full-blood count that often overlaps with normal values (7,8).

HUMAN KIDNEY DEVELOPMENT
The functions of mammalian kidneys include removal of metabolic waste products, regulation of body fluid composition and volume, maintaining blood pressure and bone density. Kidney development in mammals occurs in three consecutive phases; pronephros, mesonephros, metanephros from cranial (anterior) to caudal (posterior) development from the intermediate mesodermal cells extending from the embryonic heart region to the tailbud (19). The metanephric kidney is the final stage of kidney development by mid-gestation (20). Nephrogenesis in humans occurs before birth and the nephron matures further postnatally (21). In 1997, Endo & Oka was the first to report abnormalities in the renal tubular epithelium found in hydrops foetalis (3). A study by Sumboonnananda et al., 2003 has shown that significantly higher levels of urine N-acetyl-β-D-glycosaminidase, malondialdehyde (MDA) and β2-microglobulin were found in both HbH and HbH/HbCS (Hb Constant Spring) groups with or without splenectomy compared to normal children. They also reported that patients with only marginally increased serum ferritin levels have the same degree of renal dysfunction as those of their β-thalassaemia patients (4). We hypothesize that renal injuries could have happened during development in utero due to oxidative stress caused by α-thalassaemia as haemoglobin switching involving the β-globin chain only occurs 6 months after birth which is when β-thalassaemia manifestations begin. A brief overview of nephrogenesis is essential to elucidate the possible mechanisms involved in the renal dysfunction in α-thalassaemia.

Pronephros
Pronephros is not a functioning human kidney, but it is the first set of kidneys that develops in humans (22,23). The pronephric duct is developed at E18 (embryonic day) for humans with associated nephrogenic mesenchyme in the cervical region of the nephrogenic cord until it extends rostro caudally and fuses with cloaca (21,22). Adjacent to the pronephric ducts, the intermediate mesoderm is condensed to form pronephroi which is a non-functional nephron units, which usually degrade by day 25 as it is not functional in humans (22).

Mesonephros
The mesonephros is entirely lost during development of the later foetal/adult metanephros except the mesonephric duct (21). In the next most caudal region, the Wolffian duct (WD) developed nephrogenic cord and adjacent intermediate mesoderm condensate to form mesonephroi. (22) The mesonephros stage begins at 3.5 weeks of gestational age (wga) as a WD caudal (23). The duct extends downwards in intermediate mesoderm towards cloaca, and later urogenital sinus (21). There are around 40 pairs of mesonephroi and mesonephroi located at lumen 1-3 continue to distinguish in order to form functional excretory units. WD's epithelial buds is attracted to mesonephric mesenchyme and going through a series of changes to develop identifiable nephrons (23). Around twenty of those nephrons are capable of excreting small amounts of fluid between sixth to tenth weeks of development in amnion. The ducts degenerates in females but not in males as the embryonic structures survive and grow to epididymis, seminal vesicles, vas deferens and ejaculatory ducts. To humans, the ureteric bud protrudes from the nephric duct caudal end and permeates the metanephric mesenchyme blastema (21,22).

Metanephros
Extension of mesonephric ducts and fusing with cloaca stimulates sacral intermediate mesoderm which then form metanephric blastema aggregates (22). Metanephric mesenchyme group of cells induce signals to caudal Wolffian duct and starts ureteric bud which is a posterior outgrowth of epithelial cells. The ureteric buds then invade metanephric mesenchyme and the interaction of the buds and mesenchyme cells causes the subset of metanephric mesenchyme cells to concentrate around the tip of ureteric bud. Such process is called mesenchymal condensation and the cells are called condensing mesenchyme or cap mesenchyme cells. These initial steps allow ureteric bud to be branched into 'T-shaped' structure of two ureteric buds tips or ampulla and a stalk which is the trunk. Morphogenesis and nephrogenesis are branched from this induction (23).

Each of the collecting tubules' tips stimulates the blastemal caps to form nephric vesicles to develop functional nephrons. The nephrons undergo differentiation into nephric tubules consisting of the proximal and distal tubules, the S-shaped Bowman's capsule and the loop of Henle. VEGF2 which is secreted by the podocyte precursors which line the S-shaped body starts the glomerulus formation. VEGF2 creates primitive vascular tuft by attracting endothelial cells. The interaction between the precursors of podocyte and the endothelial cells promotes the differentiation of the

podocyte. Glomerular basement membrane forms at the dividing line between the two. Uriniferous tubule is formed by fusion of collecting duct with the distal convoluted tubule (distal end of the nephric tubule) (21,22) (Fig. 2). We believe that the damage occurs mainly at this stage as Endo & Oka (1997) has reported unusually thin proximal convoluted tubules (PCT) and reduced cytoplasmic areas as well as narrow lumina. Their study showed that Leu-7-positive cells (marker for lymphoid cells expressing natural killer activity) can be seen in the S-form and junction between Bowman's capsule and PCT suggesting abnormal differentiation of renal tubular cells (3). Embryonic haemoglobin is predominant from 3 weeks post-conception to 3 months before foetal haemoglobin takes over as the predominant haemoglobin (24). α-globin chains increases dramatically after 6 weeks post-conception thus any effects of α-globin insufficiency can only be seen accumulated after this period. The lack of α-globin expression leads to increased oxidative stress which most probably leads to the abnormal cellular differentiation of the renal tubules. We hypothesize that this impairment during development causes the more severe renal dysfunction seen in α-thalassaemia compared to α-thalassaemia.
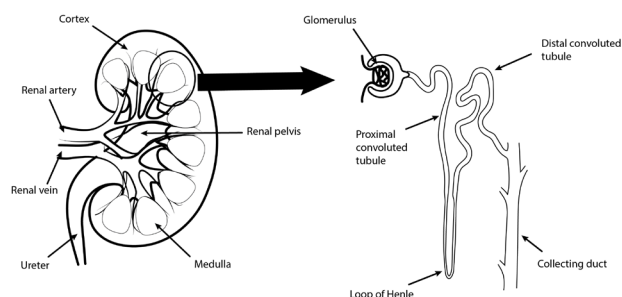

Fig. 2 : Outline of the human kidney and nephron

POSSIBLE MECHANISM OF HAEMOGLOBIN SYNTHESIS AND KIDNEY DEVELOPMENT

Excess gamma chains are found in α-thalassaemic neonates while excess beta chains are found in the adults due to the loss of alpha-globin chains. Both haemoglobins are unstable and some precipitate within the cell. These haemoglobins are more vulnerable to oxidant injury and has poor oxygen-carrying capacity (25). They have ten times more oxygen affinity than HbA with an irregular oxyhaemoglobin dissociation curve, thus causing tissue hypoxia (25,26). Changes in relative oxygen tension levels are quite normal during development, but additional hypoxia is known to have a negative impact on foetal development (27).

When prenatal hypoxia happens, the developing foetus displays a preferential redirection of blood flow, including oxygen and nutrient supply, to the brain and the heart over less vital organs such as the kidney (28). A research performed by Kasey et al. in 2020 found that prenatal hypoxia does not affect embryonic

kidney development, but instead it renders the kidney susceptible to long-term injury (28). Mice exposed to prenatal hypoxia demonstrated increased susceptibility to cisplatin injury without apparent structural defects (28). The mechanism of the injury is still unclear, although few possible mechanisms have been identified by the authors of the study, including the reactive oxygen species associated with Nox4 genes. ROS-mediated stress has generally been associated with the severity of cisplatin-kidney injury, and prenatal exposure may have made the kidneys more vulnerable later in life (28).

However, in the event of placenta insufficiency, the loss of oxygen and nutrient availability prevents the proper development of other organs, including the kidney (27). Impaired kidney development may decrease the number of nephrons develop, and foetal hypoxia may limit the flow of renal blood and render the kidney to be pathologically hypoxic (27). This observation is supported by a study in 2016 which showed that hypoxia reduced the number of nephrons in rat neonates and decreased body and kidney weight (29). If the metanephric kidneys of the mice are under hypoxia, the differentiation and patterning of the vessels is completely blocked and the number of glomerular cells is reduced (29). The kidneys are very sensitive to altered oxygenation in order to fulfil their physiological function and very susceptible to hypoxic damage (29).

POSSIBLE MECHANISMS OF RENAL DISEASE IN α-THALASSAEMIA

Postnatally, the other possible mechanisms of renal dysfunction in β-thalassaemia is similar to β-thalassaemia but compounded by the developmental impairment. Sumboonnanonda et al., 2003 observed high levels of urine NAG, MDA and β2-microglobulin, calcium, phosphate, magnesium, uric acid, amino acids and malondialdehyde in α-thalassaemia children with proximal tubular dysfunction (4).

Iron overload have been suggested to cause tubular cell damage and encourage wounded cells to migrate to the interstitium and cause tubulointerstitial scarring and glomerular sclerosis through the release of cytokines and growth factors leading to more decline in (30). Hemosiderin deposits can be seen in the glomeruli and proximal tubule and exhibit signs of remarkable glomerulosclerosis, interstitial fibrosis and tubular atrophy (30). Transferrin releases iron into the proximal tubules and causes damage to the tubular membrane's brush borders and cellular injury through generation of oxidative species. Lipid peroxidation through the removal of hydrogen atoms from lipid bilayer of the organelle's fatty acids by free iron also contributes to tubular damage (4). A number of studies have shown a strong link between serum ferritin levels and tubular toxicity markers and also reduction of tubular damage following iron chelation therapy (30).

Ineffective erythropoiesis leads to severe hypoxia and chronic anaemia. These complications increase oxidative stress which causes lipid peroxidation and cellular tubular damage (30). In vitro studies and animal models have shown that hypoxia can induce endothelial and tubular apoptosis (4). Advani et al. (1992) observed globin-generated ROS when there is depletion of free thiols under thiol-disulfide exchange chromatography in Hb H disease (31). Several studies have shown that excessive MDA due to increased lipid peroxidation may cause cross-linking of phospholipids and protein which alters the lipid bilayer structure of beta-thalassaemic red blood cell membranes (32).

Anaemia decreases systemic vascular resistance which leads to glomerular hyperfiltration and renal hyperfusion because hyperdynamic circulation elevates GFR and renal plasma volume (30,4). Glomerular dysfunction is attributed to glomerular capillary wall stretching with time resulting in injuries in the epithelial and endothelial layers and macromolecule leakages into the mesangium. Subsequently, these lead to a gradual GFR decrease (30). The accumulation of these oxidative stressors is much longer in α-thalassaemia individuals compared to β-thalassaemia as β-globin chain is only predominant 6 – 8 months after birth.

RENAL DYSFUNCTION IN α -THALASSAEMIA
The studies on the effects of α-thalassaemia on the kidneys are still limited. Elucidating the underlying mechanisms of nephropathy in α -thalassaemia is timely as better treatment and management has improved the patient's quality of life as well as prolonged their lifespan (33). There seems to be a correlation between the duration of the disease and increased kidney complications (34). Renal abnormalities such as higher renal plasma flow, reduction in the ability to concentrate urine and renal tubular acidosis have been identified. It is well-known that chronic anaemia, tissue deposition of iron due to intermittent blood transfusion and deferoxamine therapy damage many organs, including the heart, kidneys, liver and lungs amongst others (33,34).

Hyperfiltration
Glomerular hyperfiltration is defined as excessively increased glomerular filtration rate (GFR), escalated filtration fraction or filtration per nephron i.e. excessive creatinine clearance (35). This is commonly seen in thalassaemia which could be due to complications of chronic anaemia or iron-mediated glomerular and tubular injuries (33). Autopsies in patients with thalassemia revealed hemosiderin deposits in the proximal and distal tubules (36). Iron deposits in proximal tubules, glomeruli, and interstitium have resulted in mild proteinuria and associated with interstitial fibrosis, glomerular and tubular atrophy (36).

Hypercalciuria
Hypercalciuria is frequently seen in thalassaemia due to higher transfusion intensity and use of deferasirox as treatment (33,37). Typically, hypercalciuria attributed to tubular dysfunction and increased cell turnover has been linked with uric acid urolithiasis in the general population (38). Hypercalciuria has been associated with osteoporosis and urolithiasis as a predisposing factor and also a common sign for tubulopathy (37,38). These compounding multiple risk factors of bone and renal disorders have proven to be a challenging issue in the management of thalassaemia (37).

Albuminuria
Most patients with thalassaemia have albuminuria, but it is not associated with transfusion intensity (33). Albuminuria in thalassaemia is caused by iron deposition-related glomerular injuries leading to excessive large molecular weight plasma protein filtration or diabetic kidney indirectly as a complication of pancreatic iron overload damage (39).

Renal tubular dysfunction
Renal tubular dysfunction has been reported in thalassaemia patients with hypercalciuria, albuminuria, low molecular weight proteinuria, and excretion of β2-microglobulin but with normal GFR (33,40). Dysfunctions and abnormalities may be associated with transfusion period, chelation therapy, iron accumulation and frequency of magnetic resonance imaging of body iron. Haemolysis may also contribute to renal dysfunction due to heme and iron release through decreased bioavailability of nitric oxide (33).

Proximal tubular dysfunction has been reported in children with alpha-thalassaemia. Characteristics of this dysfunction include excessive amounts of urine N-acetyl-b-D-glucosaminidase (NAG), malondialdehyde (MDA) and β2-microglobulin, calcium, phosphate, magnesium, uric acid and amino acids from peroxidation of membrane lipids (33,40). In the initial stages of renal damage i.e. idiopathic membrane nephropathy, proteinuria tubular toxicity will release NAG into the urine as it is a widely distributed lysosomal enzyme in tubular epithelial cells. As NAG is not derived from the plasma nor filtered through the glomeruli, increased NAG is attributed to tubular proteinuria and dysfunction (34).

The cause of tubular dysfunction in alpha-thalassaemia is still unknown. It was suggested that unstable haemoglobin subunits from excess unpaired globin chains and the abundant intracellular non-haemoglobin bound iron concentration produce reactive oxygen species that trigger progressive oxidative damage leading to membrane protein injuries which alters normal tubular structure and function (34).

Glomerular injury
Glomerular hyperfiltration occurs in 20 – 40 % of severe thalassaemia cases (40). These injuries could be attributed to recurrent infections and continuous desferal

treatment, which lowers the kidney's competency in removing immune complexes, thus increasing GFR or albuminuria (34). Chronic hypoxia of tubular cells with elevated metabolic demand triggers apoptosis or epithelial-mesenchymal transition, culminating in glomerulosclerosis (41).

Anaemia can reduce systemic vascular resistance, result in hyperdynamic circulation and increase the flow of renal plasma and GFR. The changes eventually lead to the stretching of the glomerular capillary wall. This leads to a long-term decline in GFR. Other than this, the damage to tubular cells induced by heavy iron overload that enable injured cells to migrate into the interstitium, release cytokines and growth factors that may induce glomerular sclerosis and further decrease in GFR (41). Decreased GFR is rarely documented in early age but gradually occurs with progressive renal damage and begins to appear in adult patients. The decline in estimated GFR (eGFR) is more pronounced in patients with tubular damage. Decreasing GFR reflects the accumulation of long-term kidney damage (40).

Urolithiasis
Hypercalciuria and proteinuria also commonly coexist with urolithiasis. Kidney stones have a mixed composition but mainly are calcium-based (40). Greep et al. and Kalef-Ezra et al. have different opinions on osteoporosis from hypercalciuria as Greep et al. reported hypercalciuria as a risk factor while the Kalef-Ezra et al. did not determine such a risk (42,43). However, in children with thalassemia, hypercalciuria is a risk factor for urolithiasis (44). Kalman et al. reported statistically significant difference of higher calciuria in children with thalassemia than healthy children (44).

OTHER COMPLICATIONS OF α-THALASSEMIA
Apart from kidney disorders, other complications of α-thalassemia include heart, liver, and spleen problems. Most of these complications are due iron overload caused by the need for multiple blood transfusions, particularly in Hb H patients, and also increased absorption of intestinal iron. Excess iron overload in visceral organs such as the heart, liver, and endocrine glands are common and most deaths are caused by cardiac complications (1). Origa et al, 2006 found heart dilation to be one of the complications in children with Hb H disease, while most complications are more common in adults. Chen et al, 2000 also observed three cases of heart failure due to iron overload but the abnormalities were found in a small group of patients (45).

High levels of serum hepatic enzymes such as alanine aminotransferase (ALT) and aspartate aminotransaminase (AST) are known to be elevated in transfusion-dependent thalassemia. ALT is formed primarily in the liver. Normally, the level of ALT is increased in any hepatic injury. For thalassaemia patients, the elevated level is attributed to numerous blood transfusions. AST is also a transaminase group and present in nearly all body tissues particularly in the liver and heart. Elevated AST levels are commonly observed in intrahepatic cholestasis, extrahepatic biliary tract blockage, infiltrative and inflammatory hepatic diseases. Excess cellular iron is stored as ferritin and hemosiderin. Continual iron deposition causes cellular toxicity although the exact pathophysiological pathway for liver cell damage and fibrosis has not been completely established. Suggested mechanisms include oxidative damage of organelle membranes, accelerated lysosomal fragility and reduced oxidative metabolism of the mitochondria. Iron has also been attributed to the degradation of collagen synthesis microsomal enzyme changes (46).

Hypersplenism is a common complication due to increased destruction of transfused red blood cells and increased transfusion requirements. It is also associated with iron overload as well as extramedullary haematopoiesis (47).

α-THALASSAEMIA TREATMENT AND MANAGEMENT
Generally, α-thalassaemia carriers do not require any treatment. Intermittent red cell transfusion may be required in non-deletional α-thalassaemia and Hb H individuals depending on the severity of the clinical conditions (1,17). Iron overload has been reported in older individuals with multiple transfusions as humans cannot remove excess iron physiologically. Iron chelation therapy is recommended in these circumstances (1).

Genetic counselling is given when both couples are α-thalassaemia carriers and are at risk of having Hb Bart's hydrops foetalis offspring. Prenatal diagnosis is carried out during pregnancy using foetal blood obtained by cordocentesis or amniocentesis as hydrops foetus can cause serious maternal toxaemic complications and postpartum bleeding (1,17,48). Intrauterine transfusion has been attempted at early prenatal detection and overall pregnancy-related loss is approximately 1% but most surviving foetus experience a high incidence of congenital malformations or neurological abnormalities (17,40,48). Intrauterine transfusion requires monitoring of foetal haemoglobin as it is associated with bleeding and foetal bradycardia (48). Serial intrauterine transfusions followed by aggressive postnatal management or haematopoietic stem cell therapy appear promising to minimise morbidity and mortality as well as long-term neurological outcomes of Hb Bart's hydrops foetalis, however, life-long transfusion and iron chelation therapy would be necessary for most of them (40,48).

CONCLUSION

In comparison to β-thalassaemia, there have been limited studies carried out in α-thalassaemia especially in terms of emerging complications due to increased quality of life and lifespan due to better treatment and

management these days. These complications should be identified and more studies should be done to alleviate the complications as well as provide better management particularly when the patients are older. Renal dysfunction has been increasingly seen in α-thalassaemia patients even in young children and it is yet unknown as to why α-thalassaemia patients suffer a higher severity of nephropathy although clinically the patients are similar to other β-thalassaemia patients. Further research is required to understand the mechanisms of glomerular and tubular injury in α-thalassaemia to provide better treatment and management for these patients as they grow older. Currently, there is a need for close monitoring and follow up of renal function in α-thalassaemia patients as their renal function seems to deteriorate faster than β-thalassaemia patients. Progress of research and meta-analysis in this field would allow the identification of renal dysfunction in hope of preventing, if not reversing, the progression of renal injury.

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